VOLUME 1

Briefing Book
July 30, 2009 PDAC
Saphris (asenapine) Sublingual Tablets

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M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 24, 2009

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: July 30, 2009 Meeting of the Psychopharmacologic Drugs Advisory Committee (PDAC)

TO: Members, PDAC

This one-day PDAC meeting will focus on safety and efficacy issues for NDA 22-117 (asenapine). This drug is an atypical antipsychotic (5HT2 and D2 receptor antagonist) that is available in an immediate release sublingual tablet formulation. This NDA seeks claims for (1) the acute treatment of schizophrenia, and (2) for the acute treatment of mania/mixed episodes in bipolar 1 disorder, in a dose range of 5 mg bid to 10 mg bid.

In FDA's background package, we have provided FDA's various review documents for this application (primary medical officer reviews, team leader memos, and division director memos, and reviews from the Office of Clinical Pharmacology). The sponsor's background package will also provide data to support the safety and efficacy for asenapine in these indications. Although the Division has not yet reached a final conclusion for this application, we generally are in agreement that the sponsor has provided adequate support to suggest effectiveness for asenapine for the claimed indications. In addition we view the safety profile for this product in the populations studied to be qualitatively similar to that observed for other atypical antipsychotic drugs, and to be acceptable. Chemistry, toxicology, and biopharmaceutics issues for this application have also been resolved, and we are currently discussing proposed labeling for this product with the sponsor.

Schizophrenia and bipolar disorder are serious illnesses and represent a substantial burden for both patients and their families. At the present time there are already a number of antipsychotic drugs approved for the treatment of these conditions. Having multiple treatment options is important in these conditions because not all patients respond to or adequately tolerate available treatments. If approved, asenapine would represent an additional treatment option.

All of the drugs in the class of atypical antipsychotics have significant risks that must be considered, both by FDA in deciding whether or not to approve these claims and also by clinicians in deciding whether or not to use these medications in treating these serious disorders. Adverse reactions that can occur with drugs in the class of atypical antipsychotic drugs include,

among others, somnolence, weight gain, increases in blood lipids and glucose, acute extrapyramidal symptoms, and tardive dyskinesia.

Formal presentations of data at the meeting will include a summary of the safety and efficacy data for these expanded claims by the sponsor. FDA will not be making separate presentations, since we are in essential agreement with the data to be presented by the sponsor.

The Division of Psychiatry Products has not yet reached a final conclusion on these applications, and seeks the advice of the PDAC before reaching a conclusion.

After you have heard all the findings and arguments, we will ask you to discuss and vote on four questions of risk and benefit for this product in the indications being sought. The questions for a vote are as follows:

1. Has asenapine been shown to be effective for the acute treatment of adult patients with schizophrenia?

2. Has asenapine been shown to be acceptably safe for the acute treatment of adult patients with schizophrenia?

3. Has asenapine been shown to be effective for the acute treatment of mania/mixed episodes in adult patients with bipolar 1 disorder?

4. Has asenapine been shown to be acceptably safe for the acute treatment of mania/mixed episodes in adult patients with bipolar 1 disorder?

cc:
HFD-130/TLaughren/MMathis/GZornberg/KKiedrow

DOC: Laughren 073009 PDAC Memo 01.doc

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 1, 2008

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for approvable action for asenapine sublingual tablets for the acute treatment of schizophrenia and for the acute treatment of mania and mixed episodes in bipolar 1 disorder

TO: File NDA 22-117
[Note: This overview should be filed with the 8-30-07 original submission of this NDA.]

1.0 BACKGROUND

Asenapine is available in an immediate release sublingual tablet formulation and is an atypical antipsychotic (5HT2 and D2 receptor antagonist). This NDA seeks a claim for the acute treatment of schizophrenia and mania/mixed episodes in bipolar 1 disorder, in a dose range of 5 mg bid to 10 mg bid. It was developed under IND 51,641 for the treatment of schizophrenia and under IND 70,329 for the treatment of mania/mixed episodes of bipolar 1 disorder. We held a number of meetings with the sponsor of this IND during the development of asenapine, including (1) EOP2 meetings on 11-20-02 and 4-27-04, and (2) preNDA meetings on 7-18-06 and 2-22-07. The NDA was submitted on 8-30-07. Asenapine is not approved in any other country at the present time.

[Note: As part of this memo, I will comment on certain safety, efficacy, and other concerns raised by Dr. Ronald Kavanagh, the primary biopharmaceutics (OCP) reviewer for this application.]

2.0 CHEMISTRY

The CMC review is completed and the data are deemed sufficient to recommend an approvable action from a CMC standpoint. One remaining issue is how to address impurity (b) (4). The sponsor has set the specification for this impurity at (b) (4), above the threshold for qualification. In our action letter, we will ask the sponsor to either lower the specification limit for this

impurity to (b) (4) or adequately qualify it. Several other minor requests for CMC information will be included in the action letter.

3.0 PHARMACOLOGY

The major deficiency from a pharm/tox standpoint was the lack of histopathology data for the low and medium dose groups in the rat and mouse carcinogenicity studies. The MTD was exceeded in the rat carcinogenicity study, leading to excessive weight loss in the high dose group. Thus, the lack of tumor findings in this group cannot be interpreted. In the mouse carcinogenicity study, there was a large increase in malignant lymphomas in the high dose females compared to the vehicle control group, but not to an untreated control group. In both instances, the slides from the lower dose groups would be needed to try to better understand these findings. Unfortunately, the sponsor did not provide histopathology findings from lower dose groups. The sponsor is aware of our concern, but has argued that these lower dose findings should not be necessary. The pharm/tox group has recommended an approvable action, pending resolution of this matter. Our responses to the sponsor's counter-arguments will be included in the action letter.

4.0 BIOPHARMACEUTICS

Asenapine is available in a sublingual formulation because oral bioavailability is very poor. It is rapidly absorbed by the sublingual route with peak concentrations in about an hour. Absolute bioavailability is about 35% by this route. The elimination half-life is about 24 hours and steady state is reached in about 3 days. Asenapine is extensively metabolized by 3 routes to yield 4 primary metabolites (2 glucuronides and 2 others, none of which is expected to contribute to the therapeutic activity of this drug). Three p450 enzymes are of primary importance in the metabolism of asenapine, in particular, 1A2, and to a lesser extent, 2D6 and 3A4. Asenapine is a weak inhibitor of 2D6. Asenapine should not be administered to patients with hepatic impairment, however, dosage adjustments of asenapine would not be needed in other patient subgroups.

A major deficiency in the application from a biopharmaceutics standpoint is a failure to adequately determine what moieties are circulating in plasma. OCP maintains that the sponsor has identified only about 3% of circulating material in plasma. Also from the standpoint of mass balance, OCP maintains that only about 30% of the dose has been characterized regarding elimination pathways. They feel that the application cannot be approved before these deficiencies are addressed. The sponsor disputes these findings, and claims that they have identified up to 30% of circulating metabolites and 70% of the dose. At this point, however, this issue is unresolved. It is true that we have substantial human experience with this drug, none of which, in my view, would mark asenapine as an outlier among the atypical antipsychotics. If OCP is correct in its assertions, however, we have little assurance that the animal carcinogenicity data or reproductive toxicity data are relevant to humans, since we would know so little about

what is circulating in humans. Until this issue is resolved, I am inclined to agree with OCP that this is a serious deficiency. However, the sponsor should be given an opportunity to have a face-to-face discussion with staff from OCP and with ODE-I staff so they can hear OCP's arguments in more detail and respond directly to these arguments.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy in Schizophrenia

Our review of this application focused on 4 short-term (6-week), double-blind, randomized, parallel group, placebo-controlled trials in adult patients with acutely exacerbated schizophrenia. The primary endpoint was change from baseline to endpoint on the PANSS total score. CGI-I was accepted as a key secondary endpoint. Three studies were fixed-dose, and 1 was flexible-dose. All 4 were active-controlled. Dosing was always on a bid basis. The primary analysis for all 4 studies was LOCF. MMRM was also done.

5.1.1.1 Study 041004

This study compared asenapine 5 mg bid, risperidone 3 mg bid, and placebo. There were roughly 60 patients per group. Dropouts were substantial, with completion rates for the 3 groups, as follows: asenapine-46%; risperidone-42%; placebo-34%. For the primary endpoint, asenapine was statistically superior to placebo (p=0.007); risperidone was numerically, but not statistically, superior to placebo (p=0.125). Both asenapine and risperidone were statistically superior to placebo on the CGI-I. The statistical reviewer seems to be troubled by the large number of dropouts, and the proportionately larger percentage of dropouts for placebo compared to active drug. I am not, however, because I would expect to see this pattern of dropouts with an effective drug. In fact, looking at time to rescue of patients in a study like this is an alternative approach to establishing efficacy (see CATIE, for example).

5.1.1.2 Study 041021

This study compared asenapine 5 mg bid, asenapine 10 mg bid, olanzapine 15 mg qd, and placebo. Neither asenapine group was statistically superior to placebo, however, the olanzapine group was superior to placebo (p=0.017). Thus, this was a negative study for asenapine.

5.1.1.3 Study 041022

This study compared a flexible dose of asenapine (5-10 mg bid) with olanzapine and placebo. Neither active drug group was statistically superior to placebo. Thus, this was a failed study that is difficult to interpret.

5.1.1.4 Study 041023

This study compared asenapine 5 mg bid, asenapine 10 mg bid, haloperidol 4 mg bid, and placebo. There were roughly 110 patients per group. Completion rates for the 4 groups were as follows: asenapine 5 mg bid-63%; asenapine 10 mg bid-67%; haloperidol-59%; placebo-57%. For the primary endpoint, asenapine 5 mg bid was statistically superior to placebo (p=0.014); asenapine 10 mg bid was not statistically superior to placebo (p=0.068); haloperidol was statistically superior to placebo (p=0.034). An MMRM analysis for asenapine 10 mg bid did yield a statistically significant finding (p=0.038). Both asenapine 5 mg bid and haloperidol were statistically superior to placebo on the CGI-I.

5.1.1.5 Summary of Efficacy Findings from 3 Informative Efficacy Studies

Summary of Efficacy Findings for 3 Informative Schizophrenia Studies						
Change in PANSS Total Score (LOCF)						
Study Number (Group Size)	**Placebo**	**Asenapine 5 mg bid**	**Asenapine 10 mg bid**	**Risperidone 3 mg bid**	**Olanzapine 15 mg qd**	**Haloperidol 4 mg bid**
041004 (60/arm)	**-4.6**	**-14.4***		**-10.0**		
041021	**-11.1**	**-14.5**	**-13.4**		**-16.5***	
041023 (110/arm)	**-10.7**	**-16.2***	**-14.9**			**-15.4***
***** **< 0.05**						

5.1.2 Comment on Other Important Clinical Issues Regarding the Efficacy Data for Schizophrenia

Evidence Bearing on the Question of Dose/Response for Efficacy

Study 041023 is the only study that could contribute useful information about dose response for asenapine. In that study, however, only the 5 mg bid dose was statistically superior to placebo on the protocol specified LOCF analysis. Although the 10 mg bid dose was statistically superior to placebo in the MMRM analysis, the effect size was still numerically inferior to that seen for the 5 mg bid dose. Dr. Zornberg argued in her initial CDTL memo for permitting the sponsor's proposed labeling that recommends dosing for schizophrenia in a range of 5-10 mg bid. This was based in part of the finding during the first week of treatment of numerical superiority for the higher dose group. However, I would prefer a more conservative approach of recommending the dose for which we have positive evidence on the primary endpoint. [Note: In her second CDTL memo, Dr. Zornberg has modified her view on this issue.] Labeling should also indicate

that the 10 mg bid dose did not appear to confer any advantage over the 5 mg bid dose. We can still say that we have safety data up to 10 mg bid, and clinicians are not precluded from using this higher dose if they wish. I just don't think we have a sufficient basis for recommending the higher dose. In fact, it would be useful for the sponsor to explore a lower dose of 2.5 mg bid, since they have not yet identified the lowest effective dose.

Secondary Efficacy Variables

We reached agreement with the sponsor on the declaration of CGI-I as a key secondary endpoint. Thus, these positive findings will be permitted in labeling.

Clinical Predictors of Response

Exploratory analyses were done to detect subgroup interactions on the basis primarily of gender, race, and age. There was no clear indication of any difference in effectiveness based on these factors.

Size of Treatment Effect

The effect sizes observed in these trials were similar to those seen in other positive schizophrenia trials. In study 41004, the asenapine effect was actually numerically to risperidone, and in study 41023, the asenapine effect was numerically superior to haloperidol. However, asenapine was numerically inferior to the olanzapine effect in study 41021.

Duration of Treatment

The sponsor presented no data pertinent to longer-term efficacy of asenapine for the treatment of schizophrenia. We will seek such data as a phase 4 commitment, should we decide to issue an approvable letter for this NDA.

5.1.3 Overview of Studies Pertinent to Efficacy in Bipolar 1 Disorder

Our review of this application focused on 2 short-term (3-week), double-blind, randomized, flexible dose, placebo- and olanzapine-controlled, parallel group studies of asenapine in adult patients with manic or mixed episodes of bipolar 1 disorder. Dosing was 5-10 mg bid for asenapine and 5-20 mg qd for olanzapine. Randomization was 2:2:1 for asenapine, olanzapine, and placebo. The primary endpoint was change from baseline to endpoint in the YMRS, and the key secondary endpoint was CGI-BP on day 21. The primary analysis model was ANCOVA (LOCF).

5.1.3.1 Study A7501004

This was a multinational trial (61 centers, including both US and nonUS sites). There were roughly 200 patients per each active group and 100 for placebo. Completion rates were as follows: asenapine-67%; olanzapine-79%; placebo-58%. Both active drug groups were statistically superior to placebo on both the primary and key secondary endpoints.

5.1.3.2 Study A7501005

This was a multinational trial (55 centers, including both US and nonUS sites). There were roughly 200 patients per each active group and 100 for placebo. Completion rates were as follows: asenapine-63%; olanzapine-80%; placebo-62%. Both active drug groups were statistically superior to placebo on both the primary and key secondary endpoints.

5.1.3.3 Summary of Efficacy Findings from 2 Informative Efficacy Studies

Summary of Efficacy Findings from 2 Informative Efficacy Studies			
	Mean Change in YMRS Total Score (LOCF)		
Study Number	Placebo	Asenapine 5-10 mg bid	Olanzapine 5-20 mg qd
A7501004	-7.8	-11.5*	-14.6*
A7501005	-5.5	-10.8*	-12.6*
* $p < 0.05$			

5.1.4 Comment on Other Important Clinical Issues Regarding the Efficacy Data for Mania/Mixed Episodes in Bipolar 1 Disorder

Evidence Bearing on the Question of Dose/Response for Efficacy

There were no data in this application pertinent to the question of dose response for the indication of mania/mixed episodes of bipolar 1 disorder. Given the findings in the schizophrenia program, the sponsor should be asked to explore a fixed dose of 5 mg bid for bipolar mania.

Secondary Efficacy Variables

As noted, both studies yielded positive results for both the primary and the agreed upon key secondary endpoints.

Clinical Predictors of Response

Exploratory analyses were done to detect subgroup interactions on the basis primarily of gender and race, because there were not sufficient data to explore differences based on age. There was no indication of any difference in effectiveness based on gender and race. There was, however, a site difference, where, for study 1004, the positive findings were coming entirely from the nonUS sites. The basis for this finding appeared to be an unusually high placebo response from the US sites. Study 1005 did not have a similar problem. Since the data for these studies are otherwise so strongly in favor of a finding for asenapine, I am inclined to discount this as an anomaly. However, it unfortunately is consistent with similar findings in other programs that signal a possible problem in the quality of data coming out of US sites for psychiatric drug trials.

Size of Treatment Effect

The effect sizes observed in these trials were similar to those seen in other positive mania/mixed episodes trials.

Duration of Treatment

The sponsor presented no data pertinent to longer-term efficacy of asenapine for the treatment of mania/mixed episodes. We will seek such data as a phase 4 commitment, should we decide to issue an approvable letter for this NDA.

5.1.5 Conclusions Regarding Efficacy Data

Schizophrenia

The data in support of short-term efficacy in schizophrenia are not overwhelming for this drug. The positive data come from 2 of the 4 studies, and only for the lower dose studied (5 mg bid). A third study can be discounted as being a failed study. However, the fourth study is a negative study where an active comparator (olanzapine) was positive. This finding is balanced, however, by 2 other studies that included active comparators in which asenapine was shown to be positive. In one of these studies the active comparator was not positive, and in the other study it was. Thus, overall, the sponsor has, in my view, provided sufficient evidence to support the claim of short-term efficacy of asenapine 5 mg bid in the treatment of schizophrenia. We will seek a maintenance study as ph 4 commitment and also an exploration of a lower dose for efficacy. In addition, we will ask for pediatric studies.

[Comment on Dr. Kavanagh's critique of the schizophrenia data: Dr. Kavanagh makes statements that the sponsor has not presented adequate data to support the efficacy of asenapine in schizophrenia. However, from what I have seen, he has not made any credible arguments to support these broad statements.]

Mania/Mixed Episodes in Bipolar 1 Disorder

The sponsor has, in my view, provided sufficient evidence to support the claim of short-term efficacy of asenapine in mania/mixed episodes of bipolar 1 disorder. We will seek a maintenance study as a phase 4 commitment and also an exploration of a lower 5 mg bid dose for efficacy. In addition, we will ask for pediatric studies.

[Comment on Dr. Kavanagh's critique of the bipolar data: Dr. Kavanagh conducted a post hoc exploratory analysis based on a separation of the sample into quintiles (on the basis of severity at screening, baseline, or other findings, which were not well-defined). His exploration of these data (pp. 397-403 of his 5-15-08 review) appears to be entirely graphical, i.e., he appears to be essentially "eye-balling" the change data based on his graphs. He concluded, based on this analysis, that there is only an effect in the most severely affected patients. I consider this a flawed approach to looking at these data. There is an obvious loss of power when the sample is arbitrarily divided into quintiles. It is also true, of course, that patients with higher baseline scores have more opportunity to change. However, these severity scores have no diagnostic significance and it would not be appropriate to suggest that baseline severity could be used to select patients for treatment. In my view, the correct interpretation of these data is that asenapine has been shown to be effective in the acute treatment of mania and mixed episodes, and I think it should be left to clinicians to decide how to select patients for treatment.]

5.2 Safety Data

5.2.1 Clinical Data Sources for Safety Review

The safety data for this NDA were derived from a total of 51 completed studies and 12 ongoing studies. The safety data that were the focus of Dr. Levin's safety review were included in the original NDA (with a cutoff date of 1-15-07) plus a 12-27-07 safety update (with a cutoff date of 10-27-07). Of the 51 completed studies, 14 were phase 2/3 schizophrenia and bipolar studies. The remaining 37 were clinical pharmacology studies. The 14 completed phase 2/3 studies included 2251 patients who received asenapine SL doses (of these, 1953 received doses in the relevant range of 10 to 20 mg/day). Dr. Levin's safety review is contained in 2 review documents, i.e., his original review dated 5-1-08 and a safety addendum dated 6-27-08. Overall, his safety review included safety data from what appears to be over 4000 asenapine SL-exposed patients. However, this is an approximation and we will ask the sponsor in the action letter to characterize the exposure more precisely, both in terms of numbers exposed and duration of exposure.

5.2.2 Common and Drug-Related Adverse Event Profile for Asenapine

The profile of common and drug-related adverse events includes: somnolence/sedation, akathisia, oral hypoesthesia, dizziness, and weight gain. If various extrapyramidal symptoms are combined, EPS is also a common AE (16% for drug vs 7% for placebo). Thus, except for oral hypoesthesia associated with asenapine (not unexpected for a SL formulation of this compound),

the common adverse events profile for asenapine is similar to what is seen for other atypical antipsychotic drugs.

5.2.3 Deaths and Other SAEs

Deaths

There were 27 deaths in the asenapine program overall (including the death in a patient in the clinical pharmacology program), including **22 in patients taking asenapine**.

-**8** of the asenapine deaths were suicides (see discussion under 5.2.4)

-**9** of the asenapine deaths were from serious medical events that are relatively common as background events [pulmonary embolism (2), pneumonia, CVA, complications of seizure, metastatic lung cancer, fetal death in premature delivery, heart failure, MI]. All of these deaths were plausible, in my view, as background events for the patients who experienced them, and there is no obvious pattern to any of these deaths. The seizure death occurred on day 204 of treatment, and it is unknown whether or not it was related to taking asenapine, but could have been. Seizure is a recognized risk of most antipsychotic drugs. (Dr. Levin fully discusses these cases and I will not further discuss them.)

-**1** of the asenapine deaths was from multiple drug overdose; this was a patient who was abusing cocaine, methadone, diazepam, and diphenhydramine, and this death should not be attributed to asenapine.

-**2** of the deaths occurred in patients who were no longer taking asenapine, and should not have been linked to asenapine (041013-28 and A7501018-10021006).

-Insufficient information was provided for **2** of the deaths (unfortunately, in both instances, it appears that follow-up information would not be obtainable):

-P25520-132017: I discuss this case under 5.2.5 (Concerns of Dr. Kavanagh). There are insufficient data to reach any conclusion about cause of death in this 44 year-old woman on day 521 of treatment.

-A750-1016002: This was an unexplained death in a 76 year-old woman who died suddenly and unexpectedly while sitting in a chair. No autopsy was performed.

Other SAEs

Most (about 94%) of the SAEs were exacerbations of psychiatric illness and I will not comment on these, since these are most likely background events representing the underlying illnesses being treated. The proportions of patients having SAEs were roughly comparable across treatment groups. Most of the non-psychiatric SAEs were common background medical events and not likely related to asenapine. Some of the SAEs, however, were likely drug-related, including syncope and NMS. There were several SAEs of particular interest:

Polydipsia/Hyponatremia/Rhabdomyolysis

In its proposed label for asenapine, the sponsor simply listed hyponatremia and rhabdomyolysis among several serious adverse reactions in the Adverse Reactions section, under "Other Premarketing Events." The question is whether or not this event deserves more prominence in labeling. There were 4 cases in asenapine-exposed patients that were characterized as possible rhabdomyolysis. In each of these cases, there was evidence of polydipsia, hyponatremia, CPK elevation, and trauma related to either seizure and/or falling. In one case, a seizure was observed. In the 3 other cases, the patients were either found unconscious (2 cases) or observed to fall (1 case). There was no evidence of primary muscle injury. The diagnoses of rhabdomyolysis seemed to be based almost entirely on the elevated CPK levels. Polydipsia, along with secondary hyponatremia and seizure, is a well-recognized phenomenon in schizophrenic patients, and it is unclear what the relationship of this is to drug use. I don't think it makes sense to consider these instances of rhabdomyolysis, but rather, cases of hyponatremia. Even for hyponatremia, the cases suggest that it was polydipsia, rather than a direct effect of drug, that led to the hyponatremia. Thus, I agree with the sponsor that it would be sufficient to mention these as possible adverse reactions in the Adverse Reactions section for now.

Neutropenia

There were 4 patients on asenapine identified by the sponsor as having "neutropenia," defined as having an ANC of < 1800 on at least 1 occasion. One was a patient (041002-1212) with a neutrophil count of 750 on day 7 of asenapine treatment. She had normal total WBC and ANC at baseline. Asenapine was discontinued on day 7. The patient was noted to have a fever on day 8, and on followup at day 14, ANC was up to 1260. Total WBC remained normal throughout. The 3 other patients with supposed neutropenia had transient ANCs of between 1300 and 1500, but were never symptomatic. Two of these patients returned to normal ANCs despite continued treatment and the third was discontinued and had complete resolution. Apparently there were 3 other patients with reports of ANCs less than 500 on 1 occasion, but that returned to normal ANCs on subsequent visits, despite continued treatment with asenapine, and thus, most likely represented laboratory error. There was no signal for any WBC effects for asenapine from the mean change or outlier data, and I don't think there is a sufficient basis for labeling this drug as having such an effect. The one case of interest can be noted in Adverse Reactions and we can monitor for this potential effect postmarketing, if this drug is approved at some point.

Thrombocytopenia

The sponsor reported 1 case of thrombocytopenia, however, we have no details on the case, except the fact that this finding did not lead to discontinuation and apparently resolved despite continued treatment with asenapine. We will ask for more details.

Anemia

In his original review, Dr. Levin referred to 5 cases of anemia, however, in his 6-27-08 addendum he revised that to 1 case. This was a patient with a history of anemia and hematuria and the finding on asenapine treatment was most likely not related to asenapine. Her anemia resolved despite continued treatment with asenapine. There was no signal for an RBC effect for asenapine from the mean change or outlier data. We can, however, ask the sponsor to give us more details on the other cases they identified as representing anemia.

5.2.4 Other Adverse Events of Particular Interest

Orthostatic Hypotension and Syncope

Asenapine has a modest orthostatic effect, likely related to its alpha antagonism. Syncope was reported in both the schizophrenia program (0.2% drug vs 0.2% placebo) and in the mania program (0.3% drug vs 0% placebo). Neurally mediated reflex bradycardia (NMRB), sometimes with sinus pause, was seen in normal volunteers in the clinical pharmacology program (4 in subjects getting asenapine and 1 in a placebo patient). One of these cases required resuscitation, however, that was a patient who received asenapine IV. NMRB was not seen in the clinical program, except possibly in one schizophrenic patient. This issue was reviewed by the QTIRT and they agreed with the sponsor's assessment of these cases, i.e., like orthostasis, this is likely related to alpha-blockade, and is similar to that seen with olanzapine and other atypical antipsychotic drugs. This potential, including the potential for NMRB, will need to be prominent in labeling, since there is some risk of a treatment naïve patient experiencing NMRB upon first exposure to asenapine.

QTc Increases

A thorough QT study for asenapine involving doses in a range of 5 mg bid to 20 mg bid revealed a small mean increase in QTc for asenapine of about 5-10 msec. There was not a clear dose response relationship for QT prolongation, however, the upper 95% confidence interval exceeded 10 msec for all 4 doses. Thus, this was a positive study. Quetiapine was an active control in this study and had a roughly comparable effect on QT prolongation. Asenapine should have the standard warning language for drugs with a modest QT prolonging effect, but would not be expected to be associated with Torsade des Pointes under ordinary circumstances of use.

Hyperprolactinemia

There was no clear signal for mean change from baseline in prolactinemia in this NDA, however, that may be a result of the insensitivity of detection methods in this program and the fact that patients may have been coming off of other antipsychotics that have an even greater potential effect. An outlier analysis, however, did reveal higher proportions of patients on asenapine with marked increases in prolactin compared to those on placebo. Asenapine will get the standard language regarding hyperprolactinemia.

Transaminase Increases

There was a finding of transaminase increase in both the schizophrenia trials (proportions of patients with >3XULN for ALT, 3.3% drug vs 1.9% placebo) and for mania trials (proportions of patients with >3XULN for ALT, 2.5% drug vs 0.6% placebo). However, there were no deaths or SAEs associated with liver injury, and no Hy's Law cases. [Note: (1) In her second team leader memo dated 6-12-08, Dr. Zornberg seemed to suggest (p.11) that there may have been Hy's Law cases, i.e., instances of transaminase elevation in temporal association with bilirubin increases. I asked her to clarify this statement, and she indicated in a 6-19-08 e-mail to me that she is not aware of any such cases and does not believe there is any evidence for significant hepatic toxicity for asenapine in this NDA. She also clarified that she agrees that the reason for avoiding asenapine use in patients with compromised hepatic function is not due to concern for further hepatic compromise, but rather, due to concern that asenapine levels would be increased to levels beyond those needed for effectiveness. (2) There was also some confusion about whether or not there was a finding of bilirubin elevation with asenapine, separate from transaminase increases. Dr. Kavanagh refers to such a finding in several places in his various review documents. My understanding is that there is, in fact, no such finding. Rather, there appears to have been confusion about the units for the values reported, and Dr. Kavanagh acknowledges his confusion about this on p. 421 of his 5-15-08 review.] Thus, the modest transaminase finding for asenapine can be noted in Adverse Reactions, and does not need a Warnings/Precautions statement.

Weight Gain

For schizophrenic patients, there was a mean weight gain of approximately +1.1 kg in the asenapine group vs about +0.1 kg on placebo. About 4.9% of asenapine patients met a weight gain criterion of $\geq$ 7% of body weight vs about 2.0% for placebo.

For bipolar patients, there was a mean weight gain of approximately +1.3 kg in the asenapine group vs about +0.2 kg on placebo. About 5.8% of asenapine patients met a weight gain criterion of $\geq$ 7% of body weight vs about 0.5% for placebo.

Suicidality

There were 12 suicides in the program overall, including 8 on asenapine and 4 on olanzapine. There were no suicides in patients taking placebo, risperidone, or haloperidol. When adjusted for exposure, the suicide rates were identical for asenapine and olanzapine, i.e., 1.3 per 100 PY. Except for 1 asenapine suicide in a short-term placebo-controlled mania trial, all occurred in long-term, active controlled trials (1 year duration). The distribution of time of treatment to occurrence of suicide was somewhat unusual for asenapine, i.e., 8, 12, 18, 31, 33, 96, 152, and 257 days. The comparable numbers for olanzapine were as follows: 13, 37, 191, and 376 days. The sponsor also looked at incidence of suicidality (suicidal ideation and behavior overall, including suicides). Asenapine generally looked no worse than, and often better than, placebo

and active comparators in this analysis. The one finding that stood out in this suicidality analysis is the early onset of suicide for asenapine among the 8 asenapine suicides. Suicide is a common background event in schizophrenia trials (the lifetime risk of suicide in schizophrenia is about 10-15%), but it is unusual to see the suicides occurring so soon after the onset of treatment (still, as noted earlier, when suicides are adjusted for overall exposure time, the rates are identical for asenapine and olanzapine). It is noteworthy that 5 of the 8 asenapine suicides occurred in a single large year-long trial comparing asenapine and olanzapine. In my view, the standard suicidality warning language for antipsychotic drug labeling would be sufficient for asenapine.

5.2.5 Comment on Concerns Raised by Dr. Kavanagh

Dr. Kavanagh produced 4 documents, including his original review (dated **5-15-08**), an e-mail he sent to Dr. Temple listing cases of concern to him (**5-27-08**), and what he refers to as Amendments #1 and #2 to his original review (dated **6-18-08** and **6-30-08**, respectively). The 5-27-08 e-mail does not appear to have been entered into DFS, however, the cases noted in that e-mail appear to be the same ones mentioned in his 3 review documents. I will focus my comments primarily on statements pertaining to clinical issues that Dr. Kavanagh made in his 5-15-08 review and the 2 amendments. There are a number of other statements made in Dr. Kavanagh's documents that I have not addressed either because they involve issues that I feel are adequately addressed by other reviews and memos in the file, or they deserve no further comment.

At the outset, I would note that Dr. Kavanagh's views on various safety issues are difficult to address because they are wide-ranging in scope, and often unsupported by specific data. Although Dr. Kavanagh notes a very large number of clinical cases that he is concerned about, with the exception of very few, he does not provide specific discussion of the case or any specific reason for his concern. Instead, he relies on unsupported speculation about mechanism to try to make his case. (See discussion of his mechanistic focus below). He seems to be suggesting with his comments that almost all the deaths and SAEs can be attributed to asenapine, but he does not provide sufficient justification, in my view, for considering most individual cases to be attributable to asenapine. For most of the deaths and SAEs there are obvious alternative interpretations.

In the discussion that follows, I will first comment on some of the specific cases of concern to Dr. Kavanagh, and then I will discuss some of the broader issues that he raises.

Comment on Specific Cases of Concern to Dr. Kavanagh: I will comment specifically on only a few of the many cases noted in Dr. Kavanagh's 4 documents, i.e., those for which he does offer some commentary. Dr. Levin and I have already commented on all the asenapine-associated deaths and non-psychiatric SAEs, and it is my understanding that there is overlap in these cases and the serious cases that Dr. Kavanagh mentions in his documents. In some of these cases, Dr. Kavanagh speculates about data we simply do not have, and for others, he offers no explanation regarding why he thinks the case can be considered causally related to asenapine exposure.

Neonatal Death: This was subject 51241008 from ongoing study A7501007. Dr. Kavanagh cites this case as an example of his concern about neonatal toxicity (pp. 8, pp.30-32 of Amendment #1). This was a case of premature delivery (32 weeks) and fetal death within 5 minutes of that delivery in a woman exposed to asenapine at some time during the pregnancy. Dr. Kavanagh acknowledges that this occurred in a woman who had a history of multiple bad outcomes with pregnancies. I do not believe he has made a credible argument that asenapine had any role in this death.

Unexplained Death that Dr. Kavanagh Considers to Represent Asenapine-Related Aplastic Anemia: This was subject 132017 in study P25520. She was a 44 year-old woman who was found dead on day 521 of treatment. Cause of death was not determined. She had a hematocrit and hemoglobin that were at the low end of the normal range at weeks 52 and 64, as was a WBC at week 64. However, other hematological parameters were essentially normal, including neutrophil and platelet counts. Dr. Kavanagh discusses this case on pp. 24 and 54 of Amendment #1. Oddly, he includes the case under a section entitled "Cardiopulmonary Safety Signals…..," but considers this patient to represent a case of either fatal aplastic anemia or agranulocytosis. He acknowledges that there are no data to support such a conclusion, but seems to feel that it is reasonable to speculate that, if data were available from the time of death, they would support his conclusion. I do not find this kind of speculation even remotely credible.

Death from Pulmonary Embolism that Dr. Kavanagh Apparently Considers to Represent Asenapine-Related Agranulocytosis: This was subject 241041 in study P25520. She was a 57 year-old woman who was treated with asenapine for 470 days. Four days after stopping asenapine, she died, with cause of death noted to be pulmonary embolism. Hematological parameters were all normal at her last visit for which lab data were collected. Dr. Kavanagh discusses this case on pp. 24 and 54 of Amendment #1. He apparently considers this patient to represent a case of agranulocytosis. He acknowledges that there are no data to support such a conclusion, but seems to feel that it is reasonable to speculate that, if data were available from the time of death, they would support his conclusion. Again, I do not find this kind of speculation even remotely credible.

Death From Complications of Surgery for Umbilical Hernia: Dr. Kavanagh discusses this case on pp. 45-46 of Amendment #1. This was subject 10021006 in Study A7501018. This was a single dose study in subjects with hepatic impairment. This subject received a single dose of asenapine (5 mg) and had surgery to repair an umbilical hernia 10 days after completing the study. The subject died 46 days after completing the study, from complications of the surgery. Dr. Kavanagh apparently cites this case to suggest that asenapine might weaken connective tissue, presumably leading to umbilical hernia, and he links this to what he refers to as "several cases of umbilical issues in animal teratogenicity studies." In a separate 6-24-08 memo, Dr. Rosloff, supervisory pharmacologist in DPP, notes that he is not aware of "any effects on skeletal muscle or connective tissue" in the animal studies.

Stab Wound: This was patient 118012 from study 25543 that Dr. Kavanagh includes in a list of "suspicious SAEs from 120 day safety update," on p.47 of his Amendment #1. This patient was clearly assaulted by his girlfriend, sustaining a stab wound in his chest. Dr. Kavanagh describes the ultrasound findings of the wound, and then comments that it is "unclear from description if this is related to stab wound or not." Again, Dr. Kavanagh seems to be trying to tie this case to the drug despite all evidence to the contrary.

Mechanistic Focus of Dr. Kavanagh's Reviews: A major difficulty with Dr. Kavanagh's assertions about asenapine-relatedness for certain adverse events is that they are based on his views of what he believes to be the mechanistic basis for what he considers to be asenapine-related toxicity. For example, he alleges that asenapine has the potential to cause cardiovascular toxicity secondary to causing "pulmonary arterial hypertension," "direct and indirect effects on the myocardium," and "indirect effects on platelet aggregation." Unfortunately, he provides no data to support any such mechanisms. He makes statements alleging other general effects, e.g., "connective tissue disorders," "increases in motor activity," "cognitive impairment," and many others, without providing specific examples of actual cases where such effects have been observed. He also identifies what he believes to be an underlying receptor effect that explains many of these alleged toxicities, i.e., 5HT2B agonism. This is perplexing because what receptor data we do have for asenapine suggest that it is an antagonist at this receptor, and not an agonist.

Animal Data: On pp. 33-45 of Amendment #1, Dr. Kavanagh discusses various preclinical findings. In a 6-24-08 memo, Dr. Rosloff, supervisory pharmacologist in DPP, states with reference to Dr. Kavanagh's commentary that "I do not find his arguments convincing." I refer the reader to Dr. Rosloff's memo for more detailed commentary on Dr. Kavanagh's assertions about the animal findings, and I will not address those assertions further here.

Discussion of Metabolites, Degradants, and Impurities (pp.58-63 of Amendment #1): I will not comment on this 6-page discussion of metabolites and impurities that Dr. Kavanagh presumably included to support his concerns about toxicity. These issues have been fully addressed by the chemistry and pharm/tox groups, and the additional discussion provided by Dr. Kavanagh is mostly speculations.

Discussion of Risks with other Agents: On pp. 73-83 of Amendment #1, Dr. Kavanagh provides a very speculative discussion of a variety of other agents and what he believes to be their common risks in humans. I think this discussion is irrelevant to decisions about this particular application, and I will not comment on it in this memo.

Allegations of Misconduct: Part of Dr. Kavanagh's concerns focus on his view that the sponsor designed the asenapine program to minimize the finding of important information and intentionally misrepresented the data coming from the program to try to obscure problematic information. On p. 7, he states that criminal investigations should occur for "failure to report

deaths, attempting to mislead reviewers by various devices that are apparently intended to obfuscate and hide data required for review and that are needed to make safety assessments that would effect approval….." He goes on to suggest that such failures may have been intended to cause harm that would necessitate purchasing other products from these same sponsors, apparently to treat asenapine-induced adverse reactions. In other words, he seems to be suggesting that the sponsor expects to profit from harm caused by asenapine by virtue of other medications of the sponsor being prescribed to treat this adversity. On p. 8, he also alleges that "these include possible violations of law by FDA personnel." On pp. 63-67 of his Addendum #1, Dr. Kavanagh does list what he considers to be specific deficiencies in the NDA, and prefaces this list with the same kinds of statements, i.e., that they "appear to be intentional so as to hide critical information….." However, the items in the list that fall within Dr. Kavanagh's area of expertise, i.e., clinical pharmacology, are mostly complaints about study design, and the designs of these studies do not seem to differ very much, in my view, from what we typically see in drug development programs. If the program was so deficient from a clinical pharmacology perspective, he and his supervisor could have recommended that the NDA be refused for filing, but they did not do so. His other complaints in this list that fall within the clinical realm are without merit, in my view. In any case, I don't see any examples listed of specific critical safety information that was available to the sponsor and not submitted to FDA, or of data that was so misrepresented as to be misleading. Indeed, it is my impression that all the cases he cites are reported in the application. So I do not share his view that the sponsor failed to report critical safety information that they possessed, or that they misrepresented what they did submit in an attempt to mislead, at least based on what I have reviewed.

5.2.6 Conclusions Regarding Safety of Asenapine in the Treatment of Schizophrenia

In summary, my view is that asenapine has a safety profile quite similar to what we have seen for other atypical antipsychotic drugs, and this profile can be adequately characterized in labeling. We will have a few clarifying questions to ask the sponsor in an action letter.

5.3 Clinical Sections of Labeling

We have made a number of modifications to the sponsor's proposed labeling, and have asked the sponsor to make a number of changes, and in some cases, provide new information.

6.0 WORLD LITERATURE

The sponsor provided a warrant that they reviewed the literature and found no relevant papers that would adversely affect conclusions about the safety of asenapine in the treatment of schizophrenia or bipolar disorder.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, asenapine is not approved anywhere at this time for the treatment of schizophrenia or bipolar disorder.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this application to the PDAC. There are several previously approved atypical antipsychotic agents similar in overall activity to asenapine, and an evaluation of the safety data for asenapine did not reveal particular safety issues that were unexpected for this class. Furthermore, the design and results of the efficacy trials did not pose particular concerns. Overall, there were no controversial issues that would have benefited from advisory committee discussion.

9.0 DSI INSPECTIONS

Inspections were conducted at 3 sites, and data from these sites were deemed to be acceptable.

10.0 LABELING AND ACTION LETTER

10.1 Labeling

We have prepared an extensively modified version of labeling to accompany an approvable letter, if that is the action for this application.

10.2 Foreign Labeling

Asenapine is not approved anywhere at this time.

10.3 Action Letters

The approvable letter includes our proposed labeling and requests for phase 4 commitments.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that the sponsor has submitted data generally supportive of a conclusion that asenapine is likely to be effective and acceptably safe in the acute treatment of schizophrenia and mania/mixed episodes with bipolar 1 disorder. However, before we can take a final action, the

sponsor needs to respond to various requests we have made. In particular, we need additional slides from the rat and mouse carcinogenicity studies to be reviewed, and we need a better characterization of the metabolism of asenapine. I think it is a close call whether this should be a non-approval action or approvable action, given the additional amount of work that is needed. This additional work may be substantial, and depending on the outcome, could change our views on the approvability of this application. Nevertheless, based on what we have seen thus far, I think it is reasonable to consider this an approvable application. Therefore, I am recommending an approvable action. However, given the amount of work that still needs to be done, I think an equally reasonable position would be to view this as a non-approvable application. In any case, we plan to forward an approvable package, with draft labeling.

cc:
Orig NDA 22-117
ODE-I/RTemple
HFD-130/TLaughren/MMathis/GZornberg/RLevin/KKiedrow

DOC: Asenapine_Bipolar_Schizophrenia_Laughren_AE_Memo.doc

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/s/

Thomas Laughren
8/1/2008 04:51:25 PM
MEDICAL OFFICER

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 15, 2008

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for complete response action for asenapine sublingual tablets for the acute treatment of schizophrenia and for the acute treatment of mania and mixed episodes in bipolar 1 disorder

TO: File NDA 22-117
[Note: This overview should be filed with the 8-30-07 original submission of this NDA.]

Note: This is an addendum to my division director memo dated 8-1-08. The approvable action for this NDA was delayed because of difficulties in obtaining final review documents from the Office of Clinical Pharmacology. The purpose of this addendum is to provide an update on new information obtained since my previous memo resulting in several changes in the proposed labeling for this product and the letter. The letter is now a Complete Response (CR) letter because of a change in procedures since the goal date of 6-30-07.

CMC Data: As of 8-1-08, one remaining issue was how to address impurity (b) (4). The sponsor has set the specification for this impurity at (b) (4), above the threshold for qualification. We were planning to ask the sponsor to either lower the specification limit for this impurity to (b) (4) or adequately qualify it. We have now decided to ask the sponsor to address this issue as a phase 4 commitment in the final AP letter. Several other minor requests for CMC information will still be included in the action letter.

Carcinogenicity Data: As of 8-1-08, the major deficiency from a pharm/tox standpoint was the lack of histopathology data for the low and medium dose groups in the rat and mouse carcinogenicity studies. The MTD was exceeded in the rat carcinogenicity study, leading to excessive weight loss in the high dose group. Thus, the lack of tumor findings in this group could not be interpreted. In the mouse carcinogenicity study, there was a large increase in malignant lymphomas in the high dose females compared to the vehicle control group, but not to an untreated control group. In both instances, the slides from the lower dose groups were needed to try to better understand these findings. Unfortunately, the sponsor had not provided histopathology findings from lower dose groups in the original application. The sponsor has now provided reports on these findings, as of 8-29-08. The action letter will indicate that the review of these new data will be completed in the next review cycle for this drug.

Biopharmaceutics Concerns: As of 8-1-08, a major deficiency in the application from a biopharmaceutics standpoint was a failure to adequately determine what moieties are circulating in plasma. OCP maintained that the sponsor had identified only about 3% of circulating material in plasma. Also from the standpoint of mass balance, OCP maintained that only about 30% of the dose has been characterized regarding elimination pathways. They felt that the application could not be approved before these deficiencies were addressed. We of course did have substantial human experience with this drug, none of which, in my view, marked it as an outlier among the atypical antipsychotics. If OCP were correct in its assertions, however, we would have little assurance that the animal carcinogenicity data or reproductive toxicity data were relevant to humans, since we would know so little about what is circulating in humans.

Over a period of several weeks, the sponsor provided additional data to address these concerns, and we held a telcon with the sponsor on 9-15-08 to further discuss this matter. OCP has provided an additional review to address these new data and discussions (see OCP memo dated 9-30-08). In the end, we agreed with the sponsor that they had identified roughly 50% of circulating species, and we were also reassured that there were no other major metabolites that were not unidentified among the remaining unidentified metabolites. Thus, in our view, this issue is resolved.

Labeling/CR Letter: The draft labeling that we had prepared for the 6-30-08 goal date has been updated to incorporate this new information, and will be included with the CR letter. Otherwise, this version of labeling is the same as our draft label prepared earlier in the review cycle.

Conclusions and Recommendations: I continue to believe that the sponsor has submitted data supportive of a conclusion that asenapine is likely to be effective and acceptably safe in the acute treatment of schizophrenia and mania/mixed episodes with bipolar 1 disorder. However, before we can take a final action, we need to have an opportunity to review the new animal histopathology data, we have to reach agreement with the sponsor on final labeling, and the sponsor needs to respond to the requests we have made in the CR letter.

cc:
Orig NDA 22-117
ODE-I/RTemple
HFD-130/TLaughren/MMathis/GZornberg/RLevin/KKiedrow

DOC: Asenapine_Bipolar_Schizophrenia_Laughren_CR_Memo.doc

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/s/

Thomas Laughren
10/15/2008 09:55:14 AM
MEDICAL OFFICER

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 14, 2008

FROM: Gwen L. Zornberg, M.D., Sc.D.
Cross Discipline Team Leader
Division of Psychiatry Products
HFD-130

SUBJECT: Recommendations for approvable action for asenapine maleate (sublingual tablets) in adults in two indications:
1. Schizophrenia
2. Bipolar disorder, acute manic or mixed episodes

TO: File NDA 22117
SN 000
Standard Priority Original NDA of a new molecular entity

Reviewers
Chemistry: Tele Chhagan, Ph.D.
Pharmacology/Toxicology: Elzbieta Chalecka-Franaszek, Ph.D.
Clinical: Robert Levin, M.D.
Biometrics: Yeh-Fong Chen, Ph.D. (schizophrenia)
George Kordzakhia, Ph.D. (bipolar disorder)

Consultant Reviewers
QTIRT: Christine Garnett, Ph.D., Suchitra Balakrishnan, Ph.D.
DSI: Diane Tesch
DMEP: Felicia Duffy, R.N., B.S.N., M.S.Ed.
OSE Risk Management Plan Review:
Clinical Pharmacology: Ronald Kavanaugh, Ph.D. (review pending)
Controlled Substances Staff: Katherine Bonson, Ph.D.

1.0 BACKGROUND

Asenapine is an atypical antipsychotic including 5HT2, D_2 and α_1-adrenergic receptor antagonist properties. The applicants submit that they have developed the sublingual formulation for clinical use due to extensive hepatic metabolism of the oral formulation leading to reduced exposure. Asenapine (sublingual tablet) was developed under IND 51-641 (schizophrenia) and IND 70-329 (bipolar disorder).

We held a number of meetings with the sponsors. At the End-of Phase 2 meeting held 20 November 2002, the sponsor formulated that asenapine 5 mg BID was the minimum effective dose in the treatment of schizophrenia. Due to the extensive primary metabolism by CYP 1A2, the Division recommended that a drug interaction study with omeprazole be conducted. The Division inquired also about data on the n-oxide-asenapine and d-methyl-asenapine primary metabolites.

As the end of the review cycle approached, Dr. Laughren decided that there were no critical review issues that needed input from the PDAC.

2.0 CHEMISTRY

Dr. Tele Chhagan completed his review after a great deal of team process to align our communications with the sponsors on 11 April 2008. His prompt and thorough review was very important to the acceleration of the progress of this pilot GRMP NME NDA process of the team work by allowing a measured discussion of questions to pose to the sponsors early to allow them to improve the quality of the data in the NDA regarding, potential impurities and degradants that were in jeopardy of not meeting guidelines.

Dr. Chhagan clarified that the acceptable limits for impurities should not be based on strength. He required that the sponsors reduce the acceptance criteria for (b) (4) strengths for total degradation products to the levels that are more consistent with their data. In addition, he required that the sponsors revise unspecified each individual impurity for both strengths to no more than (b) (4) based on maximum daily dose of 20 mg/day. No Post-marketing commitments were required.

I am not aware of any CMC issues at this point that would preclude an approvable action for this NDA

3.0 PHARMACOLOGY

In rat and mouse models, Dr. Chalecka-Franaszek found that sponsors had not provided adequate data for review. For example, in the low and medium dose groups were not routinely examined in the rat study entitled "104 week subcutaneous administration oncogenicity study with Org 5222 in the rat", while the MTD was clearly exceeded in males at all dose levels and in females at the high dose with dose-dependent decrease in weight that lowered the risk of tumor formation and pre-neoplastic changes. The sponsors' response to the Pharmacology/Toxicology request for additional carcinogenicity data will be reviewed by the Executive Carcinogenicity Assessment Committee (CAC).

Dr. Chalecka-Franaszek requested a consultation by CSS based on her review of a non-clincial study. In terms of non-clinical models evaluating potential for abuse, the rodent ICSS study in the filing was found by Dr. Bonson as explained in her review (13 May

2008) to not support the proposed statement in the sponsor's proposed label concerning lack of abuse potential of asenapine in rats. She concluded that in rats trained to deliver intra-cranial self-stimulation, asenapine acted in a manner similar to risperidone and olanzapine.

At this point, the primary concerns that may preclude an approvable action for this NDA, arise from outstanding concerns regarding risk of carcinogenicity that the Pharmacology/Toxicology reviewers have concluded has not been adequately evaluated in submitted rat and mouse studies. The requests of Pharmacology/Toxicology need to be addressed through additional data and analyses from the sponsors. In view of these unresolved obstacles to an adequate review of safety, at best an approvable action is recommended. We are waiting for the conclusions and recommendation of the executive CAC on 27 May 2008 to inform how we proceed. These issues will likely, at best, preclude an approval action.

4.0 BIOPHARMACEUTICS

The Clinical Pharmacology review to inform the regulatory processing of this application by the Division Director has not been completed as of 14 May 2008. Based on the review of the drug-drug interaction studies included in this efficacy supplement regarding adjunctive treatment, Dr. Kavanaugh and Baweja may recommend a number of hitherto unknown changes to asenapine labeling regarding drug-drug interactions with commonly used antidepressant s evaluated in the double-blind, placebo-controlled trials.

If, as Dr. Kavanaugh stated on 12 May 2008 that more than 99% of circulating radioactivity has not been identified, than an approval could not be considered. This statement requires verification by OCP. The full characteristics of drug-drug interaction require clarification for labeling.

At present, biopharmaceutics issues that would preclude an approvable action for this NDA remain undefined. After the Clincial Pharmacology review is signed off and filed with confirmed pharmacokinetic data and analyses, the review and labeling recommendations will taken into consideration for regulatory processing by Drs. Laughren and then by Dr. Temple.

5.0 CLINICAL DATA

5.1 Efficacy Data – Schizophrenia (SZ)

5.1.1 Overview of Studies Pertinent to Efficacy (SZ)

My review of the efficacy of asenapine in the acute treatment of schizophrenia in this application focused on the 3 informative short-term (6-week), fixed dose, multicenter, double-blind, randomized, parallel group, placebo-controlled trials (41004, 41021, and 41023) of patients diagnosed with acutely exacerbated schizophrenia. The primary

efficacy (change from baseline to 6-week endpoint on the PANSS total score) and sensitivity analyses were reviewed and confirmed by Dr. Chen as detailed in her review (completed 18 April 2008). As summarized in Dr. Chen's review, there were 2 positive (41004 and 41023) trials and one negative (41021) trial supporting adequate efficacy to recommend approval of asenapine for adults in the acute treatment of schizophrenia. The magnitude of the mean effect in the 5 mg BID treated patients appears comparable to that found in other NDAs on review of the effect sizes in other trials. In the schizophrenia program, no key secondary endpoint analyses were pre-specified and analyzed.

A major issue for regulatory processing by the Division and Office Director is whether to restrict use to the asenapine-10 mg (i.e., asenapine 5 mg BID), or to allow use over the range from asenapine -10 mg to asenapine-20 mg (i.e., asenapine 5 mg BID) in the treatment of schizophrenia. This takes into consideration the variable results observed with 10 mg BID in the schizophrenia program coupled with loss of dose proportionality above a dose of 5 mg BID. Dose-finding Studies in which the dose levels were estimated too low will not be evaluated as they provide little, if any, useful information.

The fixed asenapine doses in the 3 short-term trials in the effective dosing range of the sublingual formulation were positive for the primary efficacy measure (SS= statistically significant, NS= not significant) in 2 trials. The asenapine doses were fixed throughout the trials.

Summary of Significance of Primary Efficacy Measures:3 Placebo-Controlled Trials (SZ)

Study #	ASN 10 mg (5 mg BID)	ASN 20 mg (10 mg BID)	RIS	HAL	OLZ
041004	SS		NS		
041021	NS	NS			SS
041023	SS	NS*		SS	

* Post hoc MMRM analysis (p-value = 0.04)

Study 41021 was a negative trial with significant separation from placebo by the olanzapine treatment group. Consequently, this trial does not provide support for the efficacy of asenapine 5mg BID or 10 mg BID dose levels on the 6-week primary efficacy endpoint analysis.

Study 41004

Contradictory statements in Dr. Levin's Executive Summary of Efficacy (1 May 2008 review) give the misleading impression that study "041004 was failed study", as well as demonstrating efficacy is confusing for the reader and would likely encourage an underestimate of asenapine's efficacy in the treatment of schizophrenia. In contrast, Dr. Chen's conclusion that study 041004 was a positive study is accurate (review completed 18 April 2008).

In study 041004 asenapine 10 mg daily (5 mg BID) demonstrated a satisfactory degree of short-term efficacy based on the data in the clinical study report. Moreover, in study 41004, the lack of significant separation from placebo in the risperidone group was

consistent across all 3 types of statistical analyses, i.e., the primary efficacy analysis (LOCF ANCOVA), the observed cases (OC) analyses, and the MMRM analyses, in contrast to the significant efficaciousness in the asenapine treatment group demonstrated. A limitation of this phase II study was the high drop-out rate of 60% overall, which is consistent with the inherently poor adherence to treatment associated with schizophrenia, particularly when the study is not specifically designed with measures developed to prevent study discontinuation. Dr. Chen notes that the placebo response rate was much smaller than in other asenapine studies, which is also consistent with the likelihood that genuine diagnoses were made for study entry, as a narrow definition of chronic, schizophrenia (a very serious, debilitating chronic psychotic disorder) has been consistent with low placebo response rates. Further support of adequate comparative efficacy stems from the reduced number and percentages of discontinuations due to efficacy in the asenapine group (9, 15%) compared to the risperidone (16, 27%) group, as well as the placebo group (18, 29%).

One of the outstanding efficacy issues for regulatory processing, I would submit, is the potential clinical utility of the asenapine 20 mg daily (10 mg BID) dose level in addition to the 5 mg BID dose in the treatment of schizophrenia, given the limited data to guide evidence-based judgment. As represented by the primary efficacy analysis in the table above, the asenapine 20 mg daily (10 mg BID) dose group failed to achieve statistically significant separation from placebo at the five per cent level on the *a priori* LOCF analysis in the 41023, supported by lack of significant visit-wise LOCF and OC analysis results for the higher dose in the trial in contrast to the significant improvement in the asenapine 5 mg BID treatment group compared to placebo. Dr. Chen conducted sensitivity analyses and noted in her review that there was a high discontinuation rate in this trial. Schizophrenia, however, is associated inherently with high drop-out rates reflecting poor treatment adherence. As concluded accurately in Dr. Levin's s review (completed 1 May 2008), that the rates are within the range of discontinuation rates commonly found in trials of patients diagnosed with schizophrenia. He argues, however, against the claim in labeling for dosing in the acute treatment of schizophrenia the 10 mg to 20 mg daily range proposed by the sponsors.

In a more in depth examination of the 41023 data, while the significant findings for the 10 mg BID group in the MMRM analysis was limited by the fact that it was *post-hoc* and it was not the primary efficacy analysis, it can be argued that the MMRM is a more appropriate analysis. On MMRM analysis, the results for the asenapine 20 mg group were statistically significant suggesting that further consideration of this dose level for clinical use in the acute treatment of schizophrenia may be warranted. Thus it is interesting that, although study 41023 was not powered to examine differences in response during the first week of treatment, there is evidence to suggest greater efficaciousness of the higher asenapine 10 mg BID dose level than the lower 5 mg BID dose level compared to placebo in the first week of treatment. In terms of early LOCF analyses, there was a greater reduction in the LS mean values of the PANSS total score on Days 4 and 7 at the higher asenapine 20 mg dose group (-1.7, -3.2), respectively, than observed in the asenapine-10 mg group (-1.2, -3.1) and was superior numerically on day 4 while equivalent on Day 7 to the haloperidol-8 mg (-1.5, -3.2) group, respectively.

Similarly, though not a key secondary parameter, the improvement (reflected in percent responders on the CGI-I) seen in the asenapine-20 mg (9.6%) group on Day 4 was greater than double the improvement on the CGI-I observed in the asenapine-10 mg (4.6%) daily group or the haloperidol (3.6%) treatment group in this study. These data suggest some clinical superiority may be possible, at least in a subset of patients, and that in a study designed to examine differences in response during the first week of asenapine treatment, greater improvement on the higher asenapine 20 mg daily dose level may possibly be observed.

For longer term use beyond the first week of asenapine in the acute treatment of schizophrenia, the numerical superiority of the asenapine-20 mg group receded and only the lower asenapine 10 mg dose was positive at endpoint in this trial, consistent with the positive finding as the only asenapine dose group in study 41004. Taken together asenapine at the 5 mg BID dose level was positive in 2 trials base don the primary efficacy analyses. This provides support for asenapine 10 mg (5 mg BID) as the recommended target dose in labeling. There was only one positive trial in which both asenapine doses were studied resulting in limited data. On analysis of the limited data fothe 10 mg BID patient group, there is a suggestion of a potential for greater effectiveness in the first week of treatment of psychotic symptoms in the asenapine 10 mg BID group over the 5 mg BID group compared to the placebo group. Based on the findings, I recommend supporting the sponsors' claim in labeling to allow dosing in the asenapine 5 mg BID to 10 mg BID dose range, as clinically indicated based on tolerability and efficacy.

Comparison of Asenapine to Other Reviewed Atypical Antipsychotics

In order to explore further the comparability of asenapine's efficacy, I decided to focus on using placebo-corrected effect sizes with standard comparison drugs such as risperidone, which is commonly employed as the active control in antipsychotic drug development programs. Biometrics provided the effect sizes of drugs in the same study from other atypical antipsychotic drug programs, one approved as effective and one not approved for use. The placebo-corrected effect sizes for the two positive studies were provided by Dr. Yeh-Fong Chen (8 May 2008) as depicted below.

Study 41004: Effect Sizes Treatment Difference in Comparison to Placebo (LOCF)

Primary Measure	Treatment (Total Daily Dose)	Treatment Difference (vs. Placebo)	95% C.I.	P-value
PANSS Total Score	Asenapine 10mg	-9.72	(-16.70, -2.74)	0.007
	Risperidone 6mg	-5.41	(-1.52, 12.33)	0.125

Study 41023: Effect Sizes Treatment Difference in Comparison to Placebo (LOCF)

Method of Analysis	Treatment	Treatment Difference (vs. Placebo)	95% C.I.	P-value
LOCF	Asenapine 10mg	-5.48	(-9.86, -1.09)	0.015
	Asenapine 20 mg	-4.11	(-8.53, 0.31)	0.068
	Haloperidol	-4.70	(-9.04, -0.35)	0.034

As presented above in the phase II study, 41004, the placebo-subtracted effect sizes support almost a doubling of the magnitude of improvement on the asenapine-10 mg versus the risperidone-6 mg groups. In the second positive trial, at 6-week endpoint, the asenapine-10 mg effect size is greater the effect sizes in the haloperidol and asenapine-20 mg daily treatment groups.

In contrast to the comparisons to risperidone and haloperidol in the 2 positive trials, in the negative trial, both the 10 mg and 20 mg daily asenapine treatment groups failed to separate from placebo, while the magnitude improvement measured by the placebo-corrected LS means score for the olanzapine group was more than double the values for the two asenapine groups.

The findings generally in the asenapine development program in the treatment of schizophrenia are consistent with findings in the psychiatric treatment literature regarding the efficacy of other typical and atypical antipsychotic drugs. The superiority of olanzapine compared to other atypical antipsychotic drugs is generally observed and not unexpected in the negative trial. To explore this quantitatively, the effect sizes of other typical and atypical antipsychotic drugs employed as active comparators are included to roughly compare and contrast the results to gauge how well the significant findings form the asenapine trials compare to other antipsychotic drugs.

In one trial the effect sizes of treatment groups for a different atypical antipsychotic drug, I have labeled this as Drug A, are similar to the effect size for the risperidone active comparator group. Drug A has been approved by the agency and is use in the Unites States. The similar effect sizes for Drug A and risperidone below are in contrast to the greater effect size of asenapine 10 mg daily compared to risperidone in study 41004.

Primary Efficacy LOCF Analysis Results for Drug A

Endpoints	N	Baseline	Change from Baseline to Endpoint (i.e., week 4)	Treatment Difference vs. Placebo	95% CI for Difference	P-Value
PANSS Total						
Risperidone 6 mg	71	94.4	-15.0	-9.5	(-16.3, -2.8)	0.006
Drug A 20 mg	65	92.2	-15.0	-9.5	(-16.4, -2.6)	0.007
Drug A 30 mg	68	92.7	-14.5	-9.0	(-15.8, -2.2)	0.009
Placebo	78	94.4	-5.5			

In a second Drug A trial in comparison to haloperidol, the findings resemble those of the asenapine study 41023. The effect sizes of one of the Drug A treatment groups was numerically superior to the haloperidol group, which was superior numerically to the magnitude of the effect of the other Drug A group.

Primary Efficacy LOCF Analysis Results for Drug A

Endpoints	N	Baseline	Change from Baseline to Endpoint (i.e., week 4)	Treatment Difference vs. Placebo	95% CI for Difference	P-Value
PANSS Total						
Haloperidol 10 mg	59	101.7	-13.8	-12.1	(-19.7, -4.5)	0.002
Aripiprazole 15 mg	72	96.7	-14.6	-12.9	(-20.1, -5.7)	0.001
Aripiprazole 30 mg	71	99.2	-9.9	-8.2	(-15.4, -0.9)	0.027
Placebo	74	100.8	-1.7			

In contrast, drug B was not approved for marketing in the US based in large part on the insufficient effectiveness. Again, the analysis methods were ANCOVA (LOCF) with treatment, pooled center, and baseline score as independent variables.

Primary Efficacy LOCF Analysis Results for Drug B

Method of Analysis	Treatment	Treatment Difference (vs. Placebo)	Adjusted P-value
LOCF	Drug B 5 mg	-4.1	0.128
	Drug B 10 mg	0.6	1.0
	Drug B 20 mg	-5.8	0.031
	Risperidone 6mg	-10.3	<.0001

Taken together, albeit a crude approximation of the degree to which asenapine compares to the same active comparator drugs across atypical antipsychotic NDAs, the efficaciousness of asenapine 10 mg (5 mg BID) with a doubling of risperidone's effect size compared to risperidone 6 mg daily and haloperidol 10 mg daily (equivalent to Drug A and double Drug B in effect size) appears reasonably robust. The findings from the asenapine trials compare favorably to the findings from the Drug A program and are superior to those form the Drug B development program. The numerically greater improvement in the first week of treatment as well as significant efficacy on the MMRM analysis with support from secondary analyses in the one positive trial in which the asenapine 20 mg (10 mg BID) dose level was studied, provide support for the sponsor's claim in labeling for dosing permitted between 5 mg BID and 10 mg BID in the acute treatment of schizophrenia. In view of the consistent significant efficaciousness of the asenapine 5 mg BID dose and the superiority on weekly LOCF analyses after week 1, I recommend that in the treatment of schizophrenia that asenapine 5 mg BID be described in labeling as the recommended target dose, not necessarily the recommended starting dose. In the decision to restrict the dose level for schizophrenia to 5 mg BID while allowing 5-10 mg BID for bipolar disorder. In patients who present a challenging differential diagnosis between schizophrenia, schizoaffective disorder and bipolar disorder, one could easily imagine that an absurd clincial situation could arise in a realistic clinical setting given the imbalance in dosing ranges between the 2 types of

major psychoses that are part of a clinical spectrum of symptoms. For instance, if the clinician weighed in favor of schizophrenia, only 5 mg BID would be "on label". If the diagnosis shifted to schizoaffective disorder, possible bipolar disorder, the range between 5 – 10 mg BID would be "on label." Had the sponsor conducted the less desirable set of positive flexible dose studies in schizophrenia, it is likely that asenapine 5 – 10 mg BID would be accepted for labeling without much discussion, as is the case for bipolar disorder.

Asenapine in the acute treatment of Bipolar I Disorder (Manic or Mixed Episodes)

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS), the most commonly used validated instrument to measure changes in symptoms of mania. In addition, a key secondary measure of manic symptoms was the change form baseline to day 21 endpoint in Clinical Global Impression – Bipolar (CGI-BP) scale score. In both trials (n=480 for each), flexible doses of asenapine (5 to 10 mg BID) and olanzapine (5 to 20 mg QD) were compared to placebo. All patients randomized to asenapine were administered 10 mg BID to start and the dose could be adjusted within the dose range of 5 to 10 mg BID from Day 2 onward based on efficacy and tolerability. asenapine was superior to placebo on the change from baseline to Day 21 in YMRS total score and the CGI-BP Severity of Illness score (mania)

There were two highly significant trials with concurrence between Drs. Kordzakhia and Levin and that the improvement form baseline to 3-week endpoint on the YMRS total score in these 2 positive, flexible-dose acute treatment trials compared to the placebo groups adequately provide adequate evidence to support that asenapine 5- 10 mg BID is generally efficacious in the acute treatment of bipolar I disorder, manic and mixed episodes.

In the two 3-week trials combined, the mean daily dose of asenapine was 18.3 mg with a modal dose of 10 mg BID. During each week of the trials, more subjects received asenapine10 mg BID than 5 mg BID. Specifically, the percent of subjects receiving 10 mg BID during week 1 to 93% at the end of week 3, while the percent receiving 5 mg BID increased to 7% at the end of the 3-week trial (Table 1.2.C, page 1927 of the SCS). Interestingly, in the flexible dose olanzapine group at the 3-week endpoint, 60.7% were receiving 15 mg daily and 35.3% were receiving 20 mg daily. The majority of exposure at the 10 mg BID level in the flexible dose study of bipolar mania supports the conclusion that asenapine 10 mg BID is the recommended generally, though I think that flexible dosing in the range 5 mg to10 mg BID is supported for labeling to allow clinicians to optimize treatment to shifts in changing mood states.

5.1.2 Comment on Other Important Clinical Issues Regarding the Asenapine Efficacy Data

Secondary Efficacy Variables

There were no pre-specified key secondary parameters declared in the schizophrenia trials. The CGI-BP was pre-specified as a key secondary parameter in two acute treatment of bipolar mania or mixed episodes. The significant findings provided further support of the efficaciousness of asenapine in the treatment of bipolar disorder, manic or mixed episodes.

Clinical Predictors of Response

In the bipolar disorder trials, an examination of subgroups did not reveal any clear evidence of differential responsiveness on the basis of age, gender or race. In one of the two studies, the observed asenapine treatment effect compared with placebo appears to be mainly driven by the admittedly heterogeneous subgroup of non-US patients.

Long-term research of maintenance of effect in schizophrenia is ongoing though was not completed in time for filing.

5.1.3 Conclusions Regarding Efficacy Data for the Schizophrenia and Bipolar Disorder (manic or mixed episodes)

Taken together, the sponsors have, in my view, provided sufficient evidence for regulatory purposes in two positive short-term studies to support the claim of efficacy of asenapine in the treatment of schizophrenia. The sponsors have provided sufficient evidence also in two positive trials to support the claim of short-term efficacy of asenapine in the treatment of bipolar disorder, manic or mixed episodes.

An informal qualitative comparison of effect sizes with the same active comparators across studies suggests that the acute efficacy of asenapine may compare well with other atypical and conventional antipsychotics in the treatment of schizophrenia. It is easily argued, as is the case in the reviews of Drs. Chen and Levin ,that asenapine dosing in schizophrenia should be restricted to 5 mg BID in schizophrenia (positive in 2 trials), as the 10 mg BID dose group failed to clear the 5 per cent level in the one positive trial in which it was studied (it also failed to separate from placebo in the negative schizophrenia trial). In my opinion, there is supportive evidence for efficacy at least in a subgroup of patients in addition to the *post hoc* positive findings on the MMRM analysis (which is more appropriate than the LOCF analysis) to allow the 10 mg BID dose that will be allowed in labeling based on flexible dosing in 2 positive bipolar disorder trials. The sponsor has in my view, provided evidence to support consideration by the Division Director of the claim for the full dosing range from asenapine 5 mg BID to 10 mg BID in labeling in both indications. The superiority of the 5 mg BID dose level would be further communicated with the recommended target dose of asenapine 5 mg BID for the treatment of schizophrenia, particularly after the first week of treatment. A maintenance claim was not sought by the applicants in either indication.

5.2 Safety Data

5.2.1 Clinical Data Sources for Safety Review

This NDA for an NME is supported by analyses of a substantial amount of data for a from 51 completed asenapine maleate studies. There are 12 ongoing studies. In the Phase II/III schizophrenia and bipolar disorder clinical study program submitted a total of 2251 participants were administered asenapine maleate. Of there, 1953 (87%) were treated with the sublingual formulation at 10 to 20 mg dose levels (fixed or flexible). In the combined cohort of participants diagnosed with schizophrenia or bipolar disorder, the total asenapine exposure was calculated to be 645 patient-years. In long-term open-label extensions of short-term controlled trials, 908 participants diagnosed with schizophrenia and 275 diagnosed with bipolar disorder were exposed to asenapine 5-10 mg BID for up to one year. The total asenapine exposure in the open-label long-term studies was 505.7 years.

5.2.2 Common Adverse Drug Reaction Profile for Asenapine

Schizophrenia- Combined 4, Fixed-Dose, 6-Week Trial Safety Database*

Adverse Event	Placebo N=298 n, (%)	Asenapine 5 mg BID N=274 n, (%)	Asenapine 10 mg BID N=208 n, (%)	Risperidone N=120 n, (%)	Haloperidol N=115 n, (%)	Olanzapine N=194 n, (%)
Somnolence/ Sedation	34 (6.8)	**42 (15.3)**	26 (12.6)	13 (10.9)	6 (5.2)	**36 (18.6)**
Akathisia	12 (2.4)	11 (4.0)	**22 (10.6)**	5 (4.2)	**17 (14.8)**	9 (4.6)
Weight Increased	2 (0.4)	**6 (2.2)**	4 (1.9)	4 (3.3)	1 (0.9)	**13 (6.7)**
Parkinsonism	8 (1.6)	9 (3.3)	7 (3.4)	0 (0.0)	**16 (13.9)**	1 (0.5)
Dystonia	2 (0.4)	6 (2.2)	4 (1.9)	1 (0.8)	**11 (9.6)**	0 (0.0)

*Ref. pages 109-110 of the Module 2.7.4, Summary of Clinical Safety, NDA 022-117

In tabulating common adverse events, somnolence and sedation should be combined in to one term. Dr. Levin and I concur that "sedation" is a reasonable choice of terms. As shown in the comparative frequencies of common adverse reaction in the table above in the placebo-controlled schizophrenia safety database, the risk of somnolence/sedation is greater in the 5 mg BID than the 10 mg BID asenapine group, though less than in the olanzapine group. The risk of weight gain is highest in the olanzapine group and the risk was slightly greater in the asenapine 5 mg BID group than in the10 mg BID group. The

percent of patients with dystonia reported was lower in the asenapine 10 mg BID than the 5 mg BID treatment group. Taken together in terms of clinically important common adverse events observed with atypical antipsychotic drugs, there is no clear dose response pattern of more frequent common adverse events in the asenapine 10 mg BID group compared to the 5 mg BID group. Although the risk of akathisia is greater in the asenapine 10 mg BID treatment group, the clinically important risk of weight gain was reduced in the asenapine 10mg BID (1.9%) compared to the 5 mg BID (2.2%) compared to 6.7% in the olanzapine over a 6-week treatment period.

In the 2 3-week, flexible-dose trials that constituted the bipolar disorder program, in the asenapine and olanzapine groups, respectively, the percentages of sedation/somnolence (24.0%, 25.6%) were greater than placebo (6.4%); dizziness (11.1%, 7.4%) compared to placebo (3.0); weight increased (4.7%, 8.1%) compared to placebo (0.5%). These 3 week bipolar disorder trials allowed less time for weight gain than in the schizophrenia program.

Extra-Pyramidal Symptoms (EPS) Adverse Event Occurrences

In the fixed-dose, schizophrenia table above, there is a trend toward increasing risk of akathisia associated with increased asenapine dose. The percentage of akathisia in the asenapine 10 mg BID group was more than double that observed in the 5 mg BID group. However, in the 10 mg BID the occurrences of Parkinsonism were similar and dystonia were lower than the frequencies observed in the asenapine 5 mg BID group. There are lower percentages of akathisia, Parkinsonism, and dystonia in the asenapine treated patients than in the haloperidol treated patients. In the 3-week mania studies in which most patients remained on the high 10 mg BID dose, the percentages of the most frequently occurring extra-pyramidal symptom was “dystonia” were asenapine 2.9%, olanzapine 1.0% and placebo 1.0%. The rest of the EPS AEs were less frequent in the placebo-controlled bipolar trials, which coupled with the percentages of EPS lower in the asenapine treated than the haloperidol treated patients in the schizophrenia database is not suggestive of a higher than usual risk of EPS associated with asenapine use.

5.2.3 Adverse Reactions of Particular Interest

QTIRT evaluation of Risk of QT Prolongation and Other Cardiovascular AEs

The QTIRT consultants found that there was an asenapine concentration-dependent increase in the QTc interval that was mild and of little material clinical significance in the QT study review dated 29 February 2008.

Drs. Suchitra Balakrishnan and Dr. Norman Stockbridge of the Division of Cardio-Renal Products reviewed the cardiac profile in the asenapine safety database (completed on 23 April 2008). As of the 15 January 2007 database cutoff date, there were no deaths reported as sudden cardiac death or due to significant ventricular arrhythmia.

In terms of dysrythmias, the incidence of tachycardia, sinus bradycardia, heart block and ventricular extra-systoles were higher than in the placebo group and comparable to the frequencies observed in olanzapine-treated patients. The QTIRT reviewed the data supporting the statement by the sponsor and found the following to be reasonable: "In summary, NMRB [Neurally Mediated Reflex Bradycardia] occurred in four healthy volunteers receiving asenapine and one healthy volunteer receiving placebo. In the asenapine clinical program, NMRB with sinus pause was observed mainly in young and athletic volunteers with high vagal tone and occurred after a postural change following asenapine or placebo. This was not seen in psychiatric patients." It appears to the QTIRT that NMRB secondary to alpha-receptor blockade may be a plausible explanation. Also consistent with alpha1-receptor blockade, the data support the conclusion that those healthy volunteers are likely to be more susceptible to orthostatic hypotension associated with dizziness and tachycardia associated with asenapine exposure than psychiatric patients. In Phase II/III studies, the incidence of orthostatic related adverse events was similar in the asenapine group compared to the comparators. The incidence of syncope was 0.5% in the asenapine 10-20 mg daily groups, 0.4% in the olanzapine group and 0.1% in the placebo group. Based QTIRT review of the ECG and cardiovascular symptom data in the NDA and my review of the cardiovascular data in the application, the consultation by Drs. Stockbridge reads: "It appears that the arrhythmia related AEs associated with asenapine are similar to those of olanzapine and consistent with class effects based on our review of the summary of clinical safety, non-clinical summary and additional analysis of ECG intervals in Study INT 0036960." Over all, the data are suggestive of risk of cardiac conduction abnormalities similar to those reported with olanzapine. The risk of orthostatic hypotension, particularly early in treatment may be greater with asenapine than olanzapine use.

Elevations of Hepatic Transaminases

Dr. Levin reviewed the clinical and laboratory data thoroughly in the safety database. There were subjects in the database identified with elevations of transaminases, "there were a small number of cases with serum transaminase concentration greater than 3 times the upper limit of normal" (Section 8.1.8 of the Clinical Review). There were no cases of subjects with highly elevated transaminases coupled with SAEs or with elevated direct bilirubin reflecting hepatocellular dysfunction (meeting criteria for "Hy's Law) identified by either Dr. Levin in his review of the safety data in the NDA or by Dr. Ron Kavanaugh (confirmed verbally at his presentation on 12 May 2008 after he described his fears that elevated hepatic enzymes could signal future potential for hepatotoxicity, Dr. Kavanaugh's pharmacology review has not been completed). As Dr. John Senior, the FDA expert in Drug-Induced Liver Injury) advises, the lack of utility from prospective monitoring of liver function tests (LFTs) in patients taking drugs associated with LFT elevations and no cases of subjects with drug-induced liver injury were identified in the large database, I would recommend alerting clinicians and patients in the adverse reactions section of labeling and in post-marketing surveillance to be aware of the potential for hepatic toxicity. As there were no cases meeting criteria for "Hy's Law", I would not recommend elevation of hepatic enzyme abnormalities without evidence of impaired hepatocyte function in any patient in the Warnings/Precautions section of

labeling. Similar elevations are observed with other antipsychotic drugs without listings in the Warnings and Precautions section. In my opinion, this dilutes appropriate attention away from documented hazards such as weight gain and orthostatic hypotension as requiring more heightened clinical attention based on evidence of clinical occurence.

Weight gain

Approximately 5% of asenapine treated subjects gained clinically significant weight (> 7% of body weight) compared to 2% of placebo treated subjects over 3 to 6 weeks of exposure. Weight gain with elevated risk of potentially medically serious metabolic syndrome will require monitoring in post-marketing surveillance and is as possible class effect as observed with olanzapine and clozapine administration.

Hematological

Despite thorough reviews of the data by Drs. Levin and Kavanaugh, no cases of agranulocytosis were identified. To evaluate for such a rare potential adverse event, exposure in thousands of patients may be necessary.

Seizure

The risk of seizure associated with asenapine use was below 1% in the safety database. In the 6-week schizophrenia trials, there were no seizures reported in the asenapine 5 mg BID or 10 mg BID groups. Two seizures were reported, one in the < 5 mg BID asenapine group and one seizure was reported in the olanzapine group. In the bipolar trials, over 3 weeks at high doses, one seizure occurred in the asenapine treated and 1 occurred in the olanzapine treated patients.

5.2.4 Use in Elderly Patients

Hepatic function tends to become less robust with age. In view of the clincial pharmacological risk of reduced metabolism with hepatic impairment of any degree, asenapine should be used with caution in elderly patients, in my opinion, extrapolating from the pharmacokinetic data.

5.2.5 Controlled Substances Consultation

Dr. Katherine Bonson noted in her CSS consult response (dated 13 May 2008) to a request by the Division of Psychiatry Products to: a) review a preclinical study, b) determine whether the Sponsor-proposed label was justified on the basis of this study and c) identify whether the preclinical study conducted is a component of a standard abuse potential battery. She concluded that "in rats trained to deliver ICSS, asenapine acts in a manner similar to risperidone and olanzapine by shifting rate frequency curves to the right and reducing maximal responding.
After reviewing the proposed label and a study report testing asenapine in conjunction with intracranial self-stimulation (ICSS) in rats, CSS concluded that the proposed

language for the Abuse and Dependence section is not adequately supported scientifically to justify its inclusion.

There is no issue pertaining to abuse identified by CSS that would preclude an approvable action.

5.2.6 Risk: Benefit Evaluation

In view of the known morbidity and mortality of such a serious disorder as schizophrenia and bipolar disorder and the well established low likelihood of adherence compared to other serious medical conditions, additional treatment options can be beneficial. Consequently, these pivotal trials demonstrate significant efficacy in an area of clinical need, monotherapy of schizophrenia or bipolar disorder in short-term and long-term trials.

5.2.7 Conclusions Regarding the Safety of Asenapine

The adverse drug reaction profile for asenapine in the treatment of schizophrenia and the manic or mixed episodes of bipolar disorder is similar generally to that observed with similar atypical antipsychotic drugs used in the treatment of schizophrenia and bipolar disorder. Sedation, akathisia, dizziness, and weight gain with potential for elevations of serum glucose and lipids are clinically germane. In terms of monitoring for potential toxicities, clinicians should be aware of the need to be alert to elevation of LFTs and the undefined risk for agranulocytosis seen with this class of drugs. The prolongation of the QTc interval observed in the QT study appears to have vanishingly little clinical relevance in patients who are not co-administered drugs that prolong the QT interval.

5.3 Clinical Sections of Labeling

The reviewer's other than in OCP have made modifications to the sponsors' proposed asenapine labeling submitted in PLR format for the proposed schizophrenia and bipolar disorder indications. The first draft is completed today.

6.0 WORLD LITERATURE

The sponsor provided certification that they reviewed the literature and found no relevant articles that would adversely affect conclusions about the safety of asenapine in the treatment of schizophrenia or bipolar disorder.

7.0 POST-MARKETING RISK MANAGEMENT PLAN

The sponsors submitted a usual plan for pharmacovigilance activities. Mary Dempsey, of OSE, in her review (dated 25 February 2008) concluded that the potential risks of

asenapine use are "consistent and comparable" with those of already approved atypical antipsychotic drugs and that no additional safety concerns were identified.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC)

It was decided that there was no need to take this application to the PDAC in terms of the clinical data.

9.0 DSI INSPECTIONS

Inspections were conducted at three sites, and the inspectors found that the sites adhered to the applicable statutory requirement and FDA regulations governing the conduct of clinical investigations and the protection of human subjects as documented through Diane Tesch, Consumer Safety Officer, to be acceptable.

10.0 PHASE 4 COMMITMENTS

I recommend that the sponsors conduct in adult populations adequately designed, placebo-controlled maintenance studies of long-term treatment. We will discuss with the Pediatrics and Maternal Health Staff (PMHS) internally additional studies in the pediatric asenapine development program based on the findings from the pediatric pharmacokinetics study, as well as the emerging safety profile with more widespread use in adult population once on the market.

Phase 4 commitments to be recommended by Pharmacology/Toxicology will be clarifies following the executive CAC. Recommendations by Clinical Pharmacology will be clarified and confirmed through regulatory processing of the pending review.

11.0 LABELING AND APPROVABLE LETTER

We will include labeling in the PLR version of labeling with the approvable letter.

Ms. Felicia Duffy of the Division of Medication Error Prevention (DMEP) reviewed the Proprietary name of "Sycrest". She concluded that the name appears vulnerable to name confusion that could lead to medication errors. The second name [proposed by the sponsors, "Saphris" is now under review by DMEP as a Tradename.

Hyperprolactinemia will be added as class labeling.

Alternative language below was proposed for labeling by Dr. Bonson of CSS.

9.2 Abuse and Dependence

Asenapine has not been systematically studied in animals or humans for its abuse

potential or its ability to induce tolerance or physical dependence. Thus, it is not possible to predict the extent to which a CNS-active drug will be misused, diverted and/or abused once it is marketed. Patients should be evaluated carefully for a history of drug abuse, and such patients should be observed carefully for signs that they are misusing or abusing Sycrest (e.g., drug-seeking behavior, increases in dose).

12.0 CONCLUSIONS AND RECOMMENDATIONS

Contingent upon outstanding issues raised by Pharmacology/Toxicology regarding evaluation of risk of carcinogenicity, resolution of the acceptable limits for impurities clarified by CMC, and future adequate resolution of potentially confirmed issues to be raised by Clinical Pharmacology that require resolution by the sponsors, I believe that Organon/Schering-Plough has submitted sufficient data to support the conclusion that asenapine is effective and may be acceptably safe in the treatment of schizophrenia as well as the acute treatment of manic and mixed episodes of bipolar I disorder. I recommend that if the issues by CMC, Pharmacology/Toxicology and Clinical Pharmacology are resolved adequately by the action date of 7 June 2008, that an approvable action may be acceptable to be taken. At this point, it is unclear whether all of the outstanding issues can be adequately addressed in this cycle.

Given the possibility of a future approval, I would recommend consideration in post-marketing surveillance for the risk of sequelae associated with sedation and dizziness, such as accidental injury as well as for weight gain with potential for the development of metabolic syndrome. In addition in view of the potential for class effects, it will be prudent to monitor as well as the as yet unrealized potential for agranulocytosis, the sequelae of hyperprolactinemia, and liver injury with long-term asenapine exposure, as these conditions have been associated with this use of this class of atypical antipsychotic drugs.

With a focus on the clinical data with respect to the risk benefit for asenapine 10 mg BID in schizophrenia, it is worth noting that the increased magnitude of improvement in first week and supportive 6-week endpoint efficacy findings in post hoc MMRM and secondary endpoint analyses may allows patients and clinicians greater treatment options in the management of psychotic disorders where the exact diagnostic distinction between schizophrenia, schizoaffective disorder, and bipolar disorder may be elusive in clinical settings. Restriction to different dose ranges for the 2 disorders on a spectrum of symptoms may appear artificial and limiting from a clinical point of view.

I agree with the decision of Drs. Rosloff and Chalecka-Franaszek to submit the sponsors' responses to their requests for additional data to the Executive CAC to inform the decision-making of the Division and Office Directors prior to taking an action. These concerns and additional issues that may preclude an approvable that may be raised by Drs. Baweja and Kavanaugh of Clinical Pharmacology will preclude an approval action.

We will submit draft labeling, necessarily incomplete due to the outstanding issues yet to be addressed discussed above, to the applicants when FDA editing of labeling is finalized. Issuance of an approvable letter remains possible with draft labeling by the action date of 7 June 2008.

cc:
Orig NDA 22-117
ODE-I/R Temple
HFD-130
HFD-130/TLaughren/MMathis/GZornberg/RLevin/KKiedrow/BRosloff/
EChaleckaFranaszek/TChhagan/TOliver/YChen/PYang/GKordzakhia/SHardeman/
PDavid

DOC:Asenapine_Zornberg_AE_Memo.doc

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Gwen Zornberg
5/14/2008 09:09:19 PM
MEDICAL OFFICER

ADDENDUM TO
MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 12, 2008

FROM: Gwen L. Zornberg, M.D., Sc.D.
Cross Discipline Team Leader
Division of Psychiatry Products
HFD-130

SUBJECT: Recommendations for approvable action for asenapine maleate (sublingual tablets) in adults in two indications:
1. Schizophrenia
2. Bipolar disorder, acute manic or mixed episodes

TO: File NDA 22117
SN 000
Standard Priority Original NDA of an NME

Reviewers
Chemistry: Tele Chhagan, Ph.D.
Pharmacology/Toxicology: Elzbieta Chalecka-Franaszek, Ph.D.
Clinical: Robert Levin, M.D.
Biometrics: Yeh-Fong Chen, Ph.D. (Schizophrenia)
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1.0 BACKGROUND

The purpose of this addendum to the first CDTL memorandum signed off on 14 May 2008 is to provide the additional information from the Office of Clinical Pharmacology (OCP) review to aid the Office Director and Division Director in the regulatory

processing of this pilot NME NDA. Asenapine has been developed as an atypical antipsychotic with effects mediated at least in part via $5HT_2$, D_2 and α_1-adrenergic receptor antagonist properties. The OCP review was signed off on 15 May 2008 and the OCP TL memorandum was signed on 10 June 2008.

Asenapine (sublingual tablet) was developed under IND 51-641 (schizophrenia) and IND 70-329 (bipolar disorder). We held a number of meetings with the sponsors. At the End-of Phase 2 meeting held 20 November 2002, the sponsor stated that asenapine 5 mg BID was the minimum effective dose in the treatment of schizophrenia.

2.0 CHEMISTRY

Dr. Tele Chhagan clarified remaining CMC issues for the action letter.

1. Provide level of (b) (4) in all the clinical batches including the batches used in BE studies (Batch #: AN and AT).

2. Provide information on the in-process controls and the manufacturing critical process parameters that control the (b) (4) content in the final dosage form.

3. Provide information in tabular form about the physico-chemical properties of the (b) (4) (i.e., solubility, stability, etc.).

4. Include either a release and shelf-life control of the (b) (4) in the drug product through specification or a justification from for not including such control based on ICH Q6A.

I am not aware of any CMC issues at this point that would preclude an approvable action for this NDA

3.0 PHARMACOLOGY

Pharmacology/Toxicology has determined that the rat and mouse carcinogenicity studies are inadequate to support approval until all histopathology slides from the low and medium dose groups of the rat study, and the low and medium dose female groups from the mouse study have been examined and the results submitted for review. We provided the rationale for this decision in our communication of 8 April 2008 to the sponsors.

Dr. Chalecka-Franaszek found that the degree of decreased weight gain in the rat study, particularly at the high dose, was of a magnitude which may have decreased the sensitivity of the animals to drug-induced tumors. In the mouse study, a large increase in malignant lymphomas compared to the vehicle control group, but not to an untreated control group, was seen in high dose females and therefore examination of the lower dose

groups is necessary to determine if this was a true drug effect and if so, if there is a no-effect dose.

The sponsors addressed these concerns in their submission of 29 April 2008; however we still believe that examination of the additional groups is necessary. As summarized by Dr. Rosloff, the primary arguments for the rat study were as follows:

> 1. The sponsors reply read that the literature indicates that in dietary restriction studies, it is the decrease in food consumption, and not the consequent decrease in bodyweight gain, which is responsible for the decrease in tumors seen, and that food consumption was only slightly decreased in the asenapine study. However, it is our opinion that the available evidence is not sufficient to rule out a significant (or even a primary) effect of decreased bodyweight gain. There is also evidence for a role of decreased weight gain in drug studies, e.g., methylphenidate. In fact a decrease in tumors was seen in the asenapine study, (e.g., benign mammary and pituitary tumors in females, and pheochromocytomas) were also decreased in this study.
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> 2. The sponsors stated that the number of animals that remain to be examined in the lower dose groups is small, presumably since animals which died or were prematurely sacrificed in these groups were examined. The sponsors stated that "the number of animals that remain to be fully examined in these groups is… about 17% of the total number on study for both the rat and the female mouse'; however we find the number to be much greater for the low and medium dose groups in the rat study, e.g. the % alive at termination (and thus presumably not fully evaluated) ranged from 33 to 55%. Furthermore, some of the tissues from premature decedents could not be adequately evaluated due to autolysis. Additionally, animals dying or sacrificed prematurely are at lower risk for development of tumors than those which survived to termination (an effect which may be exaggerated in the face of dietary restriction/decreased weight gain—Keenan et. al., Toxicologic Pathology 24:6, 757-768, 1996).
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> 3. The sponsors stated also that the use of doses which would have caused a smaller degree (10%) of weight gain reduction would result in drug exposures in high dose males which are less than those in humans. However, Pharmacology/Toxicology concluded that this is less crucial to an assessment of carcinogenic potential than is a decrease in the sensitivity of the assay due to an excessive decrease in weight gain.

The sponsors' primary argument regarding the mouse study is that there is a high and variable incidence of malignant lymphoma in this strain and that the incidence in the asenapine study is within the historical range. Furthermore, the incidence in the untreated control group was similar to that in the high dose females. However, Pharmacology/Toxicology remains concerned with the much higher incidence in the high dose female group compared to the vehicle control group, which Pharmacology/Toxicology finds to be the most appropriate comparator group.

Examination of the low and medium dose female groups would help determine if there was a true drug effect (e.g., if there were a dose-response in incidence) and if there is a no-effect dose; alternatively if the incidences in the low and medium dose female groups were similar to those in the high dose and untreated control groups, it might be concluded that the vehicle control group was an outlier and that there was no drug effect on the incidence of this tumor.

In order to accurately describe the carcinogenic potential of asenapine in the labeling, full histopathological examination of all animals in the low and medium doses in the rat carcinogenicity study, and of all low and medium dose females in the mouse carcinogenicity study, should be performed prior to NDA approval. As communicated to the sponsors on 8 April 2008, in order to validly compare results across groups, the originally examined slides from these studies should be re-examined in concert with the newly evaluated slides by a single pathologist, and subjected to peer review. These conclusions of Pharmacology/Toxicology were confirmed twice by the Executive CAC.

In addition, Pharmacology/Toxicology recommends that the sponsors perform an embryofetal development study with (b) (4) in the rabbit to qualify this impurity or (b) (4)

That the non-clinical carcinogenicity data filed to the NDA is considered by Pharmacology/Toxicology to be "unacceptable" precludes an approval action for this NDA.

4.0 BIOPHARMACEUTICS

At present, OCP has determined that the asenapine metabolic scheme is uncertain based on the data submitted by the sponsors to this application. Dr. Baweja summarized the critical outstanding pharmacology issues.

1. From a clinical pharmacology standpoint the sponsors have not adequately ascertained what moieties are circulating in plasma. In the mass balance study, the plasma concentrations of 14C asenapine (equivalents) greatly exceed that of asenapine (cold drug) as well as the metabolites measured. The moieties looked for are asenapine, desmethylasenapine, and the N-oxide. The total AUC counts for total radioactivity (14C) is around 1550 AUC units whereas the summation of all the AUCs for the three measured moieties accounts for about 55 AUC units. Therefore, there is a vast amount of circulating material in plasma that has not been ascertained. At least 96.6% of the circulating species have not been identified. This is a matter for concern and we require an explanation for this vast gap in plasma between circulating radioactivity and moieties circulating and identified.

2. Another issue that raises concern is that the mass balance has not been adequately characterized. In a generalized manner, after the administration of the radioactive dose about 88 % of the dose was recovered with 49 % in the urine and

39 % in the feces. This is a generalized presentation of assessing the elimination pathways of the radioactivity. Specifically, what is known is that direct glucuronidation accounts for 12-21% of the dose. Furthermore, 5-16 % of the dose is that of the unchanged drug, asenapine. When these two percentages of moieties are added, only 17–37 % of the dose is represented. Therefore, 63-83 % of the dose has not been adequately characterized for the primary elimination pathways.

3. The characterization of the metabolism moieties circulating in plasma and of the human elimination pathways must be clearly delineated and properly addressed by the sponsors.

OCP raised an additional concern in the review (page 481) that was emphasized at the meeting held by Dr. Temple (27 May 2008) followed by an email that referred to an association between 5HT2b agonism (associated with "Phen-fen cardiac valvulopathy") that OCP attributed also to asenapine with a list of subjects that he thought had "Aes potentially consistent with 5HT2B agonism". In response, Dr. Chalecka-Franaszek reviewed more extensively the receptor binding affinities of asenapine and Dr. Barry Rosloff sent an email dated 11 June 2008 reading that asenapine antagonizes D2, 5HT2a and 5HT2b receptors. Dr. Levin and I are reviewing the clinical data in depth regarding the list of subjects with Aes potentially consistent with 5HT2b agonism" to find all relevant clincial and laboratory data possible. Each case will be medically reviewed by Drs. Laughren, Mathis, Levin, and I for medical adjudication on 16 June 2008.

OCP conducted a post hoc evaluation employing the Bipolar Disorder data of changes in YMRS scores (pages 397 to 402) in a section entitled 5.6.2.2.1.2 Reviewer's Exploratory Assessments of Exposure Response of Asenapine on Young Mania Rating Scale (YMRS). To summarize the general approach, OCP began by dividing the 3 treatment groups (placebo, olanzapine and asenapine) into quintiles based on YMRS score at any time before baseline (screening, baseline, "or other evaluations." The lack of uniformity of timing for severity rating for allocation into quintile adds additional variability and confounding that would likely attenuate the power of the analysis. The sparse sampling in a number of the cells detracts from the power to detect differences between changes from some time before the first dose asenapine. Consequently, in my opinion, these post hoc analyses limited by confounding and reduced statistical power provide no additional regulatory information to the review of efficacy and I do not recommend consultation by Biometrics on these analyses.

I concur with the OCP conclusions and recommendations to the Division and Office Directors that the plasma metabolic exposure profiles, the metabolic scheme, mass balance study and enzymes responsible for various elimination pathways need to be further clarified. The absence of adequate basic pharmacology data to address all of these issues precludes approval of this NDA.

5.0 CLINICAL DATA

5.1 Efficacy Data Overview

5.1.1 Overview of Studies Pertinent to Efficacy (SZ)

Summary of Significance of Primary PANSS Endpoint: 3 Placebo-Controlled Trials

Study #	Asenapine 5 mg BID	Asenapine 10 mg BID	RIS	HAL	OLZ
041004	SS		NS		
041021	NS	NS			SS
041023	SS	NS*		SS	

* Post hoc MMRM analysis (p-value = 0.04)

I concur with Drs. Levin and Chen that only the asenapine 5 mg twice daily dose meets criteria for a claim in the acute treatment of schizophrenia. In my first memorandum CDTL memorandum, after review of Dr. Chen's FDA confirmation of primary efficacy and the sensitivity analyses, I had plumbed the secondary data beyond the analysis of the primary endpoint analyses to attempt to get a sense of the potential for efficaciousness of the asenapine 10 mg BID dose level in future trials. Metaphorically speaking, this is akin to tracing the path of a comet in the sky. There were only 2 randomized controlled trials that were informative for regulatory purposes. In one trial, the asenapine 10 mg BID dose was not statistically significant and only significant on a post hoc MMRM analysis in the other trial compared to placebo. No data was found to support a claim for the 10 mg BID dose in the acute treatment of schizophrenia, despite the highly significant separation from placebo in the asenapine 10 mg BID treated patients in the bipolar mania trials.

5.1.2 Overview of Studies Pertinent to Efficacy (BP, manic or mixed episodes)

There were two highly significant trials with concurrence between Drs. Kordzakhia and Levin and that the improvement from baseline to 3-week endpoint on the YMRS total score in these 2 positive, flexible-dose acute treatment trials compared to the placebo groups provide adequate evidence to support that asenapine flexibly dosed in the range of 5- 10 mg BID is satisfies regulatory criteria to support the claim that asenapine is efficacious in the acute treatment of bipolar I disorder, manic and mixed episodes. The limitation of the findings from the 2 randomized controlled trial evaluating asenapine in the treatment of bipolar disorder is that a small minority of patients had their dose reduced from the starting dose of asenapine 10 mg BID to 5 mg BID (approximately 10%) during the two trials, and this lower dose was the only dose supported for a claim in the schizophrenia program. The magnitude of the effect compared to placebo was less than that observed with olanzapine.

5.1.3 Conclusions Regarding Acute Efficacy of Asenapine in the Schizophrenia and Bipolar Disorder (manic or mixed episodes)

Taken together, the sponsors have, in my view as well as the views of Dr. Levin, Chen, and Kordzakhia, provided sufficient evidence for regulatory purposes in two positive short-term studies to support the claim of efficacy of asenapine 5 mg BID in the treatment of schizophrenia. The sponsors have provided sufficient evidence also in two positive trials to support the claim of short-term efficacy of asenapine in the treatment of bipolar disorder, manic or mixed episodes. Qualitative review in my prior memorandum suggests that the asenapine's magnitude of effect appears to be less than that of olanzapine, and usual for the class of atypical antipsychotic drugs on the market. One issue limiting the ability to clearly describe recommended dosing is the paucity of data in the optimal clinical dosing range in fixed dose studies in both indications. The greatest need is to study the acute efficacy of asenapine 5 mg BID in bipolar disorder, manic and mixed episodes to see if for similar efficaciousness, the adverse event profile can be improved compared to the10 mg BID dose level. No clear predictors of response were identified in either the acute treatment of schizophrenia or bipolar disorder.

5.2 Safety Data

5.2.1 Clinical Data Sources for Safety Review

In my memorandum dated 14 May 2008, I referred to Dr. Levin's thorough review of the safety data in the NDA. In addition, I reviewed data that I thought required additional analysis and confirmation. It is noteworthy that the rates of death in the placebo-controlled asenapine database were 1.7 per 100 patient-years in the asenapine group and 1.9 per 100 patient-years in the placebo group. In the asenapine group, there was one death associated with asenapine exposure with symptoms of dystonia and dyspnea associated with epiglottitis and laryngitis, raising the possibility of laryngeal dystonia. There was also one death in a patient diagnosed with pulmonary embolism coupled with hyperthermia associated with asenapine exposure. The placebo patient who died was diagnosed with malignant thymoma, which was highly unlikely to be related to treatment.

OCP stated in the section on "Comments Previously Provided to the Medical Review Team" on page 42 of their review that on 1 May 2008 "this reviewer went to the medical division to discuss a death in the ongoing studies. Due to workload the medical review team requested followup midweek the following week. On Thursday May 8th, 2008 a followup email was sent to the medical review team informing them of a possible case of aplastic anemia." In the data, Dr. Levin found no evidence of pancytopenia. If this were the case, as CDTL working with Drs. Levin, Laughren and Mathis and Lieutenant Commander Kiedrow, we would have used one of our reserved meeting times to review the action plan.

5.2.2 Common Adverse Event Profile for Asenapine

Schizophrenia

The common AEs that are associated with asenapine use in the acute treatment of schizophrenia (≥ 5% and at least twice that of placebo) are consistent with the usual safety profile atypical antipsychotic drugs such as sedation, akathisia, and oral hypoesthesia (particular to the sublingual formulation) along with extra-pyramidal symptoms if all terms are combined.

Bipolar Disorder

The common AEs that are associated with asenapine use n the acute treatment of bipolar disorder, manic or mixed episodes, (≥ 5% and at least twice that of placebo) are consistent with the usual safety profile atypical antipsychotic drugs such as sedation, dizziness, weight gain, and oral hypoesthesia along with extra-pyramidal symptoms if all terms are combined.

Almost all of the AEs associated with discontinuation occurred in less than one percent of the patients in the placebo-controlled trials. In the absence of complete data employing standard AEs terms that we think are reasonable to categorize adverse drug reactions, the sponsor should submit revised complete tables of AEs with percentages greater than 1% and at least twice placebo stratified by diagnostic category.

5.2.3 Adverse Reactions of Particular Interest

Cardiac Sinus Arrest and Other Arrhythmias

During the review process, one of the clinical concerns that emerged were some of the cardiac adverse events reported in the database. In view of the complexity that the data posed to the medical reviewers, an objective review by cardiological experts was welcomed. Drs. Suchitra Balakrishnan and Dr. Norman Stockbridge of the Division of Cardio-Renal Products (DCRP) reviewed thoroughly the totality of the relevant cardiac clinical data summarized in their review dated 23 April 2008 that included data from the bioequivalence study identified by OCP. They noted that the sponsors attribute to Neurally Mediated Reflex Bradycardia (NMRB) the 9 episodes of sinus arrest and 4 reports of nodal rhythm in healthy volunteers who received asenapine < 5 mg. Dr. Stockbridge reviewed the explanations provided by the sponsor and found the explanation of NMRB secondary to α-receptor blockade to be "reasonable." In terms of other dysrythmias, the incidence of tachycardia, sinus bradycardia, heart block and ventricular extra-systoles were higher than in the placebo group and comparable to the frequencies observed in olanzapine-treated patients. The consultation by Drs. Stockbridge and Balakrishnan concludes: "It appears that the arrhythmia related AEs associated with asenapine are similar to those of olanzapine and consistent with class effects based on our review of the summary of clinical safety, non-clinical summary and additional analysis of ECG intervals in Study INT 0036960. Over all, the data are suggestive of risk of cardiac conduction abnormalities similar to those reported with olanzapine."

In the 15 May 2008 as well as in the 10 June 2008 OCP reviews, despite Dr. Stockbridge's conclusions in the DCRP review of 23 April 2008, OCP continued to conclude that the data supported a severe risk of cardiac toxicity associated with asenapine. On page 22 of the OCP review, in section 2.2.2, Summary of Major Conclusion), OCP opined that "There appears to be no margin of safety with regards to cardiac toxicity." This contradicts the conclusions of Drs. Stockbridge's and Balakrishnan's interpretations of the data and conclusions in their review.

I defer to the expertise of DCRP in the evaluation of the clinical cardiological risk profile of asenapine.

QTIRT evaluation of Risk of QT Prolongation and Other Cardiovascular AEs

The QTIRT consultants found that there was an asenapine concentration-dependent increase in the QTc interval that was mild and of little material clinical significance in the QT study review dated 29 February 2008. The greatest prolongation with a mean ($\Delta\Delta QT_cF$) of 10.5 msec with an upper bound of the 90% CI of 16.5 msec was found in the e10 mg BID asenapine group. In discussion with the QTIRT team, the inverted U-shape was most likely due to the variability stemming from small sample sizes (11 April 2008). As a result, one suggestion form the QTIRT was to consider employing the exposure-response data in labeling.

OCP (page 415) in his review of the QTIRT consultation review of the Thorough QT study stated "that some of these serious cardiac toxicities were noted in the QT study but that they hadn't been highlighted and had been explained largely as vasovagal in origin."

Dr. Stockbridge stated in discussion with regarding the QTIRT review on 11 April 2008 (with Dr. Garnett) that he found the QT interval prolongation to be relatively comparable to that seen with olanzapine and to be of little clinical significance.

Hypotension and Syncope

In the actual text from the study report of Study 25509 (Initial Sublingual Single Dose Rising Study), the sponsor summarized: "Org SL94 appears to be safe in endocrinological, biochemical and haematological terms. However single high doses of Org SL93 may induce cardiovascular adverse experiences in animal and humans…. Results from cardiotoxicity studies suggested that Org SL94 may cause postural hypotension at high doses."

In my opinion, hypotension with attendant risk of syncope remains from the initiation of phase I research a safety concern with asenapine administration in a clinical setting. Consistent with $alpha_1$-receptor blockade, the data support the conclusion that healthy volunteers are likely to be more susceptible to orthostatic hypotension associated with dizziness and tachycardia associated with asenapine exposure than psychiatric patients. Nonetheless, hypotension and the risk of syncope were observed in the psychiatric

patients especially when starting treatment. In Phase II/III studies, the frequency observed of syncope was 0.5% in the asenapine 10-20 mg daily groups, 0.4% in the olanzapine group and 0.1% in the placebo group. The risk of orthostatic hypotension, particularly early in the acute treatment of schizophrenia and bipolar disorder may be greater with asenapine than olanzapine exposure and therefore will remain a particular concern in asenapine treated patients to be monitored in clinical settings.

Elevations of Hepatic Transaminases

The potential for asenapine-induced hepatotoxicity was one of the first areas of concern identified upon first review of the asenapine NDA. Dr. Levin particularly scrutinized the data for related adverse events and liver enzymes levels and cases of any hepatic impairment in preparation for the 18 October 2007 filing meeting in order to obtain an early consultation by Dr. John Senior to evaluate for Drug-Induced Liver Injury (DILI). Dr. Levin emailed me a summary of his review of all of the DILI-related data in the NDA (in an email date 15 November 2007) of the liver-related adverse events and abnormal laboratories. By the time of the 1 February 2008 mid-cycle meeting, Dr. Levin remained unable to identify any cases consistent with Hy's Law (reflecting impaired hepatocyte function)[1] associated with asenapine exposure and he documented in his review that the percentages of elevated transaminases were higher in the olanzapine-treated patients than in the asenapine for placebo treated patients: "In the acute, controlled trials, the proportion of subjects with transaminase (ALT) elevations > *3 times ULN* in the asenapine, placebo, and olanzapine groups were 3.6% (76/2128); 1.6% (10/634); and 7.8% (66/840), respectively."

On the basis of formation of the N-oxide metabolite of asenapine, OCP informed us to evaluate for hepatotoxicity. And we did so very thoroughly. Of concern regarding accuracy of documentation, however, is the following paragraph by OCP (page 317 of the 15 May 2008 OCP review):

"The totality of the information suggests that a dose and treatment duration hepatotoxicity is of real concern with asenapine and there may be greater risk if the drug is swallowed or if children should take an adult dose. Due to these concerns this reviewer requested that the sponsor be asked to provide complete laboratory information and informed the medical reviewer so that this concern could be fully evaluated. A meeting was held with the medical division where the medical division dismissed the concern of hepatotoxcicity [sic]. However, this reviewer has been unable to find where the information request for laboratory information was ever forwarded to the sponsor or where it was ever received."

In my role as Cross Discipline Team Leader and Lieutenant Commander Keith Kiedrow in the role of Regulatory Project Manager on this NDA pilot project, we are to be notified of any issue that is not minor and to be copied on emails of any importance. I never heard of an additional request for data and I never discussed a request to the sponsor for more data. Dr. Levin confirmed with me today that he never discussed with OCP a

[1] Navarro VJ, Senior JR. Drug-related hepatotoxicity. N Engl J Med. 2006 Feb 16; 354(7):731-9.

request for additional data, so it is unclear what OCP is referring to in the sentence above cited again: "However, this reviewer has been unable to find where the information request for laboratory information was ever forwarded to the sponsor or where it was ever received."

OCP noted in their review on page 24 "the dose and time dependent hepatotoxicity observed with oral administration." Based on OCP's review of the pharmacological data, On page 37, OCP noted: "The TQT study employed higher doses than would be used clinically 15 mg - 20 mg BID and the medical reviewer was informed of the possible increased bilirubins." It is not clear what OCP means by "possible increased bilirubins." Dr. Levin meticulously reviewed the relevant liver function tests in the entire clinical database and uncovered no evidence for DILI.

In contrast to the data that we reviewed of sublingual asenapine in generally healthy adult psychiatric patients, based on OCP's review, I concur with the conclusions of Drs. Kavanaugh and Baweja (page 226 of the OCP review) that exposure in patients with any degree of hepatic impairment should be avoided. These safety precautions are addressed in draft labeling including advising that asenapine should be avoided in patients with any impairment of hepatic function. OCP found that there appears to be a narrow safety margin between therapeutic and potential hepatoxic doses of asenapine in adolescents, as well as for elders. I concur and agree with OCP's labeling language.

While OCP has continued to express concern regarding the risk of elevated transaminases and there were several outliers with enzymes greater than or equal to 3XULN coupled with Bilirubin levels greater than or equal to 2XULN, in the controlled trials and in open label extensions. Some of these enzyme elevations were associated with discontinuation from the studies. I do not think, however, that the data supports raising elevated transaminases to the levels of the "Warnings and Precautions" section of labeling as proposed by the sponsor unless there is data to support this.

Hematological

In the Clinical and OCP reviews, no confirmed actual cases of agranulocytosis had been identified. On page 437 of the OCP review, no actual lab values were provided, however, extrapolations to possible ANC values below 500 were indicated with dotted lines. In a letter dated 14 May 2008, however, the sponsors stated that 3 patients exposed to asenapine had been found with serum ANC < 500. The sponsors proposed that at least two of these cases may have been laboratory errors. Based on the uncertainty of these findings, I am inclined to recommend that we wait until we receive more definitive data on the risk of agranulocytosis before this be added into the Warnings and precautions section of proposed labeling.

In *Harrison's Textbook of Medicine*, Drs. Rappeport and Bunn state: "The term *aplastic anemia* should be restricted to conditions in which a markedly hypocellular bone marrow results in pancytopenia (anemia, neutropenia, and thrombocytopenia). At the 12 May

2008 "OCP Office Level Briefing for the Drug Asenapine, NDA 22117", Dr. Kavanaugh presented a slide that he thought identified the occurrence of aplastic anemia. Two subjects were identified (page 437). The data for subject 1 demonstrated a hematocrit above 25%, a White Blood Cell count (WBC) above 3 times and platelet counts at least 350,000/mL are not consistent with aplastic anemia. Nor are the laboratory values of hematocrit 34%, WBC at least 3.5 $10^3/mm^3$ and platelet counts greater than 200,000/mL.

Weight gain

Approximately 5% of asenapine treated subjects gained clinically significant weight (> 7% of body weight) compared to 2% of placebo treated subjects over 3 to 6 weeks of short-term treatment. Weight gain with a potential risk of potentially medically serious metabolic syndrome is an adverse event of clinical significance for asenapine.

Seizure

The risk of seizure associated with asenapine use was below 1% in the safety database. In the 6-week schizophrenia trials, there were no seizures reported in the asenapine 5 mg BID or 10 mg BID groups. Two seizures were reported in the application, one in the < 5 mg BID asenapine group and one seizure was reported in the olanzapine group. In the bipolar trials, over 3 weeks at high doses, one seizure occurred in the asenapine treated and 1 occurred in the olanzapine treated patients. I have no objection to the sponsors' proposed language.

Hyperprolactinemia

Dr. Levin in his review reported that mean change from baseline in prolactin levels (ug/L) were similar in placebo (-3.4) and asenapine treated patients (-3.2) compared to elevations in the other treatment groups: risperidone (21.2) haloperidol (2.5) and olanzapine (0.4). Mean serum prolactin levels were more reduced in the asenapine treatment groups than in the placebo group. In comparison, the levels were highly elevated in the risperidone and less elevated in the haloperidol and olanzapine groups. As expected, however, asenapine elevates prolactin in many subjects, though less than is seen with risperidone. There were 19.3% of placebo and 44.4% of asenapine treated patients who changed from low baseline to high at endpoint levels. As a result, the sponsor sent us draft labeling with hyperprolactinemia in the "Warnings and Precautions" section.

EPS

Symptoms of EPS appeared generally similar to the frequencies observed with other atypical antipsychotic drugs and less than seen with first generation antipsychotic drugs and will be in labeling accordingly.

5.2.4 Use in Elderly Patients

Hepatic function tends to become less robust with age. In view of the clinical pharmacological risk of reduced metabolism with hepatic impairment of any degree and the seriousness of syncope, dizziness and the potential for accidental injury, I concur with OCP that asenapine should be used with caution, if at all, in elderly patients in addition to avoidance in patients with any degree of hepatic dysfunction.

5.2.5 Controlled Substances Consultation

Dr. Katherine Bonson noted in her CSS consult that the proposed language for the Abuse and Dependence section is not adequately supported scientifically to justify its inclusion.

There is no issue pertaining to abuse identified by CSS that would preclude an approvable action.

5.2.6 Risk: Benefit Evaluation

The morbidity and mortality of such a serious disorder of the major psychoses, schizophrenia and bipolar disorder, is well established. Drugs that provide advantages over those on the market are needed. Overall, the safety profile is typical generally for the olanzapine-lie atypical antipsychotic drugs with out the greater efficacy of olanzapine. I concur with Dr. Levin (page 5) that the serious AEs that were most likely related to asenapine were syncope, akathisia, somnolence, rhabdomyolysis, bradycardia, and dystonia. In terms of the risk: benefit analysis, there are numerous atypical drugs on the U.S. market. Given the serious issues raised by Pharmacology/Toxicology and OCP that have emerged without resolution since the GRMP deadline of 14 May 2008 for the CDTL memorandum (filed to meet the GRMP deadline while waiting for the OCP review to be completed necessitating this addendum), asenapine does not appear to offer unique advantages over numerous other atypical antipsychotic drugs on the market. I think that adverse drug reactions such as syncope, hypotension, akathisia and weight gain detract from the risk-benefit profile compared to other drugs on the market. While the efficacy compares adequately with some representative antipsychotic drugs, the efficacy of asenapine is not clearly superior to olanzapine, which has demonstrated superior efficacy to other antipsychotic drugs in research such as the CATIE study[2].

5.2.7 Conclusions Regarding the Safety of Asenapine

Based on Dr. Levin's detailed clinical review, the short-term clinical adverse drug reaction profile for the sublingual formulation of asenapine in the treatment of schizophrenia and the manic or mixed episodes of bipolar disorder appears to be similar generally to that observed with similar atypical antipsychotic drugs used in the treatment of schizophrenia and bipolar disorder. Orthostatic hypotension and dizziness (particularly with initiation of exposure), as well as sedation, akathisia, weight gain with

[2] Lieberman JA et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. New Engl J Med 2005 Sep 22;353(12):1209-23.

potential for elevations of serum glucose and lipids, appear to be a clinically germane risk with chronic use. Further data will be needed from the sponsors on adverse drug reactions with a dose-response.

At present, while additional clinical safety data will be requested from the sponsors, there appears to be no major clinical safety issues precluding an approvable action. Nonetheless, there are grave safety issues that must be addressed in terms of metabolism and elimination as outlined by clinical pharmacology. Moreover, the risk of carcinogenicity and reproductive toxicology needs also to be adequately addressed to ensure that asenapine would be safe for clinical use.

5.3 Clinical Sections of Labeling

The first draft of labeling has been achieved by Dr. Laughren.

6.0 WORLD LITERATURE

The sponsor provided certification that they reviewed the literature and found no relevant articles that would adversely affect conclusions about the safety of asenapine in the treatment of schizophrenia or bipolar disorder. Dr. Levin reviewed the literature and confirmed the sponsor's findings.

7.0 POST-MARKETING RISK MANAGEMENT PLAN

The sponsors submitted a usual plan for pharmacovigilance activities. Mary Dempsey, of Office of Surveillance and Epidemiology, in her review (dated 25 February 2008) concluded that although "the sponsor's submission does not constitute a formal Risk Minimization Action Plan (RiskMAP), the potential risks of asenapine use are "consistent and comparable" with those of already approved atypical antipsychotic drugs and that no additional safety concerns were identified. It is premature to explore a post-marketing plan further.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC)

It was decided by Dr. Laughren that there was no need to take this application to the PDAC in terms of the clinical data, which are consistent with a typical second generation antipsychotic drug.

9.0 DSI INSPECTIONS

As summarized by Dr. John Lee (4 June 2008), inspections were conducted at two US and three non-US sites. The inspectors found that the sites adhered generally to the applicable statutory requirement and FDA regulations governing the conduct of clinical investigations and the protection of human subjects as documented to be acceptable to support the validity of the data.

10.0 FOREIGN REGULATORY ACTIONS

To the best of my knowledge, asenapine is not approved anywhere at this time for the acute treatment of schizophrenia or bipolar disorder.

11.0 PHASE 4 COMMITMENTS

It is premature to discuss Phase IV commitments, including long-term data, in view of the outstanding Pharm/Tox and OCP requirements to be considered for approval.

12.0 LABELING AND APPROVABLE LETTER

We will include labeling in the PLR version of labeling with the approvable action letter, unless Dr. Temple finds that a nonapproval action is indicated given the outstanding requirements. Dr. Laughren completed draft asenapine labeling.

13.0 CONCLUSIONS AND RECOMMENDATIONS

As an OND NME NDA pilot project, we have attempted to provide a complete review package with issues that arose during review as fully addressed as possible to the Division Director by 14 May 2008. By GRMP the entire package was due to the Office Director his package by 7 June 2008. Issues particular to this application stemming from a paucity of information with respect to critical OCP and Pharm/Tox review areas arose that prevented the ability to meet the deadline and engage in labeling discussions. The GRMP deadline of June 7th target was intended to provide our Office Director adequate time for regulatory processing by the PDUFA action date of 30 June 2008. In terms of correction of errata in my review dated 14 May 2008, I had erroneously written that 7 June 2008 was the GRMP action date. That was incorrect. 7 June 2008 was the GRMP deadline to complete the full package for the Office Director in the absence of the unusual obstacles that arose. The action date is 30 June 2008.

In order to be eligible for approval, the Office of Clinical Pharmacology requires from the sponsors the following. From a clinical pharmacology standpoint the sponsors have not adequately ascertained what moieties are circulating in plasma. In the mass balance study, the plasma concentrations of 14C asenapine (equivalents) greatly exceed that of asenapine (cold drug) as well as the metabolites measured. The moieties looked for are asenapine, desmethylasenapine, and the N-oxide. The total AUC counts for total radioactivity (14C) is around 1550 AUC units whereas the summation of all the AUCs for the three measured moieties accounts for about 55 AUC units. Therefore, there is a vast amount of circulating material in plasma that has not been ascertained. At least 96.6% of the circulating species have not been identified. This is a matter for concern and we require an explanation for this vast gap in plasma between circulating radioactivity and moieties circulating and identified. Another issue that raises concern is that the mass balance has not been adequately characterized. In a generalized manner, after the administration of the radioactive dose about 88 % of the dose was recovered with 49 % in the urine and 39 % in the feces. This is a generalized presentation of assessing the elimination pathways of the radioactivity. Specifically, what is known is that direct glucuronidation accounts for 12-21% of the dose. Furthermore, 5-16 % of the dose is that of the unchanged drug, asenapine. When these two percentages of moieties are added, only 17–37 % of the dose is represented. Therefore, 63-83 % of the dose has not been adequately characterized for the primary elimination pathways. The characterization of the metabolism moieties circulating in plasma and of the human elimination pathways must be clearly delineated and properly addressed by the sponsors.

Pharmacology/Toxicology requires the following from the sponsors before approval can be considered. In order to accurately describe the carcinogenic potential of asenapine in the labeling, full histopathological examination of all animals in the low and medium doses in the rat carcinogenicity study, and of all low and medium dose females in the mouse carcinogenicity study, should be performed prior to NDA approval. As communicated to the sponsors on 8 April 2008, in order to validly compare results across groups, the originally examined slides from these studies should be re-examined in concert with the newly evaluated slides by a single pathologist, and subjected to peer review. These conclusions of Pharmacology/Toxicology were confirmed twice by the Executive CAC. In addition, Pharmacology/Toxicology recommends that the sponsors perform an embryofetal development study with (b) (4) in the rabbit to qualify this impurity or reduce the specifications for (b) (4)) qualification limit of (b) (4)

While an approvable has not been precluded by CMC issues, the following need to be submitted. The sponsors must provide the levels of (b) (4) in all the clinical batches including the batches used in BE studies (Batch #: AN and AT). The sponsors provide information on the in-process controls and the manufacturing critical process parameters that control the (b) (4) material content in the final dosage form. The sponsors provide information in tabular form about the physico-chemical properties of the (b) (4)(i.e., solubility, stability, etc.). Include either a release and shelf-life control of the (b) (4) in the drug product

through specification or a justification from for not including such control based on ICH Q6A.

In terms of clinical safety, major concerns stem from the risk of hypotension, syncope, dizziness, sedation (combining all related terms into one term), including sequelae such as accidental injury, as well as for akathisia and weight gain with potential for the development of metabolic syndrome with asenapine use. We will also request in the absence of complete data on terms that we think are reasonable to categorize adverse drug reactions, the sponsor should submit complete lists of AEs with percentages greater than 1% and at least twice placebo stratified by diagnostic category.

In terms of evaluation for risk of agranulocytosis, I would recommend that the sponsor submit more information regarding the three patients identified in their letter dated 14 May 2008, where the Absolute Neutrophil Count (ANC) was reported to be less than 500 cells per microliter. Please provide all clinical information on these three patients including the full sequence of laboratory and medical evaluations with time course of all hematological laboratory values, concomitant medication and co-morbid medical illnesses.

Dr. Levin is providing medical review of the clinical data in depth on the list of subjects with sent by OCP on 27 May 2008. Each case will be medically adjudicated by Drs. Laughren, Mathis, Levin, and I in a meeting on 16 June 2008.

The Division agreed to a deferral on pediatric studies in meeting minutes from the EOP2 27 April 2004.

Dr. Temple may decide to submit draft PLR labeling to the applicants when the action letter is issued if the action to be taken is an approvable. Consequently, Dr. Laughren has prepared draft labeling.

cc:
Orig NDA 22-117
ODE-I/R Temple
HFD-130
HFD-130/TLaughren/MMathis/GZornberg/RLevin/KKiedrow/BRosloff/
EChaleckaFranaszek/CTele/TOliver/SHardeman/PDavid

DOC:Asenapine_Zornberg_AE_Addended CDTL Memo.doc

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/s/

Gwen Zornberg
6/12/2008 09:41:41 PM
MEDICAL OFFICER

Barry N. Rosloff, Ph.D.
6/24/08

P/T SUPERVISORY COMMENTS ON OCP REVIEW AMENDMENT #1

In his review amendment #1, filed electronically on 6/18/08, Dr. Kavanagh makes numerous comments on various aspects of the non-clinical studies submitted for asenapine, with the apparent intent of indicating that such studies showed effects which predict serious adverse reactions in humans. I do not find his arguments convincing. Many involve speculation regarding the adverse consequences of serotonergic stimulation. Aside from the fact that data indicate that asenapine itself is a serotonergic *antagonist* (although of course it is possible that its metabolites are not), the range of adverse effects which Dr. Kavanagh is speculating to be due to serotonergic agonism (as well as the wide range of drug classes he implicates) is so broad as to be useless for informing the direction of any future clinical monitoring.

As to the actual data, Dr. Kavanagh discusses the animal reproduction studies which were performed and concludes that asenapine had "dose-dependent embryo-fetal toxicity in all species and strains", caused "an increase in the postnatal loss of pups", and had effects on "skeletal muscle formation, and remodeling, including poor ossification…consequently asenapine is expected to effect bone and connective tissue especially during development, growth, and in the elderly or other populations at risk, e.g. renal failure patients".

An increase in embryofetal toxicity and postnatal loss were indeed seen, and are discussed in Dr. Chalecka-Franaszek's review and are described in our proposed labeling. (However, it should be noted that overall, the animal reproduction findings were not particularly alarming. The drug did not induce malformations. Embryofetal and pup deaths are often seen at the higher doses in these types of studies and can often be attributed to toxicity to the dams resulting in lack of maternal care, although there was some evidence that at least some of the effects of asenapine were due to prenatal drug exposure). Dr. Kavanagh stresses the "poor ossification" seen in these studies; however this is a common finding at higher doses in animal reproduction studies which may be secondary to maternal toxicity but even if not merely represents a transient, reversible delay in development, and not a direct or toxic effect on bone. Finally, I am not aware of any effects on skeletal muscle or connective tissue in these studies.

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/s/

Barry Rosloff
6/24/2008 02:03:01 PM
PHARMACOLOGIST

CLINICAL REVIEW

Application Type:	NDA
Submission Number:	22-117
Letter Date:	August 29, 2007
Stamp Date:	August 29, 2007
PDUFA Goal Date:	June 29, 2008
Reviewer Name:	Robert L. Levin, M.D.
Review Completion Date:	April 14, 2008
Established Name:	Asenapine Maleate
Proposed Trade Name:	Saphris
Therapeutic Class:	Atypical Antipsychotic
Applicant:	Organon
Priority Designation:	S
Formulation:	Sublingual rapidly disintegrating tablets
Dosing Regimen:	Twice daily
Indications:	Schizophrenia; Bipolar Disorder; Acute Manic Episode
Intended Population:	Adults

1. EXECUTIVE SUMMARY

1.1 RECOMMENDATION ON REGULATORY ACTION

I recommend that the Division take an approvable action for the two indications sought:

1. Asenapine for the treatment of Schizophrenia in adults
2. Asenapine for the treatment of acute mania associated with Bipolar Disorder in adults.

For each indication, two adequate and well controlled trials demonstrated the efficacy of asenapine. Furthermore asenapine was reasonably safe and well tolerated in subjects with a diagnosis of Schizophrenia or Bipolar Disorder, Acute Manic or Mixed Episode.

1.2 RECOMMENDATIONS ON POSTMARKETING ACTIONS

i.

1.2.1 Risk Management Activity

I recommend that the Division discuss with the sponsor specific plans for pharmacovigilance regarding the potential adverse reaction, agranulocytosis. For the safety data for asenapine reviewed to date, there is not a signal for agranulocytosis. However, agranulocytosis is associated with other atypical antipsychotics, particularly with drugs that have structural similarities with asenapine (clozapine, quetiapine and olanzapine). In my opinion, it would be helpful to have further discussion internally and with the DPP safety team about monitoring and managing the potential risk of agranulocytosis.

1.2.2 Required Phase 4 Commitments

I recommend that the Division request that the sponsor conduct adequate and well controlled long-term maintenance studies in Schizophrenia and Bipolar Disorder. For Bipolar Disorder, the maintenance study should be appropriately designed to assess the efficacy of asenapine in preventing all types of mood episodes associated with Bipolar Disorder (depression, mania, and mixed episodes).

In addition, I recommend that we discuss internally and with the Pediatrics division, the types of pediatric studies that would be indicated. This would partially depend on an assessment of the postmarketing safety profile of asenapine in adults.

1.2.3 Other Phase 4 Requests

Currently, I do not recommend any additional Phase 4 requests.

1.3 SUMMARY OF CLINICAL FINDINGS

1.3.1 Brief Overview of the Clinical Program

In the asenapine clinical program, there are 51 completed trials, and there are 12 ongoing trials. (The database cut-off date was January 15, 2007). The 14 completed Phase 2/3 studies of asenapine in Schizophrenia and Bipolar Mania include: 1) six acute, 6-week, placebo-controlled and active-controlled trials in Schizophrenia; 2) five long-term, open label studies in Schizophrenia; 3) two acute (3-week), placebo-controlled and active-controlled trials in Mania; and 4) one long-term (12-week) study in Mania. There have been 29 clinical pharmacology studies in healthy subjects and subjects with renal or hepatic impairment; and, there have been eight 8 clinical pharmacology studies in subjects with Schizophrenia or Schizoaffective Disorder.

For the indication of Schizophrenia, the sponsor conducted four pivotal, similarly designed placebo-controlled and active-controlled, 6-week trials of asenapine monotherapy in subjects with a diagnosis of Schizophrenia, acute psychotic episode. Three asenapine fixed-dose trials included dose levels of 5 mg BID and 10 mg BID rapidly-disintegrating tablets administered sublingually. The dose range in the single flexible-dose Schizophrenia trial was 5-10 mg BID administered sublingually. Asenapine was developed for sublingual administration, since it has extremely low bioavailability via the oral route. The drugs used as active controls in the Schizophrenia trials were risperidone, olanzapine, and haloperidol. A total of 1,318 Schizophrenia subjects were included in the four pivotal, controlled trials. Among these, 572 were treated with asenapine, 378 were treated with placebo, 194 were treated with olanzapine; 59 were treated with risperidone; and 115 were treated with haloperidol. The total asenapine exposure in the controlled, short-term trials was 47.9 person-years. The total exposures for placebo, olanzapine, risperidone, and haloperidol were 38.8, 15.3, 9.0, and 9.8 person-years, respectively.

For the indication of mania associated with Bipolar Disorder, the sponsor conducted two identically designed, placebo-controlled and active-controlled 3-week trials of asenapine monotherapy is subjects with a diagnosis of Bipolar Disorder, Acute Manic or Mixed Episode. Both were flexible-dose studies of asenapine 5-10 mg BID administered sublingually. Olanzapine was the active-control drug used in the acute mania trials. A total of 976 subjects participated in the controlled, short-term mania studies. Of these, 379 were treated with asenapine, 203 were treated with placebo, and 394 were treated with olanzapine. The total exposure in the controlled, short-term Mania trials was 17.2 person-years. The total exposures for placebo and olanzapine were 9.0 and 20.0, respectively.

The sponsor also conducted long-term, open-label asenapine studies that were extensions of the short-term controlled trials. In the long-term Schizophrenia studies, a total of 908 subjects were exposed to asenapine (5-10 mg BID) for up to one year. The total asenapine exposure in these long-term studies was 505.7 person-years. In the long-term

mania studies (9-12 weeks), a total of 275 subjects were treated with asenapine for a total exposure of 44.8 person-years.

In the Phase 2/3 Schizophrenia and Mania studies (short-term and long-term), a total of 2251 subjects were treated with asenapine. Of these, 298 (13%) were treated with doses of less than 10 mg/day, and 1953 (87%) were treated with 10 to 20 mg per day, as fixed or flexible doses. In the asenapine group, there were 1778 Schizophrenia subjects and 473 Bipolar, manic subjects. Overall, in the combined Schizophrenia and Mania studies (Cohort E), the total asenapine exposure was 645 patient-years.

There were 37 clinical pharmacology studies of asenapine in healthy subjects, patients with hepatic or renal impairment, and subjects with a diagnosis of Schizophrenia or Schizoaffective Disorder. A total of 745 healthy subjects and patients with hepatic or renal disease were exposed to asenapine. The majority of these subjects (88%) were exposed to asenapine doses of less than 10 mg per day. In the eight clinical pharmacology studies in subjects with psychotic disorders, a total of 363 subjects were exposed to asenapine. Most of these subjects were exposed to doses of 10-20 mg per day.

1.3.2 Efficacy

The primary objective of the controlled, short-term Schizophrenia trials was to evaluate the efficacy of asenapine (5-10 mg BID) compared to placebo, as measured by the Positive and Negative Syndrome Scale (PANSS). Two of these studies (041004 and 041023) demonstrated the efficacy of asenapine 5 mg BID SL. However, 10 mg BID was not demonstrated to be efficacious in Study 041023, as determined by the pre-specified primary statistical analysis plan (last observation carried forward). However, the results of a non-primary statistical analysis plan (mixed-model repeated measure) suggested that the 10 mg BID dose was efficacious in the treatment of Schizophrenia. In two other similarly designed studies (041021 and 041022), asenapine was not efficacious in either fixed doses of 5 mg BID or 10 mg BID or as flexible doses of 5-10 mg BID. Study 041022 was negative, as the active control (olanzapine) demonstrated efficacy. Study 041004 was a failed study; neither asenapine nor the active control (olanzapine) demonstrated efficacy.

In the controlled, short-term mania trials (A7501004 and A7501005), the primary objective was to evaluate the efficacy of asenapine compared with placebo in the treatment of subjects with manic or mixed episodes associated with Bipolar I Disorder, as measured by the Young-Mania Rating Scale. In both trials, flexible-dose asenapine (5-10 mg BID) was demonstrated to be efficacious in the acute treatment of mania.

1.3.3 Safety

Generally, asenapine 5-10 mg BID, administered sublingually, was reasonably safe and well tolerated in clinical programs for Schizophrenia and Mania. There were no new or unexpected adverse events compared to what one would expect with other atypical antipsychotic medications.

The deaths in both programs were not related to treatment with asenapine; they were associated with the illnesses under treatment or with other medical conditions. The majority of the deaths were suicides (8 of 15), and the suicide rates in the studies were similar to those in other studies of Schizophrenia and Mania. Furthermore, the suicide rates adjusted for duration of exposure were similar among treatments (asenapine, placebo, and active-control drugs).

The majority of serious adverse events were related to the illnesses under treatment (psychotic and manic symptoms). The relatively few serious adverse events that were possibly or probably related to treatment with asenapine were: syncope, akathisia, somnolence, rhabdomyolysis, bradycardia, and dystonia. Similarly, the majority of adverse events associated with discontinuation were related to the illnesses under treatment (psychotic and manic symptoms). Adverse events leading to discontinuation related to asenapine treatment were: transaminase elevation, akathisia, convulsion, sedation, oral hypoesthesia, dystonia, tremor, dizziness, weight gain

Common, drug-related adverse events were: extrapyramidal symptoms, akathisia, sedation, dizziness, weight gain, and oral hypoesthesia. Dose-related adverse events included extrapyramidal symptoms and akathisia. Extrapyramidal symptoms included dystonia, parkinsonism, dyskinesia, extrapyramidal disorder, and movement disorder. Specific cases of dystonia included: oculogyration, torticollis, blepharospasm, and macroglossia. Dyskinesia cases included tardive dyskinesia. Specific adverse reactions included under ‘parkinsonism’ were rigidity, cogwheel rigidity, hypertonia, gait disturbance, tremor, blunted affect, and masked facies. Generally, the extent of extrapyramidal symptoms related to asenapine was considerably less than that with risperidone and haloperidol.

Overall, treatment with asenapine had little effect on blood pressure and heart rate; however, there were cases of orthostatic cases without significant consequences. Treatment with asenapine was associated with a mean weight gain of approximately 1.1 kg, compared to a weight gain of 0.1 kg with placebo treatment. In a dedicated QT study, asenapine treatment was associated with a modest degree of QT prolongation which was exposure-related but not dose-related. Overall, asenapine treatment had no significant effect on clinical laboratory parameters. However, there was a modest increase in mean transaminase concentrations, and there were a small number of cases of serum transaminase concentrations greater than three times the upper limit of normal. There were no serious adverse events associated with increases in transaminase concentration. Furthermore, there was no effect on bilirubin concentration, and there were no cases meeting criteria for Hy’s law.

1.3.4 Dosing Regimen and Administration

The recommended dose for the acute treatment of Schizophrenia is 5 mg BID administered sublingually. Efficacy was not clearly demonstrated for the 10 mg BID dose

level. Furthermore, there were some important dose-related adverse drug reactions (akathisia, extrapyramidal symptoms).

For the acute treatment of Mania associated with Bipolar Disorder, the recommended starting dose is 10 mg SL BID. The dose can be decreased within the dose range of 5-10 mg BID as needed, if patients experience adverse events.

Adjustment of the dose may be necessary for patients with moderate hepatic impairment. Currently, asenapine is contraindicated in patients with severe hepatic impairment.

1.3.5 Drug-Drug Interactions

One should use caution in the coadministration of asenapine with drugs that inhibit the isoenzyme CYP1A2 (such as fluvoxamine). Inhibition of CYP1A2 by fluvoxamine increased asenapine exposure by approximately 30%. One should also use caution when co-administering asenapine with drugs that induce CYP1A2, such as carbamazepine. Coadministration with carbamazepine decreased asenapine exposure by approximately 35%. Asenapine has inhibitory effects on the isoenzyme CYP2D6. Exposure to paroxetine increased two-fold when co-administered with asenapine. Thus, one should use caution when co-administered with drugs that are metabolized significantly by CYP2D6.

One should use caution when co-administering asenapine with other drugs that have sedative and CNS-depressant effects.

1.3.6 Special Populations

1.3.6.1 Hepatic Impairment

Severe hepatic impairment can increase asenapine exposure up to 7-fold, compared to exposure in the presence of normal hepatic function. With moderate hepatic impairment, asenapine exposure can increase up to two-fold.

1.3.6.2 Renal Impairment

Based on limited pharmacokinetic data in patients with various degrees of renal impairment, dosage adjustment based on renal impairment does not appear to be necessary.

1.3.6.3 Elderly

Asenapine pharmacokinetics and pharmacodynamics were not studied in elderly patients to any significant degree. As with many drugs, one should use caution when administering asenapine in the elderly, since the elderly are at increased risk of hepatic and renal impairment.

1.3.6.4 Gender

There were no dedicated clinical pharmacology studies investigating potential differences in asenapine pharmacokinetics between male and female subjects. Among the 346 subjects in the population pharmacokinetic analysis, 15% of subjects were female. In the analysis, gender was assessed as a potential covariate on clearance, but no significant difference was observed. In addition, plasma protein binding studies indicated that there was no difference between plasma from male and female subjects. Based on the limited data, there is no evidence of gender-related differences in the pharmacokinetics of asenapine. There is no recommendation for asenapine dose adjustment based on gender.

1.3.6.5 Pregnancy and Lactation

Studies to assess the effects of asenapine on human reproduction and development have not been conducted. Treatment with asenapine is not recommended for use during pregnancy, unless it is clearly necessary. It is not known whether asenapine or its metabolites are excreted in human milk. However, animal data indicate that asenapine does cross the placenta in rats and rabbits, and it is present in the milk of lactating rats. It is recommended that women treated with asenapine should not breast-feed.

1.3.6.6 Pediatrics

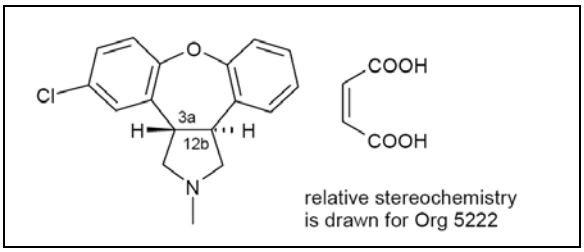
A single, small study in adolescents suggested that the pharmacokinetics of asenapine were similar between adolescents and adults. The study demonstrated that, compared to adults, adolescents swallowed a higher proportion of the asenapine dose.

2. INTRODUCTION AND BACKGROUND

2.1 PRODUCT INFORMATION

Asenapine (also referred to as ORG 5222) is a novel atypical antipsychotic agent with a receptor binding profile similar to those of other atypical antipsychotic drugs. Asenapine has been developed as a rapidly dissolving tablet for sublingual formulation, since it has poor oral bioavailability (less than 2%). Asenapine has potent antagonism at a combination of serotonin, dopamine, noradrenaline, and histamine receptors. It has high affinity for a subset of serotonergic (5-HT-2a/2B/2C/6/7), noradrenergic (a1/2) and dopaminergic (D3/4) receptors and has no appreciable activity at muscarinic cholinergic receptors. Asenapine appears to have relatively higher potency at serotonin receptors than at dopamine receptors.

The chemical name of asenapine is: trans-5-chloro-2,3,3a,12b-tetrahydro-2-methyl-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole(z)-2-buenedioae (1:1). Asenapine maleate bears the structural formula shown below2. It contains two chiral centers at C3a and C12b and is a racemate. The relative molecular mass of asenapine maleate is 401.843.



Asenapine tablets would be available in two strengths: 5 mg and 10 mg. The tablets are manufactured (b) (4)

(b) (4) The tablets dissolve in the saliva within approximately 10 seconds.

2.2 CURRENTLY AVAILABLE TREATMENTS FOR INDICATION

Numerous antipsychotic drugs are available for the treatment of Schizophrenia. Examples of earlier available typical antipsychotic drugs include chlorpromazine, haloperidol, thioridazine, fluphenazine, perphenazine, thiothixene, loxapine, mesoridazine, molindone, and trifluoperazine. More recently available atypical antipsychotics include clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole.

Drugs available for the treatment of mania include lithium, carbamazepine, valproate, lamotrigine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole.

2.3 AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE U.S

The asenapine fast-dissolving sublingual tablets would be readily available in the U.S.

2.4.1 IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS

Class effects include: extrapyramidal symptoms, neuroleptic malignant syndrome, body temperature dysregulation, tardive dyskinesia, effects on blood pressure and heart rate, metabolic effects (hyperglycemia and diabetes mellitus, hyperlipidemia, increased body weight, sedation and potential for cognitive and motor impairment, agranulocytosis, hyperprolactinemia, prolongation of the QT interval, transaminase elevation, dysphagia, increased mortality in elderly patients with dementia-related psychosis, and seizure.

2.5 PRESUBMISSION REGULATORY ACTIVITY

(Appendix 1 contains a detailed regulatory history of the asenapine clinical development program. This includes a discussion of communications between the sponsor and the division.)

Asenapine was investigated initially in Europe and Japan as intravenous and oral formulations. Due to low bioavailability and high first-pass metabolism of the oral formulation, a sublingual dosage form was developed.

On September 30, 1996, Organon submitted IND 51-641 for asenapine (ORG-5222) sublingual tablets for the treatment of Schizophrenia. The initial study conducted under IND 51-641 was protocol 041-001, entitled: a double-blind, placebo-controlled, titration study with sublingual ORG-5222 to establish the maximum tolerated dose in subjects with Schizophrenia.

On August 3, 2004, Organon submitted IND 70-329: asenapine sublingual tablets for the treatment of acute mania associated with Bipolar Disorder. Identically designed protocols A7501004 and A7501005 were entitled: a Phase 3 multicenter, multinational, randomized, placebo-controlled, double-blind, 3-week study to evaluate the efficacy and safety of sublingual asenapine versus olanzapine and placebo in patients with an acute manic episode.

3. SIGNIFICANT FINDINGS FROM OTHER DISCIPLINES

3.1 STATISTICS FINDINGS

The statistics reviewer, Yeh-Fong Chen confirmed the sponsor's efficacy results for Schizophrenia trials 041004 and 041023. Dr. Chen concluded that Study 041023 was positive for 5 mg BID and negative for 10 mg BID, using the primary, pre-specified LOCF analysis. Dr Chen agrees that, in Study 041023, 10 mg BID was efficacious ehen the results are analyzed using MMRM analysis, which was not the pre-specified, primary analysis. Dr. Chen has concerns about accepting the results of Study 041004, due to the relatively high proportion of subjects who discontinued from the study. I do not share this concern; the discontinuation proportion is within the range of that observed for other acute Schizophrenia studies. Furthermore, the study was adequately designed and conducted.

George Kordzakhia, Ph.D. conducted the statistical review of the acute mania studies. He confirmed that each trial demonstrated the efficacy of asenapine in the treatment of acute mania associated with Bipolar Disorder. In studies A7501004 and A7501005, YMRS and CGI-BP total scores were statistically significantly improved (ie, decreased) in the asenapine treatment group compared with the placebo treatment group. Based on the LOCF ANCOVA analysis, the p-values for asenapine vs. placebo with respect to YMRS total score were <0.001 in both studies. The p-values for asenapine vs. placebo with respect to CGI-BP total score were 0.0116 (Study A7501004) and 0.0017 (Study A751005).

3.2 CARDIORENAL QT INTERDISCIPLINARY REVIEW TEAM (QTIRT)

The sponsor conducted a 16-day, randomized, placebo-controlled and quetiapine-controlled QT study of asenapine 5-10 mg SL BID in subjects with a diagnosis of Schizophrenia or Schizoaffective Disorder. However, the QT Team notes that this was not a thorough QT study, and it did not use an active control such as moxifloxacin. Nevertheless, the consultants expressed confidence that one can meaningfully interpret the results of the study. The Cardiorenal QTIRT consultants concluded that the study was positive by the ICH E14 guideline: the upper 95% confidence interval exceeded a 10 msec QTc interval prolongation for all doses of asenapine studied. The results are illustrated below.

FDA Analysis: The Point Estimates and 90% CI Corresponding to the Largest Upper Bounds for Asenapine by Dose Group

Treatment	Time, h	Mean ΔΔQTcF, ms	90% CI, ms
Asenapine 5 mg b.i.d., N=30	3	5.0	-1.5, 11.4
Asenapine 10 mg b.i.d., N=27	2	10.5	4.5, 16.5
Asenapine 15 mg b.i.d., N=33	3	8.7	3.0, 14.4
Asenapine 20 mg b.i.d., N=29	4	4.9	-1.9, 11.6

The consultants noted that, due to the small sample sizes (fewer than 35 subjects in each treatment group), the study was not powered to detect a dose-response relationship using the primary endpoint. However, an exposure-response analysis conducted by both the sponsor and FDA QTIRT reviewers demonstrated that asenapine prolonged the QTcF interval in a concentration-dependent manner. The model predicted that the mean ΔΔQTcF equals 6 msec (8 msec, 90% upper confidence limit) at a mean Cmax of 10.6 ng/mL, corresponding with an asenapine dose of 20 mg BID. Asenapine 20 mg BID was the maximum tolerated dose in subjects with Schizophrenia. This dose results in a 2-fold increase in exposure over the highest clinical dose (10 mg BID), which adequately covers the plasma concentrations observed in Phase 2b/3 clinical studies. The consultants note that subjects with severe hepatic impairment have 7-fold increase in unbound AUC, and the magnitude of QT prolongation in such subjects is not known.

Because asenapine belongs to a pharmacological class of compounds associated with QT/QTc prolongation, the sponsor used quetiapine 375 mg b.i.d. as the positive control. The magnitude of quetiapine effects on the QTc interval is not well characterized. In this study, the difference from placebo in LS mean time-matched QTcF change from baseline at Tmax was 7 msec (90% CI: 1, 13) on Day 10 and 10 (90% CI: 3, 17) msec on Day 16. The exposure-response relationship for quetiapine was similar to the observed relationship in Study R076477-SCH-1014 in NDA 21-999. Therefore, assay sensitivity with quetiapine was established.

Cardiorenal QTIRT Recommendations for Asenapine Labeling of QT Results:

Section 5.9 Warnings and Precautions-QT Prolongation The effects of Sycrest® on the QT interval were evaluated in a dedicated QT study [see CLINICAL STUDIES (14.3)]. Sycrest® causes a mild increase in the corrected QT (QTc) interval. Electrocardiogram (ECG) measurements were taken at various time points during the Sycrest® clinical trial program testing therapeutic doses (5-10 mg b.i.d.) and any post-baseline QT prolongations exceeding 500 ms were reported in comparable rates to placebo in the short-term trials. Sycrest® should be used cautiously in combination with drugs that are known to prolong the QTc interval including Class 1A (e.g., quinidine, procainamide) or Class 3 (e.g., amiodarone, sotalol) antiarrhythmic medications, antipsychotic medications (e.g., chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other class of medications known to prolong the QTc interval. Sycrest® should also be used cautiously in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias.
Section 14.3 Thorough QT/QTc Trial A trial assessing the potential QT/QTc prolonging effect of Sycrest® 5 mg, 10 mg, 15 mg, and 20 mg b.i.d. and placebo was conducted in 151 clinically stable patients with schizophrenia. Electrocardiographic assessments were performed throughout the dosing interval both at baseline and steady state. There was a concentration-dependent increase in QTc interval. No patients treated with Sycrest® experienced QTc increases >60 ms from baseline measurements, nor did any patient experience a QTc of >500 ms. Additionally, there were no reports of Torsade de Pointes or any other adverse events associated with delayed ventricular repolarization.

3.3 CHEMISTRY FINDINGS

Currently, the formal Chemistry, Manufacturing, and Controls findings are not available. (Please refer to the separate review).

3.4 PHARMACOLOGY and TOXICOLOGY

Elzbieta Chalecka-Franaszek, Ph.D. has conducted the Pharmacology and Toxicology review. The primary findings are summarized below.

3.4.1 Carcinogenicity

The pharmacology/toxicology team has concluded that there is one major deficiency in the application: the carcinogenicity studies in the rat and mouse are inadequate.

In the rat carcinogenicity study, the maximum tolerated dose was clearly exceeded in males at all dose levels and in females at the high dose, based on significant and dose-dependent decreases in body weight gain and body weight. The incidence of pre-neoplastic changes and tumors (total number of tumors and tumor-bearing animals) was decreased at the high dose when compared to the vehicle controls. However, the low dose and medium dose groups were not adequately examined. Since it is known that a significant decrease in body weight can lead to a decrease in tumor development, the sponsor would be required to conduct a complete histopathologic examination of the low and mid dose males and females.

In the mouse carcinogenicity study, the incidence of pleomorphic malignant lymphomas and all combined lymphomas in the hemolymphoreticular system was statistically significantly increased in the female mice at the high dose compared to the vehicle control (7/57 and 22/60 in the vehicle control and high dose group, respectively). However, the incidence of these tumors in the female mice at the high dose was similar to that in the untreated controls (22/57). The reason for this large difference between the vehicle and untreated controls is not known. The vehicle did not appear to cause a general decrease in other tumor types.

The sponsor should provide an explanation for the large difference in the incidence of lymphomas between vehicle and untreated female controls. Furthermore, the sponsor will be required to conduct a complete histopathology examination of the low dose and medium dose female groups.

In addition, the pharmacology/toxicology team recommends that slides from all groups in the rat study and the female groups in the mouse study, including the slides from previously fully evaluated groups, be examined simultaneously by one study pathologist. Peer review should also be conducted for all of these groups.

3.4.2 Mutagenicity

Asenapine has been studied in: 1) the bacterial reverse mutation (Ames) test; 2) in vitro chromosomal aberration assay in human lymphocytes; 3) mouse lymphoma assay; 4) sister chromatid exchange test in rabbit lymphocytes; and 5) in vitro micronucleus assay in rats. All assays were negative, except for the in vitro chromosomal aberration assay in human lymphocytes. In the latter assay, asenapine minimally increased structural chromosomal aberrations in the presence of metabolic activation and numerical aberrations in the absence and presence of metabolic activation. The results of this study are considered equivocal.

3.4.3 Reproductive Toxicology

Reproductive toxicology studies demonstrated embryotoxic effects of asenapine, based on increased incidence of post implantation losses in rats and reduced fetal weights in rat and rabbits. Therefore, the pregnancy category C is recommended (consistent with

sponsor's labeling). [reviewer note: however, the agency currently does not include pregnancy categories in labeling.].

3.5 BIOPHARMACEUTICS FINDINGS

Currently, the formal Biopharmaceutics findings are not available. (Please refer to the Office of Clinical Pharmacology review).

There are several important preliminary points communicated verbally during an internal meeting held April 7, 2008. The points are outlined below.

1. Severe hepatic impairment can result in a 7-fold exposure. Thus, the use of asenapine should probably be contraindicated in patients with severe hepatic impairment. Moreover, even mild-moderate hepatic impairment can result in a 2-fold exposure, compared to the exposures with normal hepatic function.
2. There are four primary metabolic pathways in the metabolism of asenapine. These include glucuronidation as well as three pathways involving isoenzyme cytochrome P450 1A2. Metabolism by the CYP1A2 system yields major metabolites Oxy-N-desmethyl-asenapine, the N-oxide metabolite, and 11-hydroxy-asenapine.
3. CYP1A2 is the major isoenzyme in asenapine metabolism. The next most important isoenzyme is CYP3A4. Isoenzyme CYP2D6 has minor importance in the metabolism of asenapine. Inhibition of CYP1A2 by fluvoxamine increases asenapine concentrations by 30%. Induction of CYP1A2 by low doses of carbamazepine decreases asenapine concentrations by 15%.
4. Asenapine significantly inhibits CYP2D6 in vivo. Concentrations of paroxetine increased two-fold.
5. Asenapine does not appear to induce any CYP isoenzyme system.
6. Asenapine demonstrates non-linear pharmacokinetics. A doubling of dose results in a 1.7-fold exposure.

3.6 DIVISION OF MEDICATION ERRORS

The review of the sponsor’s proposed tradename (Saphris) is ongoing.

3.7. DIVISION OF SCIENTIFIC INVESTIGATION (DSI)

Currently there are no findings from the DSI inspections that would affect the approvability of the application.

4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 SOURCES OF CLINICAL DATA

Sources of clinical data include individual clinical study reports, integrated summaries of efficacy and safety, tables of clinical studies, tables of clinical safety data, case report forms, and data sets of individual safety parameter results.

4.2 TABLES OF THE PIVOTAL CLINICAL STUDIES

This section included tables for the pivotal, short-term, placebo-controlled trials. Appendix 12.2 contains tables for all of the studies in the asenapine clinical program.

4.2.1 SCHIZOPHRENIA PIVOTAL EFFICACY TRIALS

Type of trial	Protocol number and Country	Trial Design and Objective	Treatment groups	Number and Type Subjects	Demographics	Duration	Trial Status
E, S	041004 United States (21 centers)	An assessment of the efficacy and safety of a sublingual dose of Org 5222 in subjects with schizophrenia (in an acutely exacerbated state) compared to risperidone and placebo in a randomized double blind, fixed-dose 6-week trial	placebo Route: SL tablet or capsules asenapine Route: SL tablet Dose Regimen: 5 mg BID risperidone Route: capsules Dose Regimen: 3 mg BID	placebo Randomized: 62 Treated: 62 Completed: 21 asenapine 5 mg Randomized: 60 Treated: 59 Completed:27 risperidone 3 mg Randomized: 60 Treated: 59 Completed:25 schizophrenic patients	placebo Sex: 49M/13F Mean Age (min/max): 42.1 (22-68) years Race: W/B/A/O: 20/32/0/10 asenapine 5 mg Sex: 46M/13F Mean Age (min/max): 38.2 (21-70) years Race: W/B/A/O: 25/28/0/6 risperidone 3 mg Sex: 36M/23F Mean Age (min/max): 42.7 (22-61) years Race: W/B/A/O: 25/26/2/6	42 days	Started: August 2001 Completed: May 2002 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Status; Type of Report
E, S	041023 Canada (1 center), Russia (12 centers), India (8 centers), Romania (7 centers), United States (18 centers)	A multicenter, randomized, double-blind, fixed dose, 6-week trial of the efficacy and safety of asenapine compared with placebo using haloperidol positive control in subjects with an acute exacerbation of schizophrenia	placebo Route: SL tablet or capsule asenapine 5 mg Route: SL tablet Dose Regimen: 5 mg BID asenapine 10 mg Route: SL tablet Dose Regimen: 10 mg BID haloperidol Route: oral capsule Dose Regimen: 4 mg BID	placebo Randomized: 123 Treated: 123 Completed: 70 asenapine 5 mg Randomized: 114 Treated: 111 Completed: 70 asenapine 10 mg Randomized: 106 Treated: 106 Completed: 71 haloperidol Randomized: 115 Treated: 115 Completed: 68 schizophrenic patients	placebo Sex: 64M/59F Mean Age (min/max): 40.1 (18-70) years Race: W/B/A/O: 76/31/11/5 asenapine 5 mg Sex: 75M/36F Mean Age (min/max): 38.0 (18-69) years Race: W/B/A/O: 71/22/11/7 asenapine 10 mg Sex: 67M/39F Mean Age (min/max): 37.1 (19-68) years Race: W/B/A/O: 67/29/10/0 haloperidol Sex: 63M/52F Mean Age (min/max): 39.0 (18-67) years Race: W/B/A/O: 68/35/12/0	42 days	Started: June 2005 Completed: September 2006 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Status; Type of Report
E, S	041021 Russia (5 centers) United Kingdom (9 centers) United States (31 centers)	A multicenter, randomized, double-blind, fixed-dose, 6-week trial of the efficacy and safety of asenapine compared with placebo using olanzapine positive control in subjects with an acute exacerbation of schizophrenia	placebo Route: SL tablet or oral tablet asenapine Route: SL tablet Dose Regimen: 5 mg BID asenapine Route: SL tablet Dose Regimen: 10 mg BID olanzapine Route: oral tablet Dose Regimen: 15 mg QD	placebo Randomized: 106 Treated: 100 Completed: 50 asenapine 5 mg Randomized: 106 Treated: 104 Completed: 60 asenapine 10 mg Randomized: 102 Treated: 102 Completed: 51 olanzapine Randomized: 103 Treated: 102 Completed: 58 schizophrenic patients	placebo Sex: 58M/42F Mean Age (min/max): 39.5 (18-62) years Race: W/B/A/O: 46/45/0/9 asenapine 5 mg Sex: 77M/27F Mean Age (min/max): 40.4 (18-70) years Race: W/B/A/O: 50/47/3/4 asenapine 10 mg Sex: 72M/30F Mean Age (min/max): 41.2 (18-60) years Race: W/B/A/O: 49/44/2/7 olanzapine Sex: 80M/22F Mean Age (min/max): 39.7 (19-61) years Race: W/B/A/O: 44/47/2/9	42 days	Started: May 2005 Completed: May 2006 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Status; Type of Report
E, S	041022 Russian Federation (3 centers) Ukraine (5 centers) United States (23 centers)	A multicenter, randomized, double-blind, flexible-dose, 6- week trial of the efficacy and safety of asenapine compared with placebo using olanzapine positive control in subjects with an acute exacerbation of schizophrenia	placebo Route: SL tablet or oral tablet asenapine Route: SL tablet Dose Regimen: 5 – 10 mg BID olanzapine Route: oral tablet Dose Regimen: 10 mg – 20 mg QD	placebo Randomized: 93 Treated: 93 Completed: 48 asenapine Randomized: 91 Treated: 90 Completed: 42 olanzapine Randomized: 93 Treated: 92 Completed: 43 schizophrenic patients	placebo Sex: 74M/19F Mean Age (min/max): 41.9 (20-61) years Race: W/B/A/O: 42/43/0/8 asenapine Sex: 67M/23F Mean Age (min/max): 44.0 (23-67) years Race: W/B/A/O: 45/38/2/5 olanzapine Sex: 72M/20F Mean Age (min/max): 41.6 (20-63) years Race: W/B/A/O: 41/43/2/6	6 weeks	Started: February 2005 Completed: February 2006 full

4.2.2 MANIA PIVOTAL EFFICACY TRIALS

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Status; Type of Report
REPORTS OF EFFICACY AND SAFETY STUDIES INDICATION = "BIPOLAR MANIA"							
STUDY REPORTS OF CONTROLLED CLINICAL STUDIES PERTINENT TO THE CLAIMED INDICATION							
E, S	A7501004 Bulgaria (2 centers), India (6 centers), Korea (2 centers), Malaysia (2 centers), Philippines (3 centers), Romania (2 centers), Russia (4 centers), Ukraine (centers), United States (32 centers)	A Phase III, randomized, placebo-controlled, double-blind trial evaluating the safety and efficacy of sublingual asenapine vs. olanzapine and placebo in patients with an acute manic episode	placebo Route: SL tablet or oral tablet asenapine Route: SL tablet Dose Regimen: 5 mg – 10 mg BID olanzapine Route: oral tablet Dose Regimen: 5 - 20 mg QD	placebo Randomized: 98 Treated: 98 Completed: 57 asenapine Randomized: 185 Treated: 185 Completed: 124 olanzapine Randomized: 205 Treated: 205 Completed:161 bipolar patients	placebo Sex: 48M/50F Mean Age (min/max): 38.1 (18-69) years Race: W/B/A/O: 55/16/22/5 asenapine Sex: 92M/93F Mean Age (min/max): 39.1 (18-76) years Race: W/B/A/O: 104/38/40/3 olanzapine Sex: 117M/88F Mean Age (min/max): 38.4 (18-66) years Race: W/B/A/O: 110/41/44/10	21 days	Started: November 2004 Completed: April 2006 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Status; Type of Report
E, S	A7501005 Bulgaria (2 centers) India (6 centers) Korea (3 centers) Malaysia (1 center) Philippines (2 centers) Romania (2 centers) Russian Federation (4 centers) Turkey (2 centers) Ukraine (4 centers) United States (31 centers)	A Phase III, randomized, placebo-controlled, double-blind trial evaluating the safety and efficacy of sublingual asenapine vs. olanzapine and placebo in patients with an acute manic episode	placebo Route: SL tablet or oral tablet asenapine Route: SL tablet Dose Regimen: 5 mg – 10 mg BID olanzapine Route: oral tablet Dose Regimen: 5 - 20 mg QD	placebo Randomized: 104 Treated: 104 Completed: 64 asenapine Randomized: 194 Treated: 194 Completed: 122 olanzapine Randomized: 191 Treated: 190 Completed: 152 bipolar patients	placebo Sex: 52M/52F Mean Age (min/max): 41.5 (18-66) years Race: W/B/A/O: 59/19/19/7 asenapine Sex: 114M/80F Mean Age (min/max): 40.0 (18-68) years Race: W/B/A/O: 122/31/35/6 olanzapine Sex: 114M/76F Mean Age (min/max): 40.0 (19-67) years Race: W/B/A/O: 114/31/34/11	21 days	Started: December 2004 Completed: April 2006 full

4.3 REVIEW STRATEGY

I reviewed the sources of clinical data that include individual clinical study reports, integrated summaries of efficacy and safety, tables of clinical studies, tables of clinical safety data, case report forms, and data sets of individual safety parameter results. I also utilized the reviews of all consultants (when available).

4.4 DATA QUALITY AND INTEGRITY

Generally, the quality and integrity of the data are acceptable.

4.5 COMPLIANCE WITH GOOD CLINICAL PRACTICES

Studies comprising the asenapine clinical development program appear to have been conducted in accordance with Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki, and in compliance with the FDA regulations for informed consent and protection of patient rights as described in 21 Code of Federal Regulations 50, 56, and 312 and with Directive 2001/83/EC, Part 4, B Conduct of trials, Good Clinical Practice. All studies were approved by Institution Review Boards (IRB)/ Independent Ethics Committees (EC). All studies have undergone regular monitoring by Organon, Pfizer, and/or appointed Contract Research Organizations (CRO), including site visits to investigators and regular contact with study sites and responsible medical monitors. Most clinical trial reports have been written in compliance with the format of the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3); some early clinical trial reports meet the content requirements of ICH E3 for content but are in various formats. All study reports have also been reviewed extensively within Organon (and/or Pfizer) and 46 study centers have been audited. The studies performed during the asenapine Phase 3 development have been and still are being evaluated on a regular (3

monthly) basis by an independent Drug Safety Monitoring Committee (DSMC), and no relevant safety issues have been reported by the DSMC during the entire period.

4.6 FINANCIAL DISCLOSURE

The sponsor has submitted financial certification and financial disclosure forms from investigators. It appears that there are no potential conflicts of interest that would affect the potential approvability of the NDA.

5. CLINICAL PHARMACOLOGY

5.1 PHARMACOKINETICS

5.1.1 Absorption

The bioavailability of asenapine via the oral route is extremely low (approximately 2%). Therefore, the sponsor developed asenapine as a rapidly disintegrating tablet for sublingual administration, to bypass ---. In clinical pharmacology studies, sublingual administration of a 5 mg tablet yielded a mean absolute bioavailability of 36%. Following sublingual administration, asenapine is rapidly absorbed, with peak plasma concentrations occurring within 0.5 to 1.5 hours. At steady-state, the average peak concentrations of 5 mg and 10 mg BID were 3.58 ng/mL and 7.0 ng/mL, respectively.

Sublingual bioavailability can be significantly variable, depending on the amount of saliva, amount of active drug swallowed, food and water intake, and anticholinergic status. A three-way administration study (sublingual vs. supralingual vs. buccal)—
Tablet administration results in asenapine dissolution of 4 mg/mL.
Drinking water sooner than 10 minutes after administration of sublingual asenapine reduced the bioavailability of asenapine by approximately 12-20%. However, drinking water 10 minutes or more after sublingual administration did not affect exposures. Therefore, one should avoid drinking or eating for at least 10 minutes after sublingual administration of asenapine. This restriction was recommended for the clinical trials. A high-fat meal immediately before sublingual administration reduced asenapine exposure by 20%. The AUC was reduced by 13% when food was given 4 hours after asenapine administration. This was likely due to increased clearance of asenapine related to an increase in hepatic blood flow following food intake. No additional restrictions with regard to food intake were applied in the clinical trials.

5.1.2 Exposure

After single sublingual doses of asenapine 5 mg, the weighted mean $AUC_{0\text{-}inf}$ was 32.2 ng*h/mL in studies of subjects with normal hepatic and renal function. The range of the $AUC_{0\text{-}inf}$ was 21.3 to 55 ng*h/mL. At steady state, the weighted mean $AUC_{0\text{-}inf}$ was 33.6 ng*h/mL, with a range of 15.5 to 41.7 ng*h/mL.

5.1.3 Distribution

Asenapine has a large volume of distribution (approximately 1700 L), indicating that there is extensive extravascular distribution. At therapeutic and supratherapeutic concentrations, asenapine is highly bound (~95%) to plasma proteins, including albumin and a1-acid glycoprotein. Asenapine and N-desmethylasenapine have low to moderate effective permeability for human P-glycoprotein (P-gp). They are weak substrates of the human P-gp transporter. Thus, it is unlikely that P-gp has a significant impact on the in vivo disposition of asenapine and N-desmethylasenapine.

5.1.4 Metabolism

The parent drug, asenapine appears to be the active moiety. There are 38 metabolites of asenapine that have been identified. However, exposures to each are quite low after administration of asenapine, and none are highly prevalent. None of the metabolites account for greater than 7% of the radioactivity collected in urine.
Asenapine is metabolized extensively in human hepatocytes via several biotransformation pathways. The three primary routes are glucuronidation, demethylation and hydroxylation. The N+-glucuronide, N-desmethyl, N-desmethyl-carbamoyl-glucuronide, and 11-O-sulfate of asenapine were detected in plasma following sublingual administration of (14C)-asenapine. Asenapine N+-glucuronide and, to a lesser extent, asenapine were quantified as the two major drug moieties in plasma. However, none of the above metabolites are expected to contribute to the pharmacological activity of asenapine, due to their lower affinity for relevant receptors or their inability to cross the blood brain barrier. Therefore, unchanged asenapine appears to be the drug moiety mainly responsible for the pharmacological effects of the drug.

In vitro and clinical data suggest that the CYP1A2 isoenzyme is the most important human cytochrome P450 enzyme involved in the metabolism of asenapine. Inhibition of CYP1A2 by fluvoxamine increased asenapine exposure by approximately 30%. Induction of CYP1A2 by carbamazepine decreased asenapine exposure by approximately 20%. The CYP3A4 and CYP2D6 isoenzymes appear to have a role. However, CYP2B6 and CYP2C19 would not be expected to have a significant role in the metabolism of asenapine. UGT1A4 mediates the formation of asenapine N+-glucuronide.

A study of the effect of enzyme induction by smoking did not demonstrate a significant effect; however, it is difficult to interpret the results, since most of the subjects were smokers.

Asenapine significantly inhibits CYP2D6 in vivo. Asenapine could be considered the new index compound for CYP2D6 metabolism.

5.1.5 Elimination

Hepatic and renal routes contribute approximately equally to the elimination of asenapine and its metabolites. Following a single sublingual dose of [^{14}C]-labeled asenapine,

approximately 50% of radioactivity was recovered in the urine, and approximately 40% was recovered in the feces. After intravenous administration, asenapine has a high rate of clearance (52 L/h). After a single sublingual dose, the mean terminal half-life of asenapine was approximately 23 hours, across the clinical pharmacology studies in subjects with normal hepatic and renal function. The mean $T_{1/2}$ ranged from 13.4 to 39.2 hours.

5.1.6 Steady-state, Variability, Dose-proportionality, and Enantiomers

Steady state concentrations of asenapine are reached within 3 days of BID dosing. The single-dose and steady-state (BID) pharmacokinetics of asenapine are similar The N+-glucuronide, N-desmethyl, and 11-O-sulfate metabolites of asenapine demonstrate elimination kinetics similar to asenapine during BID dosing, suggesting that no that there is no accumulation of these metabolites.

The pharmacokinetic profile of asenapine has considerable variability. The overall variability estimates for Cmax and AUC are 45% and 37%, respectively. The mean inter-subject variability for Cmax and AUC was 33% and 26%, respectively. The mean intra-subject variability was similar (30% and 26% for Cmax and AUC, respectively).

Up to a dose of 5 mg BID, the Cmax and AUC for asenapine after sublingual administration increase proportionally. Within the therapeutic dose range (5-10 mg BID), there is a deviation from dose-proportionality. The Cmax and AUC increase 1.7-fold with a two-fold increase in dose. At supratherapeutic doses (> 10 mg BID), this deviation from dose-proportionality is more pronounced.

5.1.7 Intrinsic Factors

Renal Impairment

Overall, the pharmacokinetics of asenapine and N-desmethylasenapine following a single dose of 5 mg asenapine appeared to be similar among subjects with varying degrees of renal impairment and subjects with normal renal function. Thus, dosage adjustment based upon the degree of renal impairment does not appear to be necessary. However, the interpretability of the study might be limited by the small sample sizes (N = 8 in each group) and the variability of the asenapine pharmacokinetic profile observed across the clinical pharmacology studies.

Normal renal function was defined as a creatinine clearance > 80 mL/min; mild renal impairment was defined as CLcr between 51 and 80 mL/min; moderate renal impairment was defined as CLcr between 30 and 50 mL/min; and severe renal impairment was defined as CLcr < 30 mL/min; not requiring dialysis. In subjects with mild renal impairment, asenapine exposures (AUC and Cmax) were approximately 30% higher than those of subjects with normal renal function. With moderate renal impairment, AUC was 3% higher, and Cmax was approximately 20% lower than in subjects with normal renal

function. With severe renal impairment, AUC was 6% higher, and Cmax was approximately 30% lower than in subjects with normal renal function..

Hepatic Impairment

Severe hepatic impairment can result in a 7-fold exposure. Thus, the use of asenapine should probably be contraindicated in patients with severe hepatic impairment. Moreover, even mild-moderate hepatic impairment can result in a 2-fold exposure.

Asenapine is extensively metabolized in the liver. Therefore, one can expect hepatic impairment to have an effect on asenapine pharmacokinetics. In Study A7501018, the pharmacokinetic profiles of asenapine and its metabolites, N-desmethylasenapine and asenapine N+-glucuronide were assessed following a single dose of 5 mg asenapine in 32 subjects N = 8 in each group) with various degrees of hepatic impairment and in subjects with normal hepatic function. In subjects with mild hepatic impairment (Child-Pugh Class A), The $AUC_{0\text{-}inf}$ was 12% higher and the Cmax was 10% lower than in subjects with normal hepatic function. In subjects with moderate hepatic impairment (Child-Pugh Class B), the $AUC_{0\text{-}inf}$ was 12% higher and the Cmax was 43% lower than that in subjects with normal hepatic function. In subjects with severe hepatic impairment (Child-Pugh Class C), the $AUC_{0\text{-}inf}$ was 5.5-fold the AUC of healthy subjects, and the Cmax was 3% higher than in subjects with normal hepatic function. Due to decreased protein binding, the mean AUC for unbound asenapine in subjects with severe hepatic impairment was more than 7-fold the AUC in subjects with normal hepatic function. In subjects with mild and moderate hepatic impairment, the mean AUC for unbound asenapine was 39% and 34% higher, respectively, than in healthy subjects.

Thus, in Study A7501018, the pharmacokinetics were similar among subjects with mild or moderate hepatic impairment (Child-Pugh Class A and B) and subjects with normal hepatic function, indicating that dosage adjustment is not required for patients with mild or moderate hepatic impairment. In subjects with severe hepatic impairment (Child-Pugh Class C), there were substantial increases in asenapine exposure. Exposure was 7-fold for asenapine, 3-fold for N-desmethylasenapine, and 2-fold for asenapine N+-glucuronide. Therefore, asenapine should be used with extreme caution in patients with severe hepatic impairment.

In Study 25522, 32 subjects with various degrees of hepatic function (N= 8 in each group) were administered single asenapine 0.3 mg sublingually. In subjects with mild hepatic impairment (Child-Pugh Class A), the $AUC_{0\text{-}inf}$ and Cmax were 10% and 30% lower, respectively, than in patients with normal hepatic function. In subjects with moderate hepatic impairment (Child-Pugh Class B), $AUC_{0\text{-}inf}$ was 2.2-fold higher, and Cmax was approximately 35% lower than in subjects with normal hepatic function. In subjects with severe hepatic impairment (Child-Pugh Class C), $AUC_{0\text{-}inf}$ was 2-fold higher and Cmax was approximately 20% lower than in subjects with normal hepatic function.

The pharmacokinetic profile of asenapine and its metabolites has not been assessed. However, since the elderly have are at increased risk of hepatic and renal impairment, one should use caution when deciding on asenapine dosing in the elderly.

There is extremely limited experience with asenapine in a pediatric population. The steady state pharmacokinetics of asenapine and its metabolites was assessed in a single study in adolescents. The pharmacokinetic profile of asenapine in adolescents was similar to that in adults. However, it was noted that adolescents probably swallowed a larger proportion of the total dose, compared to adults. The conclusion was based on analysis of the metabolite profile.

Gender (see Clinical Pharmacology Study Summary- pages

There was no dedicated clinical pharmacology study investigating the potential differences in asenapine pharmacokinetics between male and female subjects. Among the 346 subjects in the population pharmacokinetic analysis, 15% of subjects were female. In the analysis, gender was assessed as a potential covariate on clearance, but no significant difference was observed. In addition, plasma protein binding studies indicated that there was no difference in results between plasma from male or female subjects. Based on the limited data, there is no evidence of gender-related differences in the pharmacokinetics of asenapine. There is no recommendation for asenapine dose adjustment based on gender.

Race (see Clinical Pharmacology Study Summary- pages

the pharmacokinetics between Caucasian and Japanese subjects was similar. In a population pharmacokinetic analysis, a significant effect of ‘race’ was observed on asenapine clearance. In Black subjects a 13.8 % decrease in clearance was observed as compared to subjects from other ethnic origin (distribution of race in the dataset was White, 49 %; Black 20 %, Asian 9 %, Other 22 %). However, the magnitude of the covariate effect can be considered relatively small in relation to the variability in pharmacokinetics observed for asenapine. No effects of race on the pharmacokinetics of asenapine were found, except for a 13.8 % lower clearance in Black subjects. In view of the small magnitude of this covariate effect, no dose adjustments for race are required.

Pregnancy and Lactation

Studies to assess the effects of asenapine on human reproduction and development have not been conducted. not recommended for use during pregnancy unless it is clearly needed. It is not known whether asenapine or its metabolites are excreted in human milk. However, available nonclinical data indicate that asenapine does cross the placenta in rats and rabbits and is present in the milk of lactating rats. It is recommended that women receiving asenapine should not breast-feed.

5.1.8 Extrinsic Factors

Drug Interactions

Coadministration with fluvoxamine, a strong CYP1A2 inhibitor, can be expected to result in relevant increases in asenapine plasma concentrations. In vivo, asenapine has a modest inhibitory effect on CYP2D6, as exemplified by a twofold increase in paroxetine concentrations and a similar decrease in DX/DM ratio167. With the exception of CYP1A2 inhibition, the CYP450 interaction studies resulted in mild to modest effects on exposure to N-desmethylasenapine: 18% increase by paroxetine, 34% decrease by carbamazepine, and no effect by imipramine.

Effects of CYP2D6 Inhibition by Asenapine

In vitro studies indicated that asenapine inhibits CYP2D6 at concentrations that are near the therapeutic plasma concentration range181. The in vivo potential of asenapine to inhibit the metabolism of drugs metabolized by CYP2D6 has been investigated in drug-drug interaction studies with paroxetine and imipramine. Although paroxetine is a much stronger CYP2D6 inhibitor than asenapine, asenapine coadministration (5 mg BID) resulted in an approximate two-fold increase in paroxetine concentrations This may be explained by the fact that CYP2D6 inhibition by paroxetine is mechanism-based, and therefore, relatively limited following a single dose, leaving room for CYP2D6 inhibition by asenapine. In the same study, the inhibitory effect of asenapine assessed by the effects on dextrorphan/dextrometorphan (DX/DM) ratio was found to be approximately 10-fold lower than that of paroxetine itself (2.5 times and 30 times for asenapine and paroxetine, respectively). This relatively small inhibitory effect on CYP2D6 was confirmed by the lack of effects observed on the pharmacokinetics of imipramine, and in particular its metabolite desipramine. Since desipramine is primarily a CYP2D6 substrate, one might expect higher desipramine plasma concentrations upon co-administration with asenapine due to asenapine's ability to block CYP2D6. This was not observed. Therefore, the sponsor proposes that asenapine's potential to inhibit CYP2D6 will generally not lead to effects on pharmacokinetics of CYP2D6 substrates, only if those substrates are already to some extent inhibiting the enzyme themselves. In summary, asenapine appears to have a modest inhibitory effect on CYP2D6. This is expected to result in effects on the concentrations of CYP2D6 substrates that are predominantly metabolized via CYP2D6 and simultaneously inhibit this enzyme, such as paroxetine. The effects of asenapine 10 mg BID on CYP2D6 inhibition have not been investigated, but should be anticipated to be more pronounced as a result of the approximately 70% higher plasma concentrations than attained with 5 mg BID186.

Food and Water

In summary, drinking water sooner than 10 minutes after sublingual asenapine administration reduces bioavailability to some extent, but drinking water 10 minutes or more after asenapine administration does not affect bioavailability. A high fat meal immediately before asenapine administration reduced exposure by about 20%, and exposure was reduced by 13% when food was given 4 h after asenapine.

5.2 PHARMACODYNAMICS

Asenapine has high potency for blocking serotonin and dopamine receptors. Asenapine has the greatest potency at serotonin receptors. It also has potent antagonistic activity at ά-adrenergic receptors. It has minimal affinity for muscarinic receptors. It is hypothesized that the efficacy of asenapine appears is mediated, at least in part, through a combination of antagonist activity at the dopamine D2 and serotonin 5-HT2A receptors. Actions at other receptors (e.g., 5-HT2C, 5-HT6, 5-HT7 5-HT1A, 5-HT1B, D3, and ά-2-adrenergic receptors) might also be relevant in its clinical effects. Antagonism of ά-1- adrenergic receptors appears to be associated with the cardiovascular effects of asenapine, such as orthostatic hypotension and neurally mediated reflex bradycardia. Antagonism of histamine H1 receptors appears to be associated with the sedative effects of asenapine. However, as is the case of many psychopharmacologic drugs, the precise mechanism of action of asenapine in Schizophrenia and Mania associated with Bipolar Disorder, is unknown.

In human PET studies, the occupancy at the dopaminergic D2 receptor in the putamen by asenapine was used as a putative biomarker for the clinical effects. In clinical PET studies, asenapine demonstrated a dose-dependent dopamine D2 receptor occupancy (dose range 0.1-4.8 mg). There was a significant correlation between D2 occupancy and plasma concentration. Sublingual administration of 4.8 mg BID resulted in high levels of D2 occupancy; there was a mean occupancy of 79% at approximately 3-6 h after dosing. This percentage decreased to 66% at 8 h after dosing and to 38% at 15 h after dosing. Thus, it appears that asenapine binding to D2 receptor occupancy in the brain is dependent on plasma concentration. A target occupancy of 80% occurs at a concentration of 3.2 ng/mL, which corresponds with the Cmax value of asenapine during sublingual dosing of 5 mg BID (3.6 ng/mL).

6. INTEGRATED REVIEW OF EFFICACY

6.1 SCHIZOPHRENIA

The sponsor conducted four pivotal, placebo-controlled and active-controlled trials of asenapine in acute treatment of Schizophrenia (studies 041004, 041021, 041022, and 041023). The studies had virtually identical designs. On face, studies 041004 and 041023 demonstrated the efficacy of asenapine 5 mg SL BID in the treatment of Schizophrenia. However, asenapine 10 mg BID did not demonstrate efficacy in Study 041023. (10 mg BID was not studied in Study 041004). In Studies 041021 and 041022 none of the dose levels of asenapine demonstrated efficacy. The doses included fixed-doses of 5 mg or 10 mg BID and flexible doses of 5-10 mg BID. Olanzapine demonstrated efficacy in Study 041021, which was a negative study. Olanzapine was not efficacious in Study 041022 (a failed study). Thus, asenapine 5 mg SL BID was efficacious in the acute treatment of Schizophrenia.

Table. Summary of Efficacy Results in Schizophrenia Studies

NOP	Treatment Methods		Placebo	Asenapine 5 mg BID	Risperidone
041004	LOCF	Mean Change	-4.64	-14.37	-10.05
		S.E.	2.53	2.58	2.59
		Diff. vs. placebo	-	-9.72	-5.41
		SE (Diff)	-	3.53	3.51
		P-value		0.007	0.125
	MMRM	Mean Change	-8.5	-19.8	-16.2
		S.E.	3.41	3.25	3.28
		Diff. vs. placebo	-	-11.33	-7.72
		SE (Diff)	-	4.68	4.69
		P-value		0.018	0.104

NOP	Treatment Methods		Placebo	Asenapine 5 mg BID	Asenapine 10 mg BID	Olanzapine
041021	LOCF	Mean Change	-11.14	-14.51	-13.44	-16.54
		S.E.	1.64	1.59	1.63	1.64
		Diff. vs. placebo	-	-3.38	-2.30	-5.40
		SE (Diff)	-	2.21	2.24	2.24
		P-value		0.128	0.305	0.017
	MMRM	Mean Change	-13.2	-16.4	-17.1	-19.9
		S.E.	1.95	1.83	1.93	1.9
		Diff. vs. placebo	-	-3.12	-3.88	-6.68
		SE (Diff)	-	2.66	2.73	2.71
		P-value		0.241	0.157	0.015

NOP	Treatment Methods		Placebo	Asenapine 5-10 mg BID	Olanzapine
041022	LOCF	Mean Change	-9.89	-9.44	-11.20
		S.E.	1.74	1.73	1.72
		Diff. vs. placebo	-	0.45	-1.31
		SE (Diff)	-	2.36	2.36
		P-value		0.848	0.579
	MMRM	Mean Change	-15.6	-11.6	-15.9
		S.E.	2.03	2.11	2.12
		Diff. vs. placebo	-	3.99	-0.25
		SE (Diff)	-	2.92	2.93
		P-value		0.174	0.932

NOP	Treatment Methods		Placebo	Asenapine 5 mg BID	Asenapine 10 mg BID	Haloperidol
041023	LOCF	Mean Change	-10.7	-16.2	-14.9	-15.4
		S.E.	1.57	1.66	1.69	1.63
		Diff. vs. placebo	-	-5.48	-4.11	-4.70
		SE (Diff)	-	2.23	2.25	2.21
		P-value		0.014	0.068	0.034
	MMRM	Mean Change	-14.6	-21.3	-19.4	-20.0
		S.E.	1.61	1.70	1.68	1.70
		Diff. vs. placebo	-	-6.77	-4.86	-5.47
		SE (Diff)	-	2.33	2.32	2.33
		P-value		0.004	0.038	0.020

6.1.1 **Subject Selection Criteria for the Schizophrenia Studies**

The subject selection criteria were appropriate for a trial in acute Schizophrenia. The key inclusion and exclusion criteria for studies 041004, 041021, 041022, and 041023 are outlined below.

6.1.1.1 Inclusion Criteria

1. Men or women ≥ 18 years of age with a diagnosis of Schizophrenia per DSM-IV-TR criteria (paranoid, disorganized, catatonic, or undifferentiated subtypes)
2. Women must not have been pregnant or lactating
3. Women must have been using a medically acceptable method of contraception
4. Subjects must have had a caregiver or an identified responsible person (eg, family member, social worker, nurse) who could provide support to the subject to ensure compliance with treatment and outpatient visits
5. Subjects must have had a current acute exacerbation of Schizophrenia as evidenced by a PANSS score of ≥ 60 at both screening and baseline, a CGI-S score of ≥ 4 (moderately ill) at baseline, and a PANSS items scores of ≥ 4 on at least two of the five core positive symptoms items (delusions, conceptual disorganization, hallucinatory behavior, grandiosity, and suspiciousness/persecution) at screening and baseline.
6. Baseline total PANSS score must have been ≥ 80% of the screening PANSS score
7. Subjects must have responded previously to an antipsychotic drug other than clozapine, if they had been treated previously with antipsychotic medication
8. Must have discontinued the use of antipsychotic medication at least 3 days before the baseline evaluation
9. Must have discontinued other psychotropic medication at least 5 days before the baseline evaluation
10. Must not have been treated with any investigational medication within 30 days
11. Medical conditions must have been well controlled

6.1.1.2 Exclusion Criteria

1. Women who were pregnant or lactating
2. Diagnosis of Schizophrenia, Residual Subtype or Schizoaffective Disorder
3. Primary psychiatric diagnosis other than Schizophrenia
4. Had been treated with clozapine within 12 weeks of screening
5. History of drug or alcohol abuse within 30 days of screening
6. Required concomitant treatment with psychotropic medication, other than zolpidem, zaleplon, chloral hydrate, or benzodiazepines
7. Individual was actively suicidal during the screening period
8. Individual was previously exposed to asenapine
9. Had untreated or uncontrolled medical disorders of the following types: renal, hepatic, cardiovascular, respiratory, neurologic, cerebrovascular, hematologic, oncologic, immunologic, or endocrine
10. Had a history of neurological disease or was currently treated for seizure disorder with anticonvulsant medication
11. Had a score > 2 (mild) on the Abnormal Involuntary Movement Scale at screening
12. Had clinically significant ECG findings at the screening or baseline evaluation
13. Had clinically significant finding on clinical laboratory, vital sign, or physical examination evaluation at screening or baseline

6.1.2 REVIEW OF INDIVIDUAL STUDIES

6.1.2.1 Review of Study 041004

Study 041004 was entitled: "An Assessment of the Efficacy and Safety of a Sublingual Dose of Org 5222 in Subjects with Schizophrenia (in an acutely exacerbated state) Compared to Risperidone and Placebo in a Randomized Double Blind, Fixed-dose, 6-week Trial." Study 041004 was conducted at 21 U.S. sites. The study began in August, 2001, and it was completed in May, 2002. (For a list of investigators and study sites, please refer to the appendix).

Objectives

The primary objective was to compare the efficacy of asenapine 5 mg BID with placebo in treating the acute symptoms of Schizophrenia as measured by the changes in score on the Positive and Negative Syndrome Scale (PANSS).

The secondary objectives were to: 1) evaluate the efficacy of asenapine as measured by the Clinical Global Impressions-Improvement Scale (CGI-I); 2) evaluate the efficacy of asenapine on depression, as measured by the Calgary Depression Scale (CDS); 3) evaluate the effect of asenapine on cognitive impairment, as measured by a cognitive testing battery; 4) to evaluate the safety of asenapine treatment; 5) to characterize the population pharmacokinetics of asenapine and a major metabolite of asenapine (Org-30526); and 6) to compare the efficacy of risperidone mg/day with that of placebo, as measured by changes in PANSS scores.

Study Design

This was a Phase 2, multicenter (21 U.S.), randomized, double-blind, double-dummy, placebo-controlled and active-controlled (risperidone), fixed-dose, six-week efficacy and safety study of asenapine (5 mg BID) in the acute treatment of Schizophrenia. The study included a screening period, a washout period (3 to 7 days), a treatment period (including a 21-day inpatient phase and a 21-day outpatient phase), and a follow-up visit (for subjects who did not enter extension study 041502).

Subjects who met screening criteria were admitted to the hospital for the single-blind washout period. At the completion of the washout period, subject who met entrance criteria were randomized to one of three treatment groups: 1) asenapine 5 mg BID; 2) placebo BID; or 3) risperidone 3 mg BID. Subjects randomized to the asenapine and risperidone groups had study medication titrated over the first five days of the study. Asenapine was administered as 1 mg BID on Day 1, 2 mg BID on Day 2, 3 mg BID on Day 3, 4 mg BID on Day 4, and % mg BID on Days 5 through 42. Risperidone was administered as 1 mg BID on Day 1, 2 mg BID on Day 2, 3 mg BID on Days 3 through 42. Placebo was administered BID to subjects randomized to the placebo group. For all treatment groups, each dose was administered as one tablet, regardless of the total dose of study medication.

Study medication was given in double-dummy fashion, since asenapine and placebo could be formulated as a sublingual rapidly disintegrating tablet, whereas risperidone could only be formulated as an orally administered capsule. Subjects in the asenapine

5 mg BID group were administered one or two asenapine sublingual tablets and one placebo oral capsule twice daily. Subjects in the placebo group were administered one or two placebo sublingual tablets and one placebo oral capsule twice daily. Subjects in the risperidone group were administered one oral risperidone capsule and one placebo sublingual tablet twice daily.

Subjects were instructed to take one tablet at 8:00 a.m. and one tablet at 8:00 p.m. Tablets were to be administered sublingually. Subjects were instructed to place the sublingual tablet under the tongue and keep it under the tongue until the tablet had dissolved for at least 10 seconds.

Asenapine and matching placebo for asenapine dosage forms were prepared as indistinguishable sublingual tablets. The matching active and placebo study medications were indistinguishable with respect to appearance, shape, smell, and taste. Both asenapine and placebo sublingual tablets were designed to disintegrate in less than 10 seconds. Asenapine formulated in freeze-dried tablets containing 1, 2, and 5 mg asenapine, gelatin, and mannitol as a free base. The placebo for asenapine was formulated in freeze-dried tablets containing gelatin and mannitol. Risperidone and placebo for risperidone dosage forms were prepared as indistinguishable capsules. Risperidone was prepared as 1 mg, 2 mg, and 3 mg capsules.
Asenapine and matching placebo tablets were packaged in a blister pack to protect against light and moisture. Each blister pack included 10 tablets of a single dosage. Each tablet was individually sealed in aluminum foil on a card with an aluminum foil lid on the back with thumb peels on the end. Risperidone and matching placebo capsules were packaged in bottles.

Concomitant Medication

Concomitant use of any psychotropic medications, except for those medications listed below, was not permitted during the study. The permitted medications were not allowed on the day prior to the weekly evaluations or on the day of the evaluations until after the evaluations were completed. The use of any concomitant medication was recorded on the case report form.

Permitted concomitant medications included: 1) zolpidem up to 10 mg qhs prn insomnia; 2) zaleplon up to 20 mg qhs prn insomnia; 3) chloral hydrate up to 3000 mg qhs prn insomnia; 4) benzodiazepines (daily dose equivalent to lorazepam 10 mg/day: and 5) anticholinergic medications for treatment-emergent extrapyramidal symptoms

Efficacy Measures

Primary Efficacy Measure- Positive and Negative Syndrome Scale (PANSS)

The primary efficacy measure was the Positive and Negative Syndrome Scale (PANSS). The PANSS is an appropriate efficacy measure for acute studies in Schizophrenia. It is well validated, it has well-tested reliability, and it is widely used and accepted as the

primary efficacy instrument in studies of Schizophrenia. The PANSS consists of 30 symptom items, each rated on a 7-point scale from 1 to 7. The PANSS scale is outlined below.

Positive and Negative Syndrome Scale (PANSS)

Positive Scale	General Scale
P1. Delusions	G1. Somatic concern
P2. Conceptual disorganization	G2. Anxiety
P3. Hallucinatory behavior	G3. Guilt feelings
P4. Excitement	G4. Tension
P5. Grandiosity	G5. Mannerisms and posturing
P6. Suspiciousness/persecution	G6. Depression
P7. Hostility	G7. Motor retardation
	G8. Uncooperativeness
Negative Scale	G9. Unusual thought content
	G10 Disorientation
N1. Blunted affect	G11. Poor attention
N2. Emotional withdrawal	G12. Lack of judgment and insight
N3. Poor rapport	G13. Disturbance of volition
N4. Passive/ apathetic social withdrawal	G14. Poor impulse control
N5. Difficulty in abstract thinking	G15. Preoccupation
N6. Lack of spontaneity and Flow of conversation	G16. Active social avoidance
N7. Stereotyped thinking	

Raters must have had at least two years of experience performing clinical evaluations of schizophrenic subjects, and they must have completed documented training using the PANSS. Two PANSS raters rated each subject at screening to reach a consensus score. One of these raters was then assigned to rate that subject throughout the subject's participation in the study. PANSS ratings were obtained at screening and baseline and on days 7, 14, 21, 28, 25, and 42 or on the subject's final day of treatment.

Secondary Efficacy Measure

The key secondary efficacy measure was the Clinical Global Impressions-Improvement Scale (CGI-I). Like the PANSS, the CGI-I is well validated, reliable, and widely accepted as an efficacy measure in Schizophrenia trials. The rater qualifications and rating process were identical to those for the PANSS. The schedule for CGI-I assessments was the same as that for the PANSS.

Schedule of Assessments

Efficacy assessments were conducted weekly during the treatment period, except for vital sign assessments, which were conducted daily during the inpatient treatment phase. The schedule of assessments is outlined below.

Trial phase	Screen	Base.	Inpatient Phase			Outpatient Phase			Follow-up
Trial day	-7	0	7	14	21	28	35	42	+14/+30
Visit	Screen	Baseline	1	2	3	4	5	6	Follow-up
PANSS rating	x	x	x	x	x	x	x	x	
CGI rating		x	x	x	x	x	x	x	
Adverse events	x	x	x	x	x	x	x	x	x
EPS rating	x	x	x	x	x	x	x	x	
Physical exam	x	x	x	x	x	x	x		
Vital signs	x	x	x	x	x	x	x	x	
ECG	x	x	x	x	x	x	x	x	
Laboratory	x	x	x	x	x	x	x	x	
PK sample		x	x		x			x	
Drug screen	x								
Pregnancy test	x								
Concom. meds	x	x	x	x	x	x	x	x	x
Drug admin.		x	x	x	x	x	x	x	
Cognitive test.		x			x			x	
Telephone contact						x	x	x	

Efficacy Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint was the change from baseline in the total PANSS score at the endpoint visit. The PANSS consists of 30 symptom items, each rated on a 7-point scale from 1 to 7. The maximum total score on the PANSS is 210. PANSS scores were not to be computed if more than 5 items were missing at a given assessment. If five or fewer items were missing, then the total PANSS scores for individual subjects were computed in the following manner:

$$\frac{\text{Total score for non-missing items X total number of PANSS items (30)}}{\text{Number of non-missing PANSS items}}$$

Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint was the change from baseline in the CGI-I score at the endpoint visit.

Non-Key Secondary Efficacy Endpoints

The following exploratory secondary endpoints were not accepted by the Division as valid key secondary endpoints: 1) the change from baseline on PANSS subscales (Positive, Negative, and General Psychopathology); 2) the change in total PANSS score at each visit (1, 2, 3, 4, 5, 6/last visit): and 3) Responder analyses, based on $\geq$ 30% or $\geq$ 20% reduction in PANSS score.

Primary Pre-specified Statistical Analysis Plan

The prespecified, primary analysis was a comparison between the asenapine and placebo groups of the changes in mean PANSS score from baseline to endpoint, using a last-observation-carried-forward (LOCF) technique. All missing data on a specific post-baseline efficacy assessment within the scheduled treatment period (plus the allowed time frame of 3 days) was replaced by the last available observed post-baseline value before that specific visit.

The group mean differences were tested using an ANOVA, with treatment and site as factors. The comparison between the asenapine and placebo groups was performed using the t-test. The 95% confidence intervals for the difference in the means were calculated using the t-test and the model-based estimated standard error. The treatment by site interaction was also examined. A comparison of efficacy between the risperidone group the placebo group also was performed using the same method described above.

Although the sponsor has claimed in the NDA submission that the MMRM analysis had replaced the LOCF analysis as the primary analysis, clearly the MMRM analysis was a post-hoc analysis. Based on the study protocol, the LOCF analysis was specified as the primary analysis.

Baseline Demographics and Features of Illness

There were no significant differences in baseline characteristics among treatment groups. The mean age of the asenapine group (38) was slightly lower than the placebo and risperidone groups (42 and 43, respectively). However, the median ages were similar (39, 42, and 41, respectively). The mean and median weights were comparable (89, 90, and 85 kg; and 84, 84, and 82 kg, respectively). The mean and median heights were very similar among treatment groups. The male: female ratio was comparable between the asenapine and placebo groups (78:22% and 79:21%). In the risperidone group, the male to female ratio was 61:39%. The ethnic background of the treatment groups was comparable among treatment groups. The ratio of Black: White: Other: Asian was 47: 42: 10: 0 in the asenapine group; it was 52: 32: 16: 0 in the placebo group; and it was 44: 42: 10: and 3 in the risperidone group. The majority of subjects were unemployed (97%, 92%, and 91% in the asenapine, placebo, and risperidone groups, respectively). The majority of subjects were smokers (83%, 82%, and 71% in the asenapine, placebo, and risperidone groups, respectively).

The baseline severity of illness, as measured by the total PANSS score, was quite comparable among treatment groups. For the placebo, asenapine, and risperidone groups, the baseline total PANSS scores were 92.43, 96.48, and 92.18, respectively.

The majority of subjects had a diagnosis of Paranoid Schizophrenia (86%, 98%, and 86% in the asenapine, placebo, and risperidone groups, respectively). Most subjects had a previous episode of Schizophrenia (98%, 98%, and 100% in the asenapine, placebo, and

risperidone groups, respectively). The duration of the current psychotic episode was similar among treatment groups (most commonly 2 to 4 weeks).

Disposition of Subjects

A total of 182 subjects were randomized to treatment. There were 60, 60, and 62 subjects randomized to the asenapine, placebo, and risperidone groups, respectively. One subject in each of the asenapine and placebo groups did not receive treatment with study drug. One of these subjects experienced an exacerbation of symptoms, and one subject refused medication during the washout period. A total of 73% of subjects completed the trial. The proportion of subjects who discontinued was relatively high, especially in the placebo (58%) and risperidone (66%) groups. In the asenapine group, 54% of subjects discontinued. The disposition of subjects in Study 41004 is illustrated in the table below.

	ASENAPINE	PLACEBO	RISPERIDONE	TOTAL
Randomized subjects	60	60	62	182
Treated subjects	59	59	62	180
Discontinued	32 (54)	34 (58)	41 (66)	107 (59)
Completed	27 (46)	25 (42)	21(34)	73(41)

Reasons for Discontinuation

For all treatment groups, the most common reason for discontinuation was "Other." In the placebo, asenapine, and risperidone treatment groups, "Other" was the listed reason for discontinuation for 26%, 27%, and 24% of subjects, respectively. Under the "Other" category, withdrawal of consent was the most common reason for discontinuation.

Discontinuations categorized as Lack of Efficacy were less common in the asenapine group (15%) compared to the placebo and risperidone groups (29% and 27%, respectively). The proportions of subjects who discontinued due to Adverse Event were comparable between the placebo and asenapine groups (11% and 12%, respectively). The table below outlines the most common reasons for discontinuation.

REASON FOR DISCONTINUATION	ASENAPINE	PLACEBO	RISPERIDONE	TOTAL
Adverse event	7 (12)	7 (11)	4 (7)	18 (10)
Lack of efficacy	9 (15)	18 (29)	16 (27)	43 (24)
Other reasons*	16 (27)	16 (26)	14 (24)	46 (26)
*For "other reasons," the most common reason was Withdrew Consent				

Efficacy Results in Study 041004

The table below illustrates the primary efficacy results for the LOCF analysis in Study 041004. The baseline mean PANSS scores were quite comparable among the placebo, asenapine, and risperidone groups (92.43, 96.47, and 92.18, respectively). In the placebo group, the change in mean total PANSS score was – 4.64 (a 5% reduction). For the asenapine group, the change in mean PANSS score was – 14.37 (a 15% reduction). The difference in PANSS score changes between the asenapine and placebo group (- 9.73) was statistically significant (p = 0.007). This estimated treatment effect size (placebo-subtracted change in PANSS score of - 9.73 points) is modest; however, it is consistent with effect sizes observed in other trials in acute Schizophrenia. Furthermore, such an effect size can be clinically significant for patients.

In the risperidone group, the change in mean total PANSS score was – 10.05 (a reduction of 11%). Compared to placebo, this change was not statistically significant (p = 0.125). The placebo-subtracted change in mean PANSS score was approximately – 5.4.

The results of the MMRM analysis provide supportive evidence for the efficacy of asenapine in the treatment of Schizophrenia. The difference in PANSS score changes between the placebo and asenapine groups (-11.33 points) was statistically significant (p = 0.018). As in the LOCF analysis, the difference between the risperidone and placebo groups (-7.72) was not statistically significant (p = 0.104). Finally, the observed case analysis was not supportive of the primary efficacy results.

STUDY 041004	RESULTS OF EFFICACY ANALYSES- CHANGE IN MEAN TOTAL PANSS SCORE			
Analysis	Parameter	Placebo	Asenapine	Risperidone
	Baseline Mean PANSS	92.43	96.47	92.18
LOCF	Mean change	−4.64	−14.37	−10.05
	S.E.	2.53	2.58	2.59
	Diff. vs. placebo	--	−9.72	−5.41
	S.E. (Diff.)	--	3.53	3.51
	P-value		**0.007**	0.125
MMRM	Mean change	−8.5	−19.8	−16.2
	S.E.	3.41	3.25	3.28
	Diff. vs. placebo	--	−11.33	−7.72
	S.E. (Diff.)	--	4.68	4.69
	P-value		**0.018**	0.104
OC	Mean change			
	S.E.			
	Diff. vs. placebo	--	-7.13	-5.74
	S.E. (Diff.)	--	5.00	5.11
	P-value		0.1592	0.2657

The table below illustrates the changes in mean PANSS scores over time (at each visit). One should note that this analysis was not prospectively accepted by the Division. Furthermore, this analysis did not adjust for multiple comparisons. Nevertheless, there is some evidence that the difference in treatment effects between asenapine and placebo was significant by the end of Week 2, and the differences were significant at every week

thereafter. In contrast, the differences in treatment effects between the risperidone and placebo groups were not statistically significant at any time point.

LOCF PANSS RESULTS OVER TIME IN STUDY 041004				
Visit		Asenapine (n= 58)	Placebo (n = 60)	Risperidone (n = 56)
Baseline	n	58	60	56
	Mean PANSS	96.48	92.43	92.18
Visit 1	n	58	60	56
	Δ PANSS	−6.22	−3.88	−5.61
	p-value	0.277		0.3922
Visit 2	n	58	60	56
	Δ mean PANSS	−11.31	−5.52	−8.25
	p-value	**0.0319**		0.345
Visit 3	n	58	60	56
	Δ mean PANSS	−16.91	−6.38	−10.77
	p-value	**0.001**		0.202
Visit 4	n	58	60	56
	Δ mean PANSS	−16.88	−6.55	−10.25
	p-value	**0.0025**		0.305
Visit 5	n	58	60	56
	Δ mean PANSS	−15.98	−4.70	−10.50
	p-value	**0.0012**		0.1013
Visit 6/ Early term.	n	58	60	56
	Δ mean PANSS	−15.86	−5.27	−10.93
	p-value	**0.0024**		0.1186

Responder Analyses

The sponsor performed several responder analyses, defining "response" as a particular percentage of reduction in total PANSS score for individual subjects. The endpoints were: 1) ≥ 20% reduction in PANSS score; and 2) ≥30% reduction in PANSS score. The responder analyses were not pre-specified, primary efficacy analyses; nevertheless, the results are supportive of the primary efficacy results. In the sponsor's responder analyses, the proportion of subjects in the asenapine group who met criteria for response was greater than the proportion of placebo-treated subjects who met responder criteria. Using the criterion of a PANSS score reduction of at least 20%, the majority of asenapine group (53%) were responders, compared to 35% in the placebo group. In this analysis, 50% of the risperidone group were responders. Using the criterion of a PANSS score reduction of at least 30%, a greater proportion of the asenapine group were responders (38%), compared to the placebo group (25%). In the risperidone group, 39% of subjects were responders.

SPONSOR'S RESPONDER ANALYSIS- STUDY 041004			
RESPONSE CRITERION	ASENAPINE 5 MG BID (N = 58)	RISPERIDONE 6 MG (N = 56)	PLACEBO (N = 60)
≥ 20% reduction in	31 (53)	28 (50)	21 (35)

total PANSS score			
≥ 30% reduction	22 (38)	22 (39)	15 (25)

The table below illustrates the statistical reviewer's results of the PANSS responder analysis, based on the percentage of PANSS score reduction at Visit 6 (or Endpoint). Compared to the sponsor's results, the results below indicate that a smaller proportion of the asenapine and placebo were responders by both criteria. Furthermore, the differences between the asenapine and placebo group were smaller, and the differences were not statistically significant.

FDA STATISTICAL REVIEWER'S RESPONDER ANALYSIS- STUDY 041004						
	ASENAPINE (N=57)		RISPERIDONE (N=56)		PLACEBO (N=59)	
	n	%	n	%	n	%
≥20% reduction	23	40	22	39	15	25
P-value (vs. Placebo)*	0.11		0.14		NA	
≥30% reduction	12	21	10	18	7	12
P-value (vs. Placebo)*	0.19		0.35		NA	

* P-values were obtained by CMH stratified by Center

Other Secondary Efficacy Analyses

The table below illustrates the results of additional secondary efficacy endpoints. Only the CGI-I was accepted as a key secondary endpoint. The other analyses were considered exploratory. The CGI-I analysis was based on the change from baseline to endpoint in the mean CGI-I score. The difference in the mean CGI-I score change between the asenapine and placebo groups was statistically significant, favoring treatment with asenapine (p = 0.04). The difference between the risperidone and placebo group was also statistically significant, favoring treatment with risperidone (p = 0.024).

Exploratory efficacy results based on changes in PANSS subscales scores were also supportive of the primary efficacy results. For the PANSS Positive Syndrome subscale, the PANSS Negative Syndrome subscale, and the General Psychopathology subscale, the differences between the asenapine and placebo groups were statistically significant. The difference between the risperidone and placebo groups was significant only for changes on the Positive Syndrome subscale.

Table 3.1.2.5 Sponsor's Analysis Results for Secondary Parameters for Study 41004

VARIABLE	ASENAPINE (N=58)	RISPERIDONE (N=56)	PLACEBO (N=60)
CGI- Improvement Score			
Mean (SE)	3.25 (0.15)	3.21 (0.14)	3.73 (0.18)
P-Value (vs. Placebo)	0.04	0.024	
Positive PANSS Total Score			

Mean Change from Baseline to Visit 6 (SE)	-5.48 (0.84)	-5.13 (0.95)	-2.50 (0.75)
P-Value (vs. Placebo)	0.01	0.03	
Negative PANSS Total Score			
Mean Change from Baseline to Visit 6 (SE)	-3.21 (0.71)	-1.05 (0.75)	-0.55 (0.74)
P-Value (vs. Placebo)	0.01	0.61	
General Psychopathology PANSS			
Mean Change from Baseline to Visit 6 (SE)	-7.17 (1.34)	-4.75 (1.31)	-2.22 (1.13)
P-Value (vs. Placebo)	0.005	0.17	
Mean Change from Baseline to Visit 6 (SE)			
P-Value (vs. Placebo)			

6.1.2.2 REVIEW OF STUDY 041023

In Study 041023, there was a screening, a 2-day taper period and a 6-week active treatment period. The active treatment period was initiated on day 1 following randomization of subjects to one of the following treatments in a 1:1:1:1 distribution: asenapine 5 BID, asenapine 10 mg BID, haloperidol 4 mg BID, or placebo.

Subjects were to be hospitalized for the first 14 days of the 6-week trial period. Hospitalization beyond 2 weeks was to be approved by the sponsor. For the remainder of the trial, subjects were to continue as outpatients. Subjects who completed the protocol were offered the option of participating in the long-term extension trial (041513), in which they would have the opportunity to continue treatment for an additional 52 weeks. Subjects who did not continue in the extension trial (whether they completed the present 6-week trial or discontinued prematurely) had a follow-up visit 7 days after their end-of-treatment visit.

Efficacy Measures and Analyses

The primary efficacy measure was the Positive and Negative Syndrome Scale (PANSS). The key secondary efficacy measures included Clinical Global Impression of Severity of Illness (CGI-S) and the Clinical Global Impression of Improvement (CGI-I)

The primary efficacy endpoint was defined as the change in the PANSS total score from baseline to endpoint (in an LOCF analysis). The PANSS total score for each subject was calculated as the sum of the ratings assigned to each of the 30 PANSS items. If more than 5 PANSS individual items were missing, the total PANSS scores would not be computed. If 5 or fewer items of the PANSS were missing, then the total PANSS scores will be prorated.

The primary analysis was based on the intent-to-treat group. The ANCOVA model was used to assess treatment differences. The primary treatment comparison between groups was based on the differences in the model based least square means (LSMEANS).

Missing values for PANSS total score were replaced using the LOCF method described above. Summary statistics were presented by treatment for PANSS total score at baseline and endpoint and for change from baseline in PANSS total score to endpoint. The assumptions of the ANCOVA model were checked as described in the SAP.

In order to assess the robustness of the results against potential bias caused by missing data due to dropouts, supportive analyses based on the intent-to-treat group were conducted using two methods: 1) the previously defined ANCOVA model using observed cases (OC); and 2) a mixed model analysis using repeated measures (MMRM).

All hypothesis testing was conducted using two-sided tests with alpha = 0.05 level of significance. The primary comparisons for assessing the efficacy of treatment with asenapine on symptoms of Schizophrenia were between each asenapine treatment group and the placebo group for the primary endpoint. A Hochberg adjustment method was used to adjust the two comparisons. The haloperidol group versus placebo group comparison was made for assessing assay sensitivity only. Comparisons between each asenapine group and the placebo treatment group for all other efficacy endpoints were considered secondary and were used to support the findings of the primary analysis.

Efficacy Results for Study 41023

Patient Dispositions and Baseline Demographic Characteristics

A total of 513 subjects were screened to determine their eligibility for entry into the trial. Of the 513 screened subjects, 55 subjects were withdrawn before randomization, including 32 subjects who did not meet the entry criteria, 21 subjects who withdrew consent, 1 subject who had an adverse event, and 1 subject who was lost to follow-up. The remaining 458 subjects were randomized to treatment with placebo (N=123), asenapine 5 mg BID (N=114), asenapine 10 mg BID (N=106), or haloperidol 4 mg BID (N=115).

Of the 458 randomized subjects, 455 subjects were treated and comprised the all subjects-treated group (123, placebo; 111, asenapine 5 mg BID; 106, asenapine 10 mg BID; 115, haloperidol). The intent-to-treat group consisted of 448 subjects (122, placebo; 109, asenapine 5 mg BID; 105, asenapine 10 mg BID; 112, haloperidol).

The table below illustrates the sponsor's summary of subject disposition.The proportions of subjects in the placebo, asenapine 5 mg BID, asenapine 10 mg BID, and haloperidol treatment groups who withdrew from the trial during the double-blind treatment period were 43.1%, 36.9%, 33.0%, and 40.9%, respectively. The most common reason for discontinuation in the asenapine 5 mg BID, asenapine 10 mg BID, and haloperidol treatment groups was withdrawal of consent (18.9%, 10.4%, and 22.6%, respectively). In the placebo treatment group, the most common reason for withdrawing from the trial was lack of efficacy (17.9%).

Subject Disposition for Study 41023

Subject Disposition	Placebo	Asenapine 5mg BID	Asenapine 10 mg BID	Haloperidol 4 mg BID	All Subjects
Randomized, N	123	114	106	115	458
All-Subjects-Treated, N	123	111	106	115	455
Intent-to-Treat, N	122	109	105	112	448
Withdrew from Trial, n (%)	53 (43.1)	41 (36.9)	35 (33.0)	47 (40.9)	176 (38.7)
Adverse Event	13 (10.6)	5 (4.5)	10 (9.4)	12 (10.4)	40 (8.8)
Schizophrenia Worsening	9 (7.3)	2 (1.8)	9 (8.5)	6 (5.2)	26 (5.7)
Lack of Efficacy	22 (17.9)	12 (10.8)	8 (7.5)	4 (3.5)	46 (10.1)
Withdrew Consent	13 (10.6)	21 (18.9)	11 (10.4)	26 (22.6)	71 (15.6)
Lost to Follow-Up	2 (1.6)	3 (2.7)	2 (1.9)	4 (3.5)	11 (2.4)
Other	3 (2.4)	0 (0)	4 (3.8)	1 (0.9)	8 (1.8)
Insufficient Therapeutic Effect	31 (25.2)	14 (12.6)	17 (16.0)	10 (8.7)	72 (15.8)

As illustrated below, the asenapine 5 mg BID and 10 mg BID treatment groups included a higher proportion of males (68% and 63%, respectively) than the placebo (52%) and haloperidol (55%) treatment groups. Except for gender, the four treatment groups were well balanced with respect to demographic characteristics at baseline. Most subjects were either Caucasian (62%) or Black (26%). Subjects ranged in age from 18 to 70 years, and the overall mean age was 39 years. Subjects' BMI ranged from 17 to 51 kg/m^2; the mean BMI was 26) kg/m^2.

Summary of Demographic and Other Characteristics for Study 41023

	Placebo (N=123)	Asenapine 5 mg BID (N=111)	Asenapine 10 mg BID (N=106)	Haloperidol 4 mg BID (N=115)	All Subjects (N=455)
Characteristics					
Gender, n (%)					
Male	64 (52.0)	75 (67.6)	67 (63.2)	63 (54.8)	269 (59.1)
Female	59 (48.0)	36 (32.4)	39 (36.8)	52 (45.2)	186 (40.9)
Premenopausal	45 (76.3)	28 (77.8)	33 (84.6)	36 (69.2)	142 (76.3)
Postmenopausal	14 (23.7)	8 (22.2)	6 (15.4)	16 (30.8)	44 (23.7)
Race, n (%)					
Caucasian	76 (61.8)	71 (64.0)	67 (63.2)	68 (59.1)	282 (62.0)
Black	31 (25.2)	22 (19.8)	29 (27.4)	35 (30.4)	117 (25.7)
Asian	11 (8.9)	11 (9.9)	10 (9.4)	12 (10.4)	44 (9.7)
Other	5 (4.1)	7 (6.3)	0 (0.0)	0 (0.0)	12 (2.6)
Age category, n (%)					
18 – 64 years	122 (99.2)	108 (97.3)	104 (98.1)	114 (99.1)	448 (98.5)
≥ 65 years	1 (0.8)	3 (2.7)	2 (1.9)	1 (0.9)	7 (1.5)
Age, years					
Mean (SD)	40.1 (11.61)	38.0 (11.99)	37.1 (10.92)	39.0 (11.18)	38.6 (11.45)
Median	42.0	38.0	37.0	40.0	39.0
Range	18, 70	18, 69	19, 68	18, 67	18, 70
Weight, kg					
Mean (SD)	74.5 (17.08)	77.6 (17.43)	77.8 (21.04)	76.5 (17.42)	76.5 (18.23)
Median	73.5	75.8	76.4	75.5	75.0
Range	45, 120	48, 135	39, 154	42, 128	39, 154
BMI, kg/m^2					
Mean (SD)	26.0 (5.08)	26.7 (5.10)	26.2 (5.77)	26.5 (5.20)	26.3 (5.27)
Median	25.3	26.3	25.4	25.7	25.6
Range	17, 40	18, 39	19, 51	18, 42	17, 51

Sponsor's Efficacy Results for Primary Parameter

The primary efficacy analysis was a comparison of the LS mean change from baseline to endpoint (LOCF) in the PANSS total score in each asenapine treatment group versus the placebo treatment group using an ANCOVA model. The table below illustrates the sponsor's analysis results for the primary endpoint. At endpoint, treatment with asenapine 5 mg BID was statistically significantly superior to placebo. However, asenapine 10 mg BID did not demonstrate significant efficacy compared to placebo. Haloperidol treatment was statistically significantly superior to treatment with placebo.

Sponsor's Analysis Results for Change in PANSS Score (LOCF and MMRM Data for Study 41023)

NOP	Treatment Methods		Placebo	Asenapine 5 mg BID	Asenapine 10 mg BID	Haloperidol
041023	LOCF	Mean Change	-10.7	-16.2	-14.9	-15.4
		S.E.	1.57	1.66	1.69	1.63
		Diff. vs. placebo	-	-5.48	-4.11	-4.70
		SE (Diff)	-	2.23	2.25	2.21
		P-value		0.014	0.068	0.034
	MMRM	Mean Change	-14.6	-21.3	-19.4	-20.0
		S.E.	1.61	1.70	1.68	1.70
		Diff. vs. placebo	-	-6.77	-4.86	-5.47
		SE (Diff)	-	2.33	2.32	2.33
		P-value		0.004	0.038	0.020

At baseline, the mean total PANSS scores were quite similar among treatment groups. The baseline mean PANSS scores for the placebo, asenapine 5 mg BID, asenapine 10 mg BID, and haloperidol were 89, 88.9, 89.4, and 88.5, respectively. In the placebo group, the change in mean PANSS score at endpoint was −10.7 points. The changes in PANSS scores for the asenapine 5 mg BID, asenapine 10 mg BID, and haloperidol groups were −16.2, −14.9, and −15.4. Thus, the placebo-subtracted differences for the asenapine 5 and 10 m groups and the haloperidol group were −5.5, −4.2, and − 4.7. The estimated sizes of the apparent treatment effects were modest in these 3 treatment groups. However, an improvement of approximately 5 points on the PANSS could be

The observed-case analysis performed by the statistics reviewer confirmed the findings of the LOCF analysis for asenapine 5 mg BID. The observed-case analysis indicated that asenapine 5 mg BID and 10 mg BID, but not haloperidol, separated from placebo at day 42. Table 3.1.4.4 shows the sponsor's observed case analysis results at Day 42.

Sponsor's Observed Case Analysis Results at Day 42 for Study 41023

Variable	Placebo (N=68)	Asenapine 5 mg BID (N=70)	Asenapine 10 mg BID (N=67)	Haloperidol 4 mg BID (N=64)
Change from Baseline in Total PANSS score (SE)	-19.1 (1.46)	-23.9 (1.46)	-23.2 (1.45)	-21.9 (1.49)
P-value (vs. Placebo)		0.0171	0.0398	0.1567

Source: Sponsor's Table 11.5.1.1.4 of CSR

Sponsor's Secondary Efficacy Results

The sponsor's secondary analysis results for the CGI data are illustrated in the table below. The CGI-I and CGI-S results were significant for the asenapine 5 mg BID group but not for the asenapine 10 mg BID group. The results for the haloperidol group were also statistically significant for the CGI-I analysis.

Variable	Placebo (N=122)	Asenapine 5 mg BID (N=109)	Asenapine 10 mg BID (N=105)	Haloperidol 4 mg BID (N=112)
CGI-Severity of Illness Score				
LS Mean Change from Baseline to Endpoint (SE)	-0.63 (0.092)	-0.93 (0.098)	-0.86 (0.100)	-0.93 (0.096)
P-Value (vs. Placebo)		0.0219	0.0818	0.0220
CGI-Global Improvement Score*				
Responders, n (%)	41 (33.6)	52 (47.7)	46 (44.2)	49 (43.8)
Non-responders, n (%)	81 (66.4)	57 (52.3)	58 (55.8)	63 (56.3)
P-Value (vs. Placebo)		0.0272	0.1348	0.1016

* CGI-I responder was defined as a subject with a CGI-I score of 1 or 2.

Efficacy Conclusions

Based on the LOCF analysis results, treatment with asenapine 5mg BID was statistically significantly superior to treatment with placebo. In the primary LOCF analysis, asenapine 10 mg BID was not statistically significantly superior to treatment with placebo. However, the treatment effect of asenapine 10 mg BID was statistically significant using the mixed models (MMRM) analysis, which may be a more appropriate model, given the pattern of subject discontinuations in the study. On the other hand, the statistics reviewer, Dr. Chen concluded that the results of the LOCF model used in the primary analysis of the Study 041023 are acceptable.

Sponsor's MMRM analysis results for Total PANSS Scores for Study 41023

Variable	Placebo (N=122)	Asenapine 5 mg BID (N=109)	Asenapine 10 mg BID (N=105)	Haloperidol 4 mg BID (N=112)
LS Mean Change (SE)	-14.6 (1.61)	-21.3 (1.70)	-19.4 (1.68)	-20.0 (1.70)
Difference vs. Placebo (SE)		-6.77 (2.33)	-4.86 (2.32)	-5.47 (2.33)
P-value		0.004	0.038	0.020

6.1.2.3 REVIEW OF STUDY 041021

Study 041021 was entitled: "A multicenter, randomized, double-blind, fixed-dose, 6-week trial of the efficacy and safety of asenapine compared with placebo using olanzapine positive control in subjects with an acute exacerbation of schizophrenia." The study was conducted at 45 clinical sites in the U.S. and Russia. The study began on May 27, 2005, and it was completed on May 30, 2006. The subject selection criteria were essentially identical to the selection criteria in Study 041004. However, in Study 041021, subjects must not have had a substance use disorder for 6 months (as opposed to one month in Study 041004).

Objectives

The primary objective of the trial was to compare the effectiveness of asenapine 5 and 10 mg BID with placebo in the treatment of Schizophrenia, as measured by the Positive and Negative Syndrome Scale (PANSS). The secondary objective was to compare the effectiveness of asenapine 5 and 10 mg BID with placebo in the treatment of negative symptoms of Schizophrenia, as measured by the PANSS negative symptom subscale.

Study Design

This was a Phase 3, multicenter (U.S.), randomized, double-blind, double-dummy, placebo-controlled and active-controlled (olanzapine), fixed-dose, six-week efficacy and safety study of asenapine (5 mg BID and 10 mg BID) in the acute treatment of Schizophrenia. The study included a screening period, a washout period (0 to 2 days), a treatment period (including a 21-day inpatient phase and a 21-day outpatient phase), and a follow-up visit (for subjects who did not enter extension study).

Subjects who met screening criteria were admitted to the hospital for the single-blind washout period. At the completion of the washout period, subject who met entrance criteria were randomized to one of four treatment groups, in a ratio of 1:1:1:1: 1) asenapine 5 mg BID; 2) asenapine 10 mg BID; 3) placebo BID; or 4) olanzapine (15 mg/day). Subjects randomized to the asenapine 10 mg and olanzapine 15 mg groups had study medication titrated over the first 2-7 days of the study. Subjects in the asenapine 5 mg BID group began immediately on Day 1 with 5 mg BID. Subjects in the asenapine 10 mg group began with asenapine 5 mg BID on Day 1. On Day 2, they reached the target dose of 10 mg BID.

Group	Drug	Dosage form	Dose and administration
1	Asenapine 5 mg BID	Fast-dissolving tablets	5 mg BID SL
2	Asenapine 10 mg BID	Fast-dissolving tablets	5 mg BID SL on Day 1, then 10 mg BID SL
3	Olanzapine 15 mg QD	Film-coated oral tablets	10 mg QD PO on days 1-7, then 15 mg QD PO
4	Placebo BID	Film-coated oral tablets and Fast-dissolving tablets	One SL fast-dissolving tablet BID One PO film-coated tablet BID

Efficacy Results

This is a negative study in which asenapine did not demonstrate efficacy but the active-control (olanzapine) did.

NOP	Treatment Methods		Placebo	Asenapine 5 mg BID	Asenapine 10 mg BID	Olanzapine
041021	LOCF	Mean Change	-11.14	-14.51	-13.44	-16.54
		S.E.	1.64	1.59	1.63	1.64
		Diff. vs. placebo	-	-3.38	-2.30	-5.40
		SE (Diff)	-	2.21	2.24	2.24
		P-value		0.128	0.305	0.017
	MMRM	Mean Change	-13.2	-16.4	-17.1	-19.9
		S.E.	1.95	1.83	1.93	1.9
		Diff. vs. placebo	-	-3.12	-3.88	-6.68
		SE (Diff)	-	2.66	2.73	2.71
		P-value		0.241	0.157	0.015

The mean PANSS scores at baseline were comparable among treatment groups. The mean scores for the placebo, asenapine 5 mg BID, asenapine 10 mg BID, and olanzapine were 93.7, 90.8, 93.2, and 92.6, respectively. The change from baseline to endpoint for the placebo group was −11.14. The changes in PANSS score for the asenapine and olanzapine groups were −14.51, −13.44, and −16.54, respectively. Thus, the estimated, placebo-subtracted treatment effects were −3.37 points for asenapine 5 mg BID, −2.3 for the asenapine 5 mg BID, and −5.4 for the olanzapine group. The treatment effects were not statistically significant in the asenapine groups. The effect was significant in the olanzapine group. Treatment with asenapine also did not demonstrate efficacy using an MMRM analysis.

6.1.2.4 REVIEW OF STUDY 041022

Study 041022 was entitled: "A multicenter, randomized, double-blind, flexible-dose, 6-week trial of the efficacy and safety of asenapine compared with placebo using olanzapine positive control in subjects with an acute exacerbation of schizophrenia." The study was conducted at 30 centers, including 23 in the U.S. and 5 in Ukraine, and two in Russia. The study began in February 2005, and it was completed in February 2006.

The primary objective of this trial was to compare the effectiveness of asenapine (administered as flexible-dose 5-10 mg BID) with placebo in the treatment of schizophrenia. The key secondary objective was to compare the effectiveness of asenapine 5-10 mg BID with placebo in the treatment of negative symptoms of schizophrenia.

Design

The trial was a multicenter, randomized, double-blind, double-dummy, flexible-dose, placebo- and positive-controlled (olanzapine) efficacy trial in subjects with a DSM-IV-TR™ diagnosis of Schizophrenia who had an acute exacerbation of psychotic illness. This trial consisted of screening, a 2-day taper period (eligible severely ill subjects were permitted to be randomized immediately at the discretion of the investigator), and a six-week active treatment period. The active treatment period was initiated on Day 1 following randomization of subjects to one of the following treatments in a 1:1:1 distribution: asenapine 5-10 mg BID, olanzapine 10 to 20 mg QD, or placebo.

Subjects were to be hospitalized for the first 2 weeks (14 days) of the 6-week trial period. Hospitalization beyond 2 weeks was to be approved by the sponsor. For the remainder of the trial, subjects were to continue as outpatients. Subjects who completed the protocol were offered the option of participating in the long-term extension trial (041512), where they would have the opportunity to continue to be treated for an additional 52 weeks. Subjects who did not continue in the extension trial (whether they completed the present 6-week trial or discontinued prematurely) had a follow-up visit 7 days after their end-of-treatment visit.

Study Drug Dosing

During the first 7 days of the double-blind treatment period, subjects randomized to the asenapine treatment group received 5 mg asenapine BID (at approximately 8 AM and 8 PM), and subjects randomized to the olanzapine treatment group received 10 mg olanzapine QD (at approximately 8 AM). At the Day 7 visit, the dose could be increased in an increment of 5 mg BID for asenapine or 5 mg QD for olanzapine, or the dose could remain the same. At each visit thereafter, doses could be increased in 5 mg increments (to a maximum of asenapine 10 mg BID or olanzapine 20 mg QD), decreased (to a minimum of asenapine 5 mg BID or olanzapine 10 mg QD), or remain the same. Decisions to change the dose were to be made by the investigator at the subject's visit, and were to be based on symptomatology and tolerability. Dose decreases could be made between visits only if intolerable adverse events prohibited a delay. The first dose of trial medication was administered on the morning of Day 1. The maximum duration of treatment with trial medication was 42 days.

The table below summarizes the disposition of subjects in Study 041022.

Subject Disposition	Placebo	Asenapine 5mg/10mg BID	Olanzapine 10mg-20mg QD	All Subjects
Subjects Screened, N				347
Withdrew During Screening, N				70
Did not meet criteria				48
Adverse Event				1
Withdrew Consent				21
Randomized Subjects, N [a,b]	93	91	93	277
All-Subjects-Treated, N [a,c]	93	90	92	275
Intent-to-Treat, N [a,d]	89	85	85	259
Withdrew During Double-Blind, n (%) [e]	45 (48.4)	48 (53.3)	49 (53.3)	142 (51.6)
Adverse Event	5 (5.4)	6 (6.7)	11 (12.0)	22 (8.0)
Worsening of schizophrenia: Yes	4 (4.3)	3 (3.3)	6 (6.5)	13 (4.7)
Worsening of schizophrenia: No	1 (1.1)	3 (3.3)	5 (5.4)	9 (3.3)
Lack of Efficacy	12 (12.9)	4 (4.4)	15 (16.3)	31 (11.3)
Withdrew Consent	12 (12.9)	26 (28.9)	17 (18.5)	55 (20.0)
Lost to follow-up	9 (9.7)	8 (8.9)	4 (4.3)	21 (7.6)
Other	7 (7.5)	4 (4.4)	2 (2.2)	13 (4.7)
Insufficient therapeutic effect [f]	16 (17.2)	7 (7.8)	21 (22.8)	44 (16.0)
Completed Double-Blind	48 (51.6)	42 (46.7)	43 (46.7)	133 (48.4)
Continued into extension trial(041512)	28 (30.1)	21 (23.3)	26 (28.3)	75 (27.3)
Did not enter extension(041512)	20 (21.5)	21 (23.3)	17 (18.5)	58 (21.1)
Did not meet criteria	1 (1.1)	1 (1.1)	2 (2.2)	4 (1.5)
Did not Consent	19 (20.4)	20 (22.2)	14 (15.2)	53 (19.3)
Missing	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.4)

Efficacy Results in Study 041022

Study 41022 is a failed study. Neither asenapine nor the active-control (olanzapine) demonstrated efficacy. Furthermore, the change in mean total PANSS score was greater for the placebo group than for the asenapine group. Asenapine also did not demonstrate efficacy using an MMRM analysis.

NOP	Methods	Treatment	Placebo	Asenapine 5-10 mg BID	Olanzapine
041022	LOCF	Mean Change	-9.89	-9.44	-11.20
		S.E.	1.74	1.73	1.72
		Diff. vs. placebo	-	0.45	-1.31
		SE (Diff)	-	2.36	2.36
		P-value		0.848	0.579
	MMRM	Mean Change	-15.6	-11.6	-15.9
		S.E.	2.03	2.11	2.12
		Diff. vs. placebo	-	3.99	-0.25
		SE (Diff)	-	2.92	2.93
		P-value		0.174	0.932

At baseline, the mean PANSS scores in the placebo, asenapine, and olanzapine groups were comparable (85.8, 87, and 86.9, respectively). For the placebo group, the change in mean PANSS from baseline to endpoint was −9.89 points. In the asenapine and olanzapine groups, the changes were −9.44 and −11.2 points, respectively. The differences between placebo and the two treatment groups were not statistically significant.

6.1.3 EFFICACY FINDINGS AND CONCLUSIONS

6.2 MANIA TRIALS (A7501004 and A7501005)

6.2.1 SUBJECT SELECTION (A7501004 and A7501005)

The subject selection criteria were identical in the two acute mania trials (A7501004 and A7501005).

6.2.1.1 Inclusion Criteria

1. Subjects must have been at least 18 years of age.
2. Subjects included males and females. Females must not have been pregnant or breastfeeding; they must have been of non-childbearing potential or they must have agreed to use a medically acceptable method of contraception.
3. Subjects had a diagnosis of Bipolar I Disorder, current manic or mixed episode, and they must have had a Young-Mania Rating Scale (YMRS) score of $\geq$ 20 at screening and baseline.
4. The current manic or mixed episode must have begun no more than 3 months prior to enrollment in the study.
5. Had a documented history of at least one previous moderate-severe manic or mixed episode (with or without psychotic features).
6. Must have discontinued psychotropic medication during the study (except for medications permitted per protocol).

6.2.1.2 Exclusion Criteria

1. Presence of an uncontrolled, unstable, or clinically significant medical condition That might interfere with participation in the study or interpretation of results.
2. Presence of clinically significant abnormality on physical examination, vital sign ECG, clinical laboratory monitoring.
3. Positive serum pregnancy test
4. narrow angle glaucoma
5. seizure disorder beyond childhood or treatment with anticonvulsants
6. Diagnosis of Schizophrenia, Schizoaffective Disorder, or other psychotic disorder
7. Primary psychiatric disorder other than Bipolar Disorder
8. Substance abuse or dependence within 3 months of beginning the study (except for nicotine)
9. At imminent risk of self-harm as defined by an InterSePT Scale for Suicide Thinking (ISST) (modified) score of 2 on item 7, 10, or 11 at screening or of harm to others;
10. Mental retardation or organic brain syndrome
11. History of rapid cycling. Rapid cycling was defined as four or more (including current episode) mood episodes during the previous 12 months that met both the duration and symptom criteria for a major depressive, manic, mixed, or hypomanic episode. Each previous episode was to be demarcated by either a

period of full remission or by a switch to an episode of the opposite polarity. Manic, hypomanic, and mixed episodes were counted as being on the same pole (eg, a manic episode immediately followed by a mixed episode counted as only 1 episode). Mood episodes directly caused by a substance (eg, cocaine, corticosteroids) or a general medical condition were not to be counted as a previous episode

12. previously participated in an asenapine trial;
13. taken an investigational drug within 30 days prior to baseline;
14. been judged by the investigator to be medically non compliant in the management of their disease;
15. judged by the investigator to be unable to reduce his or her daily benzodiazepine intake (as specified in the protocol) to a maximum of 4 mg per day of lorazepam (or the equivalent dose of another short-acting benzodiazepine);
16. lithium level greater than 0.6 mEq/L, a valproate level greater than 50 µg/mL, or a carbamazepine level greater than 4 µg /mL prior to baseline, or have taken lithium, valproate, or carbamazepine within 3 days of baseline;
17. history of hypersensitivity to, or neuroleptic malignant syndrome developing from, the administration of antipsychotic compounds;
18. history of tardive dyskinesia
19. known allergy or hypersensitivity to olanzapine or asenapine
20. substance-induced psychotic disorder or behavioral disturbance that was thought to be due to substance abuse
21. received clozapine for the treatment of bipolar disorder within 12 weeks or a monoamine oxidase inhibitor within 2 weeks prior to baseline
22. inability to discontinue any excluded medications.

6.2.2 STUDY DESCRIPTION AND DESIGN

Both studies were entitled: "A Phase III, Randomized, Placebo-Controlled, Double-Blind Trial Evaluating the Safety and Efficacy of Sublingual Asenapine vs. Olanzapine and Placebo in In-Patients with an Acute Manic Episode." Study A7501004 was carried out from 30 November 2004 until 29 April 2006. The study was conducted at 61 centers, including 32 in the US, 2 in Bulgaria, 6 in India, 2 Korea, 3 Malaysia, 3 Philippines, 2 Romania, 4 Russia, and 7 in the Ukraine. Study A7501005 was carried out from November 30, 2004 until April 29, 2006. The study was conducted at 55 centers (29 in the US, 2 in Bulgaria, 6 in India, 3 in Korea, 1 in Malaysia, 2 in the Philippines, 2 in Romania, 4 in the Russian Federation, 2 in Turkey, and 4 in Ukraine).

Objectives

The primary objective of both studies was to evaluate the efficacy of asenapine compared with placebo in the treatment of subjects with manic or mixed episodes associated with Bipolar I Disorder, as measured by the Young-Mania Rating Scale.

Secondary Objectives:

1) to evaluate the efficacy of asenapine compared to placebo in treating acute mania, as measured by the Clinical Global Impression-Bipolar Disorder scale (CGI-BP);
2) to assess the effect of asenapine treatment on depressive symptoms, as measured by the Montgomery-Asberg Depression Rating Scale (MADRS);
3) to assess the effect of asenapine treatment on psychotic symptoms, as measured by the Positive and Negative Syndrome Scale (PANSS);
4) to assess the effects of asenapine on other parameters as measured by: the Readiness for Discharge Questionnaire (RDQ), Short Form-36, Treatment Satisfaction Questionnaire for Medication (TSQM), a cognitive function testing battery, and safety and tolerability parameters
5) to characterize the population pharmacokinetics of asenapine and its major metabolite (Org 30526)

Study Design

The study design was identical for the two mania studies. They were Phase 3, multicenter, international, randomized, double-blind, double-dummy, placebo-controlled and active-controlled (olanzapine 5-20 mg QD), 3-week, flexible-dose studies of asenapine (5-10 mg BID) in the treatment of acutely manic subjects with a diagnosis of Bipolar I Disorder, Manic or Mixed Episode. Subjects were randomly assigned to receive asenapine, olanzapine, or placebo treatment in a ratio of 2:2:1. Subjects were confined as inpatients for at least the first 7 days of the treatment period. After 7 days, subjects could be discharged and treated as outpatients in the study, if the investigator judged the subject to be clinically stable.

The trial included (up to) a 7-day single-blind placebo run in period during which subjects experiencing a manic or mixed episode received single-blind placebo (placebo olanzapine). After placebo run in, the active treatment period was initiated on Day 1 with placebo, asenapine 10 mg BID, or olanzapine 15 mg QD. Thereafter, treatment continued with flexible dosing (asenapine 5- 10 mg BID, olanzapine 5-20 mg QD, or placebo). Subjects remained confined to an inpatient research facility for at least the first 7 days of active treatment (through Day 7), and were subsequently discharged if deemed clinically stable by the investigator. Subjects completing the trial were eligible for enrollment in an extension trial, Protocol A7501006.

Disposition of Subjects

In Study A7501004, a total of 488 subjects were randomized to treatment with study medication: 185 subjects to asenapine, 205 subjects to olanzapine, and 98 subjects to placebo. All randomized subjects received at least 1 dose of trial medication. A total of 342 subjects completed the trial. The proportion of patients who withdrew due to an adverse event related to the disease under study (Bipolar Disorder) was higher in asenapine group (9.2%) compared with olanzapine group (3.4%) and placebo (4.1%).

Table 1. Study 1004 Summary of subject disposition and discontinuation

	Placebo	Asenapine	Olanzapine	All Subjects
Patients Randomized	98	185	205	488
Intent-to-treat Population	94	183	203	480
Withdrawn during double-blind, n (%)	41 (41.8%)	61 (33.0%)	44 (21.5%)	146 (29.9%)
Adverse Event/SAE	4 (4.1%)	17 (9.2%)	7 (3.4%)	28 (5.7%)
Lack of Efficacy	14 (14.3%)	14 (7.6%)	13 (6.3%)	41 (8.4%)
Withdrew consent	13 (13.3%)	25 (13.5%)	15 (7.3%)	53 (10.9%)
Lost to follow-up	4 (4.1%)	1 (0.5%)	6 (2.9%)	11 (2.3%)
Other	6 (6.1%)	4 (2.2%)	3 (1.5%)	13 (2.7%)
Completed double-blind	57 (58.2%)	124 (67.0%)	161 (78.5%)	342 (70.1%)

Source: Clinical Study Report A7501004, Table 5 (pg. 77)

In Study A7501005, a total of 489 subjects were randomized to treatment with study medication: 194 subjects to asenapine, 191 subjects to olanzapine, and 104 subjects to placebo (refer to Table 2). Of these, 488 subjects received at least 1 dose of trial medication. A total of 338 subjects completed the trial. In the asenapine and olanzapine treatment groups, the most common reason for withdrawal was withdrawal of consent. The proportion of subjects who withdrew due to an adverse event/SAE is higher in the asenapine group: 10.3% asenapine-treated subjects, 4.2% olanzapine-treated subjects, and 6.7% placebo-treated subjects (see Table 2).

Table 2. Study 1005 Summary of subject disposition and discontinuation

	Placebo	Asenapine	Olanzapine	All Subjects
Patients Randomized	104	194	191	489
Intent-to-treat Population	103	189	188	480
Withdrawn during double-blind, n (%)	40 (38.55%)	72 (37.1%)	39 (20.4%)	151 (30.9%)
Adverse Event/SAE	7 (6.7%)	20 (10.3%)	8 (4.2%)	35 (7.2%)
Lack of Efficacy	17 (16.3%)	16 (8.2%)	11 (5.8%)	44 (9.0%)
Withdrew consent	13 (12.5%)	28 (14.4%)	16 (8.4%)	57 (11.7%)
Lost to follow-up	2 (1.9%)	5 (2.6%)	2 (1.0%)	9 (1.8%)
Other	1 (1.0%)	3 (1.5%)	2 (1.0%)	6 (1.2%)
Completed double-blind	64 (61.5%)	122 (62.9%)	152 (79.6%)	338 (69.1%)

Source: Clinical Study Report A7501005, Table 5 (pg. 74)

Baseline Features

In Study A7501004, the treatment groups were comparable with respect to age, race, weight, and baseline YMRS total score. The proportion of male subjects was higher in the olanzapine group (57%) than in the asenapine (50%) or placebo (49%) groups (see Table 3). There were two subjects randomized to asenapine group and included in the ITT population with baseline YMRS total score of 18.

Table 3. Study 1004 Summary of demographics and baseline characteristics (all randomized patients)

Characteristics	Placebo N=98	Asenapine N=185	Olanzapine N=205	All subjects N=488
Gender				

Male	48 (49.0%)	92 (49.7%)	117 (57.1%)	257 (52.7%)
Female	50 (51.0%)	93 (50.3%)	88 (42.9%)	231 (47.3%)
Race				
Caucasian	55 (56.1%)	104 (56.2%)	110 (53.7%)	269 (55.1%)
African	16 (16.3%)	38 (20.5%)	41 (20.0%)	95 (19.5%)
Asian	22 (22.4%)	40 (21.6%)	44 (21.5%)	106 (21.7%)
Other	5 (5.1%)	3 (1.6%)	10 (4.9%)	18 (3.7%)
Age Category				
18-64 years	95 (96.9%)	179 (96.8%)	204 (99.5%)	478 (98.0%)
>=65 years	3 (3.1%)	6 (3.2%)	1 (0.5%)	10 (2.0%)
Age, years				
Mean (SD)	38.1 (12.49%)	39.1 (12.26)	38.4 (10.82)	38.6 (11.71)
Median	38.0	40.0	39.0	39.0
Range	18, 69	18, 76	18, 66	18, 76
Weight, kg				
Mean (SD)	78.1 (19.82)	75.9 (19.20)	77.9 (19.99)	77.2 (19. 65)
Median	77.3	72.6	77.3	75.4
Range	41, 166	38, 144	38, 136	38, 166
YMRS (at baseline)				
Mean (SD)	28.2 (6.27)	29.4 (6.68)	29.7 (6.61)	29.3 (6.58)
Median	26.5	28.0	28.0	28.0
Range	20, 48	18, 54	20, 56	18, 56

Source: Clinical Study Report A7501004, Table 12 (pg 86).

In Study A750100, the treatment groups were comparable with respect to age, race, and weight. The proportion of male subjects was higher in the olanzapine (60%) and asenapine groups (59%) than in the placebo (50%) groups (see Table 4). There was one patient with YMRS baseline score of 3 randomized to asenapine group. The patient was not included in the ITT population. Two patients with YMRS total score of 18 (placebo) and one patient with baseline YMRS total score of 19 (olanzapine group) were included in the ITT population.

Table 4. Study 1005 Summary of Demographics and Baseline characteristics (all patients treated)

Characteristics	**Placebo** N=104	**Asenapine** N=194	**Olanzapine** N=190	**All subjects** N=488
Gender				
Male	52 (50%)	114 (58.8%)	114 (60%)	280 (57.4%)
Female	52 (50%)	80 (41.2%)	76 (40%)	208 (42.6%)
Race				
Caucasian	59 (56.7%)	122 (62.9%)	114 (60%)	295 (60.5%)
African	19 (18.3%)	31 (16.0%)	31 (16.3%)	81 (16.6%)
Asian	19 (18.3%)	35 (18.0%)	34 (17.9%)	88 (18.0%)
Other	7 (6.7%)	6 (3.1%)	11 (5.8%)	24 (4.9%)
Age				
18-64 years	103 (99.0%)	193 (99.5%)	186 (97.9%)	482 (98.8%)
>=65 years	1 (1.0%)	1 (0.5%)	4 (2.1%)	6 (1.2%)
Age, years				
Mean (SD)	39.4 (11.99)	38.7 (11.88)	40.1 (11.30)	39.4 (11.67)
Median	41.5	40.0	40.0	40.0
Range	18, 66	18, 68	19, 67	18, 68

Weight, kg				
Mean (SD)	78.2 (19.17)	77.7 (19.11)	79.7 (19.88)	78.6 (19.41)
Median	77.1	75.5	79.2	77.1
Range	43, 181	41, 146	33, 145	33, 181
YMRS at baseline				
Mean (SD)	29.0 (6.11)	28.1 (5.77)	28.5 (5.89)	28.5 (5.89)
Median	29.0	28.0	28.0	28.0
Range	18, 47	3, 46	19, 51	3, 51

Source: Clinical Study Report A7501005, Table 12 (pg 82).

DISCUSSION OF ENDPOINTS

Results of Efficacy Analyses

Primary Analysis

For the LOCF ANCOVA analysis in both mania studies, the YMRS total scores were statistically significantly improved (i.e. decreased) from baseline to Day 21 in the asenapine and olanzapine treatment groups, compared with the placebo treatment group. The results are presented in the table below. In both studies, the baseline mean YMRS scores were comparable among treatment groups. In Study A7501004, the LS mean change from baseline to Day 21 was -11.5, -7.8, and -14.6 for the asenapine, placebo, and olanzapine treatment groups, respectively ($p=0.0065$ for asenapine vs. placebo and $p<0.0001$ for olanzapine vs. placebo). The placebo-subtracted estimated treatment effect was −3.8 points on the YMRS for asenapine and −6.9 points for olanzapine. The treatment effects were modest for both asenapine and olanzapine.

For Study A7501005, the LS mean change from baseline to Day 21 was -10.8, -5.5, and -12.6 for the asenapine, placebo, and olanzapine treatment groups, respectively ($p<0.0001$ for both comparisons with placebo). The placebo-subtracted estimated treatment effect was −5.3 points on the YMRS for asenapine and −7.1 points for olanzapine. The treatment effects were modest for both asenapine and olanzapine.

YMRS Total Score LS mean Change from Baseline to Endpoint (ITT Population)

	Placebo	**Asenapine**	**Olanzapine**
Study 1004			
Number of Patients	94	183	203
Baseline Mean (SD)	28.3 (6.32)	29.4 (6.72)	29.7 (6.64)
Day 21 Mean (SD)	20.4 (12.70)	17.7 (11.91)	14.9 (10.47)
Mean Change from Baseline (SD)	-7.9 (11.46)	-11.7 (11.34)	-14.8 (10.37)
LS Mean Change from Baseline (SE)	-7.8 (1.11)	-11.5 (0.80)	-14.6 (0.76)
P-value vs. Placebo		0.0065	<0.0001
Study 1005			
Number of Patients	103	189	188
Baseline Mean (SD)	29.0 (6.14)	28.3 (5.53)	28.6 (5.88)
Day 21 Mean (SD)	23.5 (12.57)	17.7 (11.29)	16.1 (9.43)

Mean Change from Baseline (SD)	-5.5 (10.63)	-10.5 (11.13)	-12.5 (9.71)
LS Mean Change from Baseline (SE)	-5.5 (1.01)	-10.8 (0.75)	-12.6 (0.76)
P-value vs. Placebo		<0.0001	<0.0001

Supportive analysis

Dr. Kordzakhia conducted an exploratory analysis, using the same ANCOVA model was applied to analyze change from baseline in YMRS at all assessed time points using LOCF method (see **Error! Reference source not found.** and **Error! Reference source not found.**). The results supported the results on the primary endpoint.

Study A7501004: YMRS Total Score LS Mean Change from Baseline by Day

Visits	**Placebo**	**Asenapine**	**Olanzapine**
Day 2			
Number of Patients	93	175	200
LS mean Change from Baseline (SE)	-1.7 (0.54)	-3.2 (0.40)	-4.4 (0.37)
P-value vs. Placebo		0.0222	<0.0001
Day 4			
Number of Patients	94	183	203
LS mean Change from Baseline (SE)	-3.6 (0.65)	-5.5 (0.46)	-7.4 (0.44)
P-value vs. Placebo		0.0164	<0.0001
Day 7			
Number of Patients	94	183	203
LS mean Change from Baseline (SE)	-5.4 (0.80)	-7.6 (0.58)	-9.7 (0.55)
P-value vs. Placebo		0.0240	<0.0001
Day 14			
Number of Patients	94	183	203
LS mean Change from Baseline (SE)	-6.7 (1.02)	-10.4 (0.74)	-13.3 (0.70)
P-value vs. Placebo		0.0027	<0.0001
Day 21			
Number of Patients	94	183	203
LS mean Change from Baseline (SE)	-7.8 (1.11)	-11.5 (0.80)	-14.6 (0.76)
P-value vs. Placebo		0.0065	<0.0001

Source: Clinical Study Report A7501004, Table 19 (pg 98)
Note: The reported p-values are nominal and are not adjusted for multiplicity. P-values are based on the difference in the LS means for asenapine and olanzapine treatments versus placebo.

Study A7501005 YMRS Total Score LS Mean Change from Baseline by Day

Visits	**Placebo**	**Asenapine**	**Olanzapine**
Day 2			
Number of Patients	101	183	182
LS mean Change from	-1.5 (0.47)	-3.0 (0.35)	-3.4 (0.35)

Baseline (SE)			
P-value vs. Placebo		0.0077	0.0010
Day 4			
Number of Patients	103	189	188
LS mean Change from Baseline (SE)	-3.0 (0.56)	-5.5 (0.41)	-6.6 (0.42)
P-value vs. Placebo		0.0003	<0.0001
Day 7			
Number of Patients	103	189	188
LS mean Change from Baseline (SE)	-3.1 (0.72)	-6.9 (0.53)	-8.2 (0.54)
P-value vs. Placebo		<0.0001	<0.0001
Day 14			
Number of Patients	103	189	188
LS mean Change from Baseline (SE)	-5.1 (0.92)	-9.2 (0.68)	-10.1 (0.69)
P-value vs. Placebo		0.0003	<0.0001
Day 21			
Number of Patients	103	189	188
LS mean Change from Baseline (SE)	-5.5 (1.01)	-10.8 (0.75)	-12.6 (0.76)
P-value vs. Placebo		<0.0001	<0.0001

7. EXPOSURE TO STUDY DRUG

7.1 Outline of the Phase 2/3 Asenapine Clinical Studies

In the asenapine program there have been 51 completed trials, and there are 12 ongoing trials. (The database cut-off date was January 15, 2007). The 14 completed Phase 2/3 studies of asenapine in Schizophrenia and Bipolar Mania include: 1) six (6) acute, 6-week, placebo-controlled and active-controlled trials in Schizophrenia; 2) five (5) long-term, open label studies in Schizophrenia; 3) two (2) acute (3-week), placebo-controlled and active-controlled trials in Mania; and 4) one (1) long-term (12-week) study in Mania. There have been 29 clinical pharmacology studies in healthy subjects and subjects with renal or hepatic impairment; and, there have been eight (8) clinical pharmacology studies in patients with Schizophrenia or Schizoaffective Disorder.

The safety data is presented by subject cohorts (A, B, C, D, E, F, G, and NC) as defined below:

- Cohort A: Acute (6-week), placebo-controlled trials in Schizophrenia (6)
- Cohort B: Long-term, open-label study in Schizophrenia (5)
- Cohort C: Acute (3-week), placebo-controlled trial in Bipolar d/o, Mania (2)
- Cohort D: Long-term (12-week) study in Bipolar d/o, Mania (1)
- Cohort E: **Combined Phase 2/3 studies** (acute and long-term) in Schizophrenia and Mania **(63)**
- Cohort F: Clinical pharmacology studies in healthy volunteers and subjects with renal or hepatic impairment (29)

- Cohort G: Clinical pharmacology trials, subjects with psychotic disorders (8)
- Cohort NC: Ongoing studies (12)

7.2 Overview of Exposure Data

Overall, 2251 subjects were treated with asenapine in the Phase 2/3 Schizophrenia and Mania studies. Of these, 298 (13%) were treated with doses of less than 10 mg/day, and 1953 (87%) were treated with 10 to 20 mg per day, as fixed or flexible doses. In the asenapine group, there were 1778 Schizophrenia subjects and 473 Bipolar, manic subjects. In addition, 706 subjects were treated with placebo; 899 subjects were treated with olanzapine (Schizophrenia and Mania); 120 Schizophrenia subjects were treated with risperidone; and 115 Schizophrenia subjects were treated with haloperidol. Table 1 below summarizes the number of subjects exposed to each study drug in these clinical studies.

In the combined Schizophrenia and Mania studies (Cohort E), the total asenapine exposure was 645 patient-years. The total placebo exposure was 51.9 patient-years; the total olanzapine exposure was 285 patient-years; the total risperidone exposure was 21 patient-years; and the total haloperidol exposure was 9.8 patient-years. In the acute, controlled Schizophrenia and Mania trials, the total asenapine exposures were 47.9 and 17.2 patient-years, respectively. In the long-term Schizophrenia and Mania studies, the asenapine exposures were 505.7 and 44.8 patient-years, respectively. Table 2 below summarizes the exposures in patient-years for the clinical studies (Cohorts A-E).

Table 1.Summary of Subjects Exposed in Completed Phase 2/3 Schizophrenia and Mania Studies (Cohorts A, B, C, D, and E)

Table 1.Summary of Subjects Exposed in Completed Phase 2/3 Schizophrenia and Mania Studies (Cohorts A, B, C, and D)

Study number	**PLA**	**ASEN < 10 mg**	**ASEN 10 mg**	**ASEN 20 mg**	**ASEN 10-20 (flexi)**	**ASEN 10-20 (total)**	**ASEN (All)**	**RIS 6 mg**	**OLA 10-20 mg**	**HAL 8 mg**
Schizophrenia (6-wk)										
041002	61	180					180	61		
041013	64	118					118			
041004	62		59			59	59	59		
041021	100		104	102		206	206		102	
041022	93				90	90	90		92	
041023	123		111	106		217	217			115
Total (Cohort A)	**503**	**298**	**274**	**208**	**90**	**572**	**870**	**120**	**194**	**115**
Schizophrenia (52 weeks) 25517 **(Cohort B)**					**908**				**311**	
Schizophrenia extension (up to 2 years)										
041500 (ext. of 002)	8	28						13		
041505 (ext. of 003)	7	20								
041502 (ext. of 004)	7		15					17		
041590 (x- 500, 505)		5								
Bipolar Mania (3-wk)										

A7501004 A7501005 **Total**	98 105 **203**				185 194 **379**	185 194 **379**	185 194 **379**		205 189 **394**	
Mania (9-12 weeks) A7501006 (ext of 1004, 1005)					181 94	181 94	181 94		229	
Overall Total	**706**	**298**	**274**	**208**	**1471**	**1953**	**2251**	**120**	**899**	**115**

Table 2.Summary of Drug Exposures in All Phase 2/3 Asenapine Studies (Cohorts A- E)

Table 2.Drug exposures in patient-years for the Phase 2/3 asenapine studies (Cohorts A-E)					
Exposure [patient-years]/ (Number of subjects)	placebo	asenapine	olanzapine	risperidone	haloperidol
Cohort A	(n = 503) 38.8	(n = 572) 47.9	(n = 194) 15.3	(n = 120) 9.0	(n = 115) 9.8
Cohort B		(n = 908) 505.7		(n = 311) 218.8	
Cohort C	(n= 203) 9.0	(n = 379) 17.2	(n = 394) 20		
Cohort D		(n = 275) 44.8	(n = 229) 44		
Cohort E (total)	(n = 706) **51.9**	(n = 2251) **645**	(n = 899) **285**	(n = 120) **21**	(n = 115) **9.8**

7.3 Study Drug Dosing in Short-term Schizophrenia Trials (6 weeks)

The six short-term (6-week) Phase 2/3 Schizophrenia trials included: 041002, 041004, 041013, 041021, 041022, and 041023. Schizophrenia subjects were administered study drug for up to 42 days. Study 041002 included asenapine fixed-doses of 0.4, 0.8, and 1.6 mg per day. Study 041013 included asenapine fixed-doses of 3.2 and 4.8 mg per day. The highest asenapine dose in the Phase 2 trials was 10 mg/day, administered as a fixed-dose. All three of these fixed-dose trials were placebo-controlled. Risperidone 6 mg/day was included as an active control in Studies 041002 and 041004.

In the Phase 3 short-term Schizophrenia trials, study drug was administered for up to 42 days. In studies 041021 and 041023, asenapine was administered in fixed-doses of 10 mg/day or 20 mg/day. In Study 041022, asenapine was administered as flexible doses of 10-20 mg/day. All three trials were placebo-controlled and active-controlled. Olanzapine was administered as the active control in Study 041021 (as a fixed-dose of 15 mg QD) and in Study 041022 (as flexible-doses of 10-20 mg QD). In Study 041023, haloperidol 8 mg/day was used as the active control.

7.4 Study Drug Dosing in Long-term Schizophrenia Study (52 weeks)

Study 25517 was a 52-week, randomized, double-blind, active-controlled, flexible-dose, (double-dummy) safety and efficacy study in patients with Schizophrenia and

Schizoaffective Disorder. Subjects were treated with flexible-doses of either asenapine (10 to 20 mg/day) or olanzapine (10 to 20 mg/day).

7.5 Study Drug Dosing in Short-term Bipolar, Mania Trials (3 weeks)

Studies A7501004 and A7501005 were Phase 3, randomized, double-blind, placebo-controlled and active-controlled, 3-week, efficacy and safety trials in patients with Bipolar I Disorder, Manic or Mixed episodes. In both trials, asenapine was administered in flexible-doses of 10-20 mg/day. Olanzapine was administered in flexible-doses of 5 to 20 mg/day. On Day 1, subjects began treatment with either asenapine 20 mg/day or olanzapine 15 mg/day. Beginning on Day 2, doses could be adjusted as indicated.

7.6 Study Drug Dosing in Long-term Bipolar, Mania Trials (12 weeks)

Subjects who completed one of the two 3-week acute Mani trials (A7501004 and A7501005) were eligible to participate in the 9-week, safety and efficacy extension study, A7501006. Subjects who were treated with placebo in the acute trials were administered asenapine for 9 weeks in Study A7501006. Subjects who had been treated with asenapine or olanzapine in the acute Mania trials continued with the same treatment for an additional 9 weeks.

7.7 Subjects Exposed in the Clinical Pharmacology Studies (Cohorts F and G)

In the clinical pharmacology studies, subjects included: 1) healthy volunteers; 2) subjects with renal or hepatic impairment; and 3) patients with psychotic disorders. The highest dose administered with the sublingual formulation in these studies was 40 mg/day.

In the 29 studies of healthy volunteers and subjects with renal or hepatic impairment (Cohort F), there were 745 subjects treated with asenapine and 96 subjects treated with placebo. Most subjects (657/88%) received asenapine doses < 10 mg/day.

In the eight (8) clinical pharmacology studies in subjects with psychotic disorders, there were 363 subjects who received asenapine and 61 subjects who received placebo. Most of the subjects (54%) who received asenapine in these eight clinical pharmacology studies received doses of 10 mg/day. Among the other subjects, 15% (n=55) received doses of 20 mg/day; 18% (n=66) received doses of < 10 mg/day; and 19% (n=64) received doses of > 20 mg/day (up to 30 and 40 mg). In QT study A7501001, 37 subjects received the active comparator, quetiapine to assess the effect of asenapine on the QTc interval in subjects with Schizophrenia. Table 3 below summarizes the 8 pharmacology studies in patients.

Table .Clinical Pharmacology studies in patients with Schizophrenia or Schizoaffective Disorder

Table 3. Clinical Pharmacology Studies in Patients with Schizophrenia or Schizoaffective Disorder	
Study	**Dosing and Description**
041001	Establish the maximum tolerated dose. Doses were < 10 mg/d: 0.4, 0.8, 1.2, and 1.6 mg/day

041007	Establish the maximum tolerated dose. Doses were < 10 mg/d: 0.4, 0.6, 0.8, 1.2, 4.8, 9.6 mg/d
041009	Bioavailability study testing two early formulations of asenapine: 5 and 10 mg/day
041012	Escalating dose study of doses up to 30 mg/day (n = 12) or 40 mg/day (n = 6)
041014	Bioavailability crossover study of 3 x 5 mg BID vs. 1 x 15 BID
A7501001	Assessed the effect of asenapine on the QT interval. Doses included: 10, 20, 30, 40 mg/day
A7501022	PK study adolescents (12 to 17 years old) with psychotic d/o. Doses: 2, 6, 10, 20 mg/day
A7501024	Tested preference of raspberry flavor or unflavored sublingual tablets in doses of 5 mg BID

8. INTEGRATED REVIEW OF SAFETY

The sponsor coded adverse event terms using the MedDRA 9.0 dictionary. The sponsor has provided the dictionary as well as the verbatim and preferred terms used for the analyses of the asenapine studies. The sponsor's definition of drug-relatedness is as follows: an adverse event that was reported by at least 5% of the asenapine group and reported at least twice as commonly in the asenapine group compared to the placebo group. Using these criteria, the sponsor concludes that the following AE were related to treatment with asenapine: akathisia (6.3% vs. 2.4%); sedation ( ); somnolence (7.2% vs. 2.2%); weight gain (); dizziness (); and oral hypoesthesia (5.4% vs. 0.8%). Furthermore, the sponsor has concluded that akathisia was a dose-related adverse event.

Table 4 below summarizes the adverse events, deaths, SAE, and AE associated with discontinuations in the Phase 2/3 asenapine studies.

In the Schizophrenia and Mania trials, there were 11 (0.5%) deaths in the asenapine group, one (0.1%) death in the placebo group, 3 (0.3%) deaths in the olanzapine group, and no deaths in either the risperidone or haloperidol groups. The adjusted death rates do not suggest that there were an excess number of deaths in the asenapine group. The proportion of subjects with SAE was 14% in the asenapine group, 9% in the placebo group, 10% in the olanzapine group, 18% in the risperidone group, and 7% in the haloperidol group. The proportion of subject who discontinued due to AE was 15% in the asenapine group, 10% in the placebo group, 12% in the olanzapine group, 23% in the risperidone group, and 10% in the haloperidol group.

Table 4. Summary Table of Deaths, SAE, DC due to AE, and AE in the Phase 2/3 Schizophrenia and Mania Studies

Table 4. Summary of Adverse Events for the combined short- and long-term Phase 2/3 studies (Cohort E)							
AE category N (%)	Asenapine (all) N= 2251	Asenapine (≥ 10 mg) N= 1953	Asenapine (< 10 mg) N= 298	Placebo N= 708	Olanzapine (5-20 mg) N= 899	Risperidone (6 mg) N= 120	Haloperidol (8 mg) N= 115
Deaths	11 (0.5)	9 (0.5)	2 (0.7)	1 (0.1)	3 (0.3)	0	0
SAE	325 (14.4)	275 (14.1)	50 (16.8)	61 (8.6)	87 (9.7)	21 (17.5)	8 (7)
DCAE	342 (15.2)	285 (14.6)	57 (19.1)	69 (9.8)	103 (11.5)	28 (23.3)	12 (10.4)
DCSAE	141 (6.3)	125 (6.4)	16 (5.4)	36 (5.1)	40 (4.4)	12 (10.4)	5 (4.3)
AE	1769 (79)	1523 (78)	246 (83)	483 (68)	682 (76)	105 (88)	87 (76)

8.1 SAFETY FINDINGS

8.1.1. DEATHS IN THE CONTROLLED AND OPEN-LABEL STUDIES

There were 15 deaths in the completed Schizophrenia and Mania studies. Twelve (12) of these deaths occurred in the Schizophrenia studies (4 in the short-term and 8 in the long-term studies). Three (3) deaths occurred in the mania studies (two in the acute and one in the long-term studies). Eight (8) of the 15 deaths were completed suicides. In the asenapine group, there were 6 (0.3%) completed suicides. In the olanzapine group, there were 2 (0.2%) completed suicides, and in the placebo group, there were no completed suicides.

In the asenapine group, there were 11 deaths, corresponding with an adjusted rate of 1.71 per 100 patient-years. In the placebo group, there was one (1) death, corresponding with an adjusted rate of 1.93 per 100 patient-years. In the olanzapine group, there were 3 deaths.

It appears that most (if not all) deaths were not related to treatment with asenapine. The table below provides a line listing of the deaths in the completed studies. The reported causes of death in asenapine group include: suicide, pulmonary embolism; hyperthermia; acute coronary syndrome; pneumonia; and overdose. In one asenapine case, the cause of death was not specified (041013/28; adverse events included dyspnea, dystonia, hematoma, epiglottitis, and laryngitis). The sponsor states that one death (in mania A7501004) was possibly related to treatment with asenapine. From the details provided, the nature of the possible relationship to asenapine treatment is unclear.
In the olanzapine cases, the reported causes of death were suicide, overdose. For one subject treated with placebo, the cause of death was malignant thymoma.

Table. Line listing of Deaths in completed phase 2/3 studies

Table 5.Line listing of Deaths in completed phase 2/3 studies (Cohort E)			
Subject ID	Treatment	Cause of death/AE	Relatedness to treatment (per sponsor)
041013-28	Asenapine	Epiglottitis, laryngitis, dystonia, dyspnea, hematoma	Not related
041013-48	Asenapine	Pulmonary embolism, hyperthermia	Not related
25517-115024	Asenapine	Completed suicide	Not related
25517-127004	Asenapine	Completed suicide	Not related
25517-130013	Asenapine	Completed suicide	Unlikely
25517-131010	Asenapine	Completed suicide	Unlikely
25517-186007	Asenapine	Pneumonia	Unlikely
25517-242020	Asenapine	Coronary artery insufficiency	Unlikely
25517-	Asenapine	Completed suicide	Unlikely

248014			
A7501004-A7501006	Asenapine	Accidental overdose	Not related
A7501004-	Asenapine	Completed suicide	Possibly related
041021-125010	Olanzapine	Overdose	Unlikely
25517-204011	Olanzapine	Completed suicide	Unlikely
A7501004-41331009	Olanzapine	Completed suicide	Unlikely
041023	Placebo	Malignant thymoma	Not related

2. Death in the Clinical Pharmacology Studies

There were no deaths that occurred within 30 days of the last dose that were related to treatment. However, one subject in Study A7501018 with hepatic impairment died from complications of surgery for an umbilical hernia. The surgery took place 10 days after the hepatic impairment study, and the death occurred two months later.

3. Deaths in ongoing studies (treatment randomization remains blinded)

As of the initial NDA submission, there had been nine (9) reported deaths in ongoing studies. Treatment randomization has remained blinded for these cases. These are listed in Table 6 below. There have been 4 completed suicides. Other reported causes of death include: respiratory failure, pulmonary embolism, cardiac failure, death (not specified), and neonatal death (associated with intrauterine drug exposure). Currently, the potential relationship between these deaths and study drug treatment is unclear.

4. Deaths in the Ongoing Studies (blinded treatment)

Table 6. Line listing of deaths in the ongoing studies (Cohort NC)

Subject ID	Treatment	Cause of death	Relatedness to treatment
041513-315504	Blinded	Respiratory failure	Unlikely
041513-368509	Blinded	Completed suicide	Unlikely
25543-125005	Blinded	Completed suicide	Possible
25543-125006	Blinded	Completed suicide	Possible
A7501007-50281012	Blinded	Completed suicide	Unlikely
A7501007-51241008	Blinded	Neonatal death; intrauterine drug exposure	Possible
P25520-132017	Blinded	Death- not otherwise specified	Unknown
P25520-241041	Blinded	Pulmonary embolism	Unlikely
P25520-246021	Blinded	Cardiac failure	unknown

8.1.2. SERIOUS ADVERSE EVENTS

To be categorized as a serious adverse event, an adverse event must have met at least one of the following criteria:

1. The adverse event resulted in death
2. The adverse event was life-threatening
3. The adverse event required inpatient hospitalization or resulted in prolongation of an existing hospitalization
4. The adverse event resulted in persistent or significant disability or incapacity
5. The adverse event was a congenital anomaly

Reported SAE could occur to up 30 days following the last dose of study drug or up to the last follow-up visit. Deaths and serious adverse events occurring later than 30 days and considered treatment-related are also included.

In the combined Phase 2/3 studies, the most commonly reported SAE were exacerbations of the psychiatric disorders under treatment. These included: exacerbation of Schizophrenia and other psychotic disorders; completed suicide; suicidal and self-injurious behaviors; mania, Bipolar disorder; depressed mood; and mood disturbances. Less common SAE included: 1) injury, poisoning, and procedural complications; and 2) infections and infestations. Among the 11 cases of infection, there were 6 cases of pneumonia. Other reported SAE included rhabdomyolysis, syncope, bradycardia, hyponatremia, neuroleptic malignant syndrome (NMS), agitation, and dystonia. The SAE that were probably related to treatment with asenapine include: NMS, dystonia, syncope, and drug toxicity. There were no unexpected SAE related to treatment with asenapine. The tables below illustrate details for the various cohorts.
TABLE 7.SAE with n $\geq$ 3in the combined Phase2/3 studies

Table 7.SAE with n $\geq$ 3in combined Phase2/3 studies (Cohort E)					
Adverse events N (%)	Asenapine (mcg-20 mg) N= 2251	Placebo N= 708	Olanzapine (5-20 mg) N= 899	Risperidon. (6 mg) N= 120	Haloperidol (8 mg) N= 115
Expos-yrs Any SAE Incidence	645 325 (14) 50.4	52 61 (9) 118	285 87 (10) 82	21 21 (18) 100	10 8 (7) 31
Psychotic	204 (9)	37 (5.2)	38 (4.2)	12 (10)	8 (7)
Mania/BP	28 (1.2)	8 (1.1)	16 (1.8)	0	0
Suicide	6 (0.3)	0	2 (0.2)	0	0
Suicide attempt	9 (0.5)	1 (0.1)	7 (0.8)	1 (0.8)	0
Suicidal ideation	22 (1)	1 (0.1)	6 (0.7)	1 (0.8)	0
Depression	26 (1.2)	0	8 (0.9)	3 (2.5)	0
Agitation	3 (0.1)	0	0	0	0
Anxiety	4 (0.2)	0	0	0	0
Mental d/o	4 (0.2)	0	0	0	0
Syncope	4 (0.2)	0	0	0	0
Hyponatremia	3 (0.1)	1 (0.1)	0	0	0
NMS	3 (0.1)	0	0	0	0
Rhabdomyolysis	3 (0.1)	0	1 (0.1)	0	0
Overdose	3 (0.1)	0	2 (0.2)	0	0
Alcohol poison.	3 (0.1)	0	0	0	0
Dystonia	3 (0.1)	0	0	0	0

8.1.2.1 SAE in Acute Schizophrenia Trials

In the acute Schizophrenia trials, the proportion of subjects with an SAE was similar among treatment groups (8%, 8%, 9%, 9%, and 7% in the asenapine, placebo, and olanzapine, risperidone, and haloperidol groups, respectively). The most common type of SAE reported in each treatment group was Schizophrenia/psychotic disorder (5%, 6%, 6%, 4%, and 7% in the asenapine, placebo, olanzapine, risperidone, and haloperidol groups, respectively). In the asenapine group, other SAE reported for < 1% of subjects were psychiatric disorder, COPD, and hypertension. It appears unlikely that any of these SAE were related to treatment with asenapine. There were no unexpected adverse events that were SAE.

Table 8.SAE with n ≥ 2 in 6-week acute Schizophrenia trials (cohort A)

Table 8. SAE with n ≥ 2 in 6-week acute Schizophrenia trials (Cohort A)					
Adverse events N (%)	Asenapine N= 572	Placebo N= 503	Olanzapine N= 194	Risperid. N= 120	Haloperid. N= 115
Any SAE	44 (7.7)	40 (8)	17 (8.8)	11 (9.2)	8 (7)
Schizo/psychotic	31 (5.4)	32 (6.4)	12 (6.2)	5 (4.2)	8 (7)
Psychiatric d/o	3 (0.5)	0	0	0	0
COPD	2 (0.3)	0	0	0	0
hypertension	2 (0.3)	0	0	0	0

8.1.2.2 SAE in Long-term Schizophrenia Studies

In the long-term Schizophrenia studies, the most commonly reported SAE in the asenapine and olanzapine groups were related to Schizophrenia, suicide, suicidality, and depression. These SAE are summarized below in Table 9. Schizophrenia/psychotic disorder was reported as an SAE for 14% of the asenapine group and 9% of the olanzapine group. Completed suicide occurred in 0.6% of the asenapine group and 0.3% of the olanzapine group. SAE possibly related to treatment with asenapine included agitation (possibly akathisia), syncope, somnolence, and rhabdomyolysis.

Table 9.SAE in open-label, long-term Schizophrenia Studies (n ≥ 2)

Table 9.SAE in long-term Schizophrenia studies (Cohort B)		
SAE N (%)	asenapine N= 908	Olanzapine N= 311
Schizoph/psychotic	123 (13.5)	27 (8.7)
Suicide completed	5 (0.6)	1 (0.3)
Suicide attempt	7 (0.8)	5 (1.6)
Suicidal ideation	11 (1.2)	2 (0.6)
Depression	11 (1.2)	1 (0.3)
Agitation	3 (0.3)	0
Syncope	3 (0.3)	0
Anxiety	2 (0.2)	0

Rhabdomyolysis	2 (0.2)	0
Overdose	2 (0.2)	2 (0.6)
Alcohol poisoning	2 (0.2)	0
Somnolence	2 (0.2)	0

8.1.2.3 SAE in the Short-term Mania Trials

In the short-term Mania trials, SAE were reported for 5% of the asenapine group, 7% of the placebo group, and 4% of the olanzapine group. The two most commonly reported SAE for all treatment groups were mania/bipolar disorder and depression. Mania/bipolar disorder were reported as an SAE for 4%, 4%, and 2% of the asenapine, placebo, and olanzapine group, respectively.

Table 10.SAE (with n $\geq$ 2) in acute mania trials (Cohort C)

Table 10.SAE with n $\geq$ 2 in 3-week acute mania trials (Cohort C)			
Adverse events N (%)	Asenapine N= 379	Placebo N= 203	Olanzapine N= 394
Any SAE	20 (5.3)	14 (6.9)	15 (3.8)
Mania/bipolar	14 (3.7)	9 (4.)	6 (1.5)
Depression	4 (1.1)	1 (0.5)	1 (0.3)

8.1.2.4 SAE in the Long-term mania Studies

In the long-term Mania studies, the most commonly reported SAE for the asenapine and olanzapine groups were related to the illness under treatment (Mania/Bipolar Disorder, depression, and suicidal ideation). Details of the two cases of drug toxicity are currently not clear.

Table 11.SAE (for n > 2) in long-term mania trials (Cohort D)

Table 11.SAE in long-term mania trials (for AE n $\geq$ 2) (Cohort D)		
Adverse events N (%)	Asenapine N= 275	Olanzapine N= 299
Any SAE	33 (12.7)	22 (9.6)
Mania/bipolar	12 (4.4)	10 (3.3)
Depression	12 (4.4)	7 (3.1)
Suicidal ideation	6 (2.2)	3 (1.3)
Drug toxicity	2 (0.7)	0

8.1.2.5 SAE in Clinical Pharmacology Studies

There were 7 SAE cases in the asenapine group. These SAE included: severe sinus bradycardia (possibly asystole); neurally mediated reflex bradycardia (NMRB); atrial

fibrillation; chest pain; dystonia oropharynx; gastroesophageal reflux. The cases of NMRB and dystonia were probably related to treatment with asenapine.

8.1.2.6 SAE in Ongoing Studies

For these SAE cases, the treatment randomization remains blinded. Reported SAE include: Schizophrenia (136); Mania (29); Depression (19); Psychotic Disorder (19); and Bipolar Disorder (10).

8.1.2.7 SAE in other studies

SAE reported in other studies include: rhabdomyolysis with hyponatremia; syncope; hypotension; propranolol overdose; seizure and hyponatremia; pneumonia (2); asystole and neutrally mediated reflex bradycardia; and heart block and bradycardia.
The details of these cases are currently unclear.

8.1.3. DISCONTINUATIONS DUE TO ADVERSE EVENTS

8.1.3.1 Overview of Adverse Events leading to Discontinuation

Most of the adverse events that led to discontinuations were psychiatric disorders and nervous system disorders (e.g., Schizophrenia, psychotic disorders, and movement disorders). The risperidone group had the highest proportion of discontinuations due to adverse events (23%), followed by asenapine < 10 mg/day (19%), asenapine 10- 20 mg/day (15%), olanzapine (11%), and placebo (10%). Based on the patient-years exposure analysis, the rate (per 100 patient-years of exposure) of discontinuations due to AE for the asenapine 10- 20 mg/day group was 47 was less than for placebo (133) and higher than the rate in the olanzapine group (36). The tables below illustrate details for the various cohorts.

Table 12.Discontinuations due to AE in all Phase 2/3 studies (n ≥ 4 asenapine group) (Cohort E)

Adverse event N (%)	Placebo N = 706	Asenapine N =2251	Olanzap. N = 899	Risperid. N =120	Haloperid. N = 115
Any Adverse event Exposure (pt-years) Incidence	69 (10) 52 133	342 (15) 645 53	103 (12) 285 122	28 (23) 21 133	12 (10) 10 36
Schizophren/psychotic	39 (	144	24	20	7
Mania/bipolar	6	21	8	0	0
Suicidal ideation	3 (0.4)	12 (0.5)		2 (0.2)	0
Suicide attempt	1 (0.1)	6 (0.3)	5 (0.6)	1 (0.8)	0
Depression	2 (0.3)	23 (1)	6 (0.7)	2 (1.7)	0
Agitation	5 (0.7)	15 (0.7)	5 (1)	1 (1)	0
Anxiety	1 (0.1)	14 (0.6)	1 (0.1)	0	1 (0.9)
Akathisia	1 (0.1)	17 (0.8)	0	0	1 (0.9)
Sedation	0	12	7	0	0
Hypoesthesia, oral	0	7 (0.3)	0	0	0

Insomnia	0	5 (0.2)	4 (0.4)	1 (0.8)	0
Dystonia	0	5 (0.2)	0	0	1 (0.9)
Vomiting	1 (0.1)	5 (0.2)	3 (0.3)	1 (0.8)	
Nausea	2 (0.3)	4 (0.2)	4 (0.4)	1 (0.8)	1 (0.9)
Aggression	1 (0.1)	4 (0.2)	2 (0.2)	0	0
Dizziness	1 (0.1)	4 (0.2)	4 (0.4)	2 (1.7)	0
ALT increased	0	4 (0.2)	1 (0.1)	0	0
Alcohol poisoning	0	4 (0.2)	1 (0.1)	0	0

8.1.3.2 Discontinuations due to AE in Short-term Schizophrenia Trials (for n > 2)

In the short-term Schizophrenia Trials, the majority of AE leading to discontinuation in all treatment groups were related to the illness under treatment (Schizophrenia/psychotic disorder). Other SAE reported were agitation, akathisia, aggression, anxiety, dystonia, and tremor. AE likely related to treatment with asenapine were akathisia, dystonia, and tremor.

Table 13.Discontinuations due to adverse events in acute Schizophrenia trials (for n ≥ 2) (Cohort A)

Table 13.Discontinuations due to adverse events in acute Schizophrenia trials (for n ≥ 2) (Cohort A)					
Adverse event N (%)	Placebo N= 503	Asenapine N= 572	Olanzap. N= 194	Risperid. N= 120	Haloperid. N= 115
Any AE	51 (10)	51 (9)	21 (11)	14 (12)	12 (10)
Schizophren/psychotic	31 (6.2)	27 (4.7)	6 (3.1)	7 (5.8)	7 (6.1)
Agitation	3 (0.6)	5 (0.9)	2 (1)	0	0
Akathisia	0	5 (0.9)	0	0	1 (0.9)
Aggression	0	2 (0.3)	0	0	0
Anxiety	0	2 (0.3)	0	0	1 (0.9)
Dystonia	0	2 (0.3)	0	0	1 (0.9)
Tremor	0	2 (0.3)	0	0	0

8.1.3.3 DC due to AE in long-term Schizophrenia Studies

The most common SAE reported were related to the illness under treatment (Schizophrenia and Schizoaffective Disorder). This was an AE leading to discontinuation for 8% of the asenapine group and 6% of the olanzapine group. In the asenapine group, akathisia, depression, sedation, and suicidal ideation each were AE associated with discontinuation for 1% of subjects. Adverse events probably related to treatment with asenapine were akathisia, convulsion, bradycardia, weight gain, dizziness, and tremor.

Discontinuations due to adverse events in long-term Schizophrenia trials (for n ≥ 2)

Table 14.Discontinuations due to adverse events in long-term Schizophrenia trials (for n ≥ 2) (Cohort B)		
Adverse event N (%)	Asenapine N= 908	Olanzapine N= 311

Any AE	150 (17)	38 (12)
Schizophrenia/psychotic	72 (8)	17 (6)
Akathisia	10 (1)	0
Depression	9 (1)	1 (0.3)
Sedation/somnolence	9 (1)	1 (0.3)
Suicidal ideation	5 (0.6)	0
Suicide attempt	4 (0.4)	4 (1.3)
Agitation	3 (0.3)	1 (0.3)
Anxiety	3 (0.3)	0
Hypomania	2 (0.2)	0
Vomiting	3 (0.3)	1 (0.3)
Convulsion	2 (0.2)	0
Rhabdomyolysis	2 (0.2)	0
Bradycardia	2 (0.2)	0
Overdose	2 (0.2)	1 (0.3)
Weight gain	2 (0.2)	6 (2)
Hyponatremia	2 (0.2	0
Dizziness	2 (0.2	0
Tremor	0	2 (0.6)
Nausea	2 (0.2)	2 (0.6)
Headache	2 (0.2)	0
Fatigue	2 (0.2)	1 (0.3)
Alcohol poisoning	2 (0.2	0
Insomnia	2 (0.2)	0

8.1.3.4 DC due to AE in the short-term Mania Trials

In the short-term Mania trials, mania was the most common adverse event leading to discontinuation. Mania was the reason for discontinuation for 3%, 3%, and 1% of the placebo, asenapine, and olanzapine group, respectively. AE leading to discontinuations that were probably related to asenapine included oral hypoesthesia, dizziness, and dystonia.

Discontinuations due to AE in 3-week, acute mania trials (for AE with N > 2 in asenapine group)

Table 15.Discontinuations due to AE in 3-week, acute mania trials (AE n ≥ 2) (Cohort B)			
Adverse event N (%)	Placebo N= 203	Asenapine N= 379	Olanzapine N= 394
Any AE	12 (6)	38 (10)	22 (6)
Mania	6 (3)	10 (3)	4 (1)
Anxiety	0	4 (1)	2 (1)
Hypoesthesia oral	0	4 (1)	0
Depression	2 (1)	3 (1)	0
Agitation	0	2 (1)	2 (1)
Dizziness	0	2 (1)	0
Dystonia	0	2 (1)	0
Irritability	0	2 (1)	0
Alcohol poisoning	0	2 (1)	2 (1)

8.1.3.5 AE Leading to Discontinuation in the Long-term Mania Studies

In the long-term mania study, the most common AE leading to discontinuations were related to the illness under study. These AE were: depression, mania, Bipolar Disorder, and suicidal ideation. AE leading to discontinuations that were probably related to asenapine treatment were ALT increased, oral hypoesthesia, drug toxicity, and somnolence.

Discontinuations due to AE in long-term (12-week) Mania trials (for AE with n $\geq$ 2 in asenapine group)

Table 16.DC due to AE in long-term (12-week) Mania trials (for AE with n $\geq$ 2) (Cohort C)		
Adverse event N (%)	Asenapine N= 275	Olanzapine N= 229
Any AE	41 (15)	24 (11)
Depression	10 (4)	5 (2)
Mania/bipolar disorder	8 (3)	4 (2)
Suicidal ideation	4 (2)	2 (1)
ALT increased	3 (1)	0
Anxiety	2 (1)	0
Hypoesthesia, oral	2 (1)	0
Drug toxicity	2 (1)	0
Insomnia	1 (0.4)	2 (1)
Somnolence	1 (0.4)	1 (0.9)
Weight increased	0	3 (1)

8.1.3.6 Discontinuations due to AE in healthy subjects (clinical pharmacology studies)

Discontinuations due to AE in healthy subjects (clinical pharmacology studies)		
Adverse event n (%)	Placebo N = 96	Asenapine N = 745
Any AE	0	26 (4)
Headache	0	3 (0.4)
ALT increased	0	3 (0.4)
AST increased	0	2 (0.3)
Bradycardia	0	2 (0.3)
Hypotension	0	2 (0.3)
Dyspnea	0	2 (0.3)
Opisthotonus	0	2 (0.3)
Restlessness	0	2 (0.3)
Dystonia	0	2 (0.3)
Anxiety	0	2 (0.3)
Nightmare	0	2 (0.3)
Somnolence	0	2 (0.3)

8.1.4 OTHER SIGNIFICANT ADVERSE EVENTS

8.1.4.1 Hepatic Adverse Events

In the asenapine group, there were no deaths or SAE related to abnormal liver findings. There were no cases meeting criteria of Hy's Law [define]. In the asenapine group, 8 subjects discontinued due to liver-related AE (↑ transaminase (7); and liver disorder 1 (0.05). None of these events was an SAE.

In the placebo group, 3 subjects discontinued due to elevated transaminase concentrations In the olanzapine group, there were 3 discontinuations due elevated transaminase concentration. One risperidone subject had an elevated transaminase concentration that was an SAE leading to discontinuation.

In the acute, controlled trials, the proportion of subjects with transaminase (ALT) elevations > *3 times ULN* in the asenapine, placebo, and olanzapine groups were 3.6% (76/2128); 1.6% (10/634); and 7.8% (66/840), respectively.

Liver-related Adverse Events in Phase 2/3 Studies (Cohort E)

Liver-related Adverse Events in Phase 2/3 Studies (Cohort E)					
	Asenapine N= 2251	Placebo N= 706	Olanzapine N= 899	Risperidone N= 120	Haloperidol N= 115
Investigations					
ALT increased	33 (1.5)	2 (0.3)	45 (5)	0	1 (0.9)
AST increased	14 (0.6)	0	26 (2.9)	0	1 (0.9)
Bilirubin increased	3 (0.1)	0	6 (6.7)	0	1 (0.9)
GGT increased	7 (0.3)	2 (0.3)	0	0	1 (0.9)
Hepatic enzyme abn	0	0	8 (0.9)	0	0
Hepatic enzyme ↑	14 (0.6)	4 (0.6)	11 (1.2)	0	0
Liver fx test abn	3 (0.1)	2 (0.3)	2 (0.2)	2 (1.7)	1 (0.9)
Transaminase ↑	(0.04)	0	2 (0.2)	0	0
Hepatobiliary d/o					
Chronic hepatitis	1 (0.)	0	0	0	0
Hepatic fx abn	0	0	1 (0.1)	0	0
Hepatic pain	1 (0.04)	0	0	0	0
Hepatitis	1 (0.04)	0	0	0	0
Liver disorder	2 (0.1)	0	0	0	0
ALT (U/L) **N**	2128	632	840	116	106
Baseline mean	26.8	29.8	24.2	27.7	23.2
Change fr base.	2.3	-1.5	3.8	1.4	-1.7
N (%) L/N to high	472 (27)	67 (12.9)	299 (42.4)	20 (21.5)	8 (8.4)
N (%) H/N to low	18 (0.9)	8 (1.3)	3 (0.4)	0	0
>3 X ULN	76 (3.6)	10 (1.6)	66 (7.8)	5 (4.3)	1 (0.9)
AST (U/L) N	2127	629	839	116	106
Baseline mean	22.7	24.4	24.2	22.7	22.2
Change fr base.	1.9	-0.1	3.8	1.2	-2.1
N (%) L/N to high	381 (19.6)	71 (12.8)	214 (28.3)	22 (21)	11 (11)
N (%) H/N to low	21 (1)	13 (2.1)	6 (0.7)	7 (6.3)	1 (1)
>3 X ULN	32 (1.5)	6 (1)	16 (1.9)	1 (0.9)	0

GGT (U/L) N	2130	633	841	116	106
Baseline mean	31.2	33.6	33.8	35.3	24.7
Change fr base.	0	-1.5	5.3	0.1	-0.2
N (%) L/N to high	215 (11.7)	38 (6.9)	129 (17.8)	10 (9.8)	4 (4)
N (%) H/N to low	76 (3.7)	8 (1.3)	32 (4)	6 (5.3)	2 (2)
>10 X ULN	4 (0.2)	0	3 (0.4)	0	0

Bilirubin Findings in Phase 2/3 Studies

Total bilirubin (umol/L)	Asenapine	Placebo	Olanzapine	Risperidone	Haloperidol
(n)	2104	617	830	111	98
Baseline mean	7.5	7.2	7.6	6.9	7.7
Change from BL	0.4	1.2	− 0.2	− 0.1	0.6
n (%) L/N to high	84 (4.1)	24 (4)	25 (3.1)	1 (0.9)	5 (5.2)
n (%) H/N to low	202 (10.3)	49 (8.8)	67 (8.4)	25 (27.5)	9 (10)
> 2 X ULN	7 (0.3)	1 (0.2)	4 (0.5)	0	1 (1)

Sponsor's Summary

Transient elevations in serum transaminases (primarily ALT) occurred with asenapine treatment. However, asenapine treatment was not associated with clinically significant changes in liver enzyme or bilirubin levels.

8.1.4.2 Extrapyramidal Symptoms (EPS)

Treatment with asenapine was associated with extrapyramidal symptoms, as would be expected with an atypical antipsychotic drug. There were no unexpected findings. Akathisia was dose-related. Generally, the extent of extrapyramidal symptoms related to asenapine was considerably less than that with risperidone and haloperidol.

Adverse Events Terms by Extrapyramidal Symptom Category				
Akathisia	**Dyskinesia**	**Dystonia**	**Parkinsonism**	**Unspecified**
Akathisia	Dyskinesia	Dystonia	Parkinsonism	Extrapyramidal d/o
Hyperkinesia	Tardive dyskinesia	Blepharospasm	Cogwheel rigidity	Movement disorder
		Macroglossia	Gait disturbance	
		Oculogyration	Hypertonia	
		Torticollis	Masked facies	
			Blunted affect	
			Parkinsonian tremor	
			tremor	

Asenapine treatment was associated with extrapyramidal symptoms in the Schizophrenia and Mania studies. In the asenapine 5-10 mg BID group, 16% of subjects reported EPS, compared to 7% of the placebo group. In the asenapine < 5 mg BID group, 6% of subjects reported EPS. In the olanzapine, risperidone, and haloperidol groups, 8%, 10%, and 39% of subjects reported EPS. In the short-term Schizophrenia trials, the occurrence of EPS was dose-dependent. In the placebo, asenapine < 5 mg BID, asenapine 5mg BID,

and asenapine 10 mg BID, EPS was reported for 8%, 6%, 11%, and 18% of subjects, respectively.

EPS adverse event	Placebo	ASEN 5 BID	ASEN 10 BID	ASEN Flexible	RISP 6 mg	HALOP 8 mg	OLAN 5-20 mg
	N= 706	N= 274	N= 208	N= 90	N= 120	N= 115	N= 899
Akathisia	19 (3)	11 (4)	23 (12)	3 (3)	6 (5)	17 (15)	44 (5)
All EPS minus akathisia	37 (4)	26 (9)	29 (14)	8 (9)	8 (7)	45 (39)	55 (6)
Dyskinesia	5 (1)	1 (	4 (2)	1 (1)	1 (1)	3 (3)	4 (-)
Dystonia	6 (1)	6 (2)	4 (2)	4 (4)	1 (1)	11 (10)	8 (1)
Blepharospasm	0	0	0	0	0	0	2 (-)
Dystonia	4 (1)	6 (2)	4 (2)	4 (4)	1 (1)	11 (10)	5 (1)
Macroglossia	0	0	0	0	0	0	0
Oculogyration	2 (-)	0	0	1 (1)	0	0	0
Torticollis	0	0	0	0	0	1 (1)	0
Parkinsonism	19 (3)	17(6)	21 (	3 (	3 (	30	41 (5)
Blunted affect	0	0	0	0	0	0	1 (-)
Cogwheel rigidity	0	0	0	0	0	1 (1)	1 (-)
Gait disturbance	0	0	0	0	0	0	2 (-)
Hypertonia	0	0	0	0	0	0	6 (1)
Masked facies	0	0	0	0	0	0	0
Park. Rest tremor	0	5 (2)	0	0	0	0	0
Parkinsonism	8 (1)	9 (3)	7 (3)	1 (1)	0	16 (14)	12 (1)
Tremor	12 (2)	0	9 (4)	1 (1)	2 (2)	5 (4)	20 (2)
Rigidity	0	3 (1)	5 (2)	1 (1)	1 (1)	8 (7)	0
Unspecified	7 (1)	2 (1)	0	0	3 (3)	1 (1)	2 (-)
Extrapyramidal d/o	7 (1)	2 (1)	0	0	3 (3)	0	2 (-)
Movement disorder	0	0	0	0	0	1 (1)	0

(-) = < 1

By AE reports, asenapine EPS profile appears to be: (depending on dose) compared to risperidone, olanzapine, and haloperidol. EPS is dose-dependent.

EPS in Short-term, controlled Schizophrenia Trials (Fixed Doses Only)

EPS AE	Placebo	ASEN 10 mg	ASEN 20 mg	RISP 6 mg	OLAN 10-20 mg	HALOP 8 mg
	N= 503	N= 274	N= 208	N= 120	N= 194	N= 115
Akathisia	13 (3)	11 (4)	22 (11)	5 (4)	9 (5)	17 (15)
Dyskinesia	5 (1)	1 (-)	4 (2)	1 (1)	0	3 (3)
Dystonia	4 (1)	6 (2)	4 (2)	1 (1)	2 (1)	11 (10)
Parkinsonism	14 (3)	14 (5)	16 (8)	0	6 (3)	22 (19)
Unspecified	6 (1)	2 (1)	0	0	0	0

EPS in Short-term, controlled Mania Trials (flexible-doses)

EPS AE	Placebo	ASEN 10-20 mg	OLAN 5-20 mg
	N= 203	N= 379	N= 394
Akathisia	5 (3)	15 (4)	21 (5)
Dyskinesia	0	4 (1)	0
Dystonia	2 (1)	12 (3)	4 (1)
Parkinsonism	3 (2)	16 (4)	17 (4)

8.1.5 COMMON ADVERSE EVENTS

Generally, asenapine 5-10 mg BID, administered sublingually, was reasonably safe and well tolerated in clinical programs for Schizophrenia and Mania. There were no new or unexpected adverse events compared to what one would expect with other atypical antipsychotic medications. The table below summarizes the common adverse events reported in the controlled Schizophrenia trials. Common, drug-related adverse events were: extrapyramidal symptoms, akathisia, sedation, dizziness, weight gain, and oral hypoesthesia. Dose-related adverse events included extrapyramidal symptoms and akathisia. Extrapyramidal symptoms included dystonia, parkinsonism, dyskinesia, extrapyramidal disorder, and movement disorder. Specific cases of dystonia included: oculogyration, torticollis, blepharospasm, and macroglossia. Dyskinesia cases included tardive dyskinesia. Specific adverse reactions included under 'parkinsonism' were rigidity, cogwheel rigidity, hypertonia, gait disturbance, tremor, blunted affect, and masked facies. Generally, the extent of extrapyramidal symptoms related to asenapine was considerably less than that with risperidone and haloperidol.

Adverse events (for n > 2) in Acute (6-week) Schizophrenia Studies- (Cohort A)

Adverse events (for n > 2) in Acute (6-week) Schizophrenia Studies- Cohort A									
Adverse Event N (%)	PLA	ASE <10 mg	ASE 10 mg fixed	ASE 20 mg fixed	ASE 10-20 flexible	ASE 10- 20 all	RIS 6 mg	HAL 8 mg	OLANZ 10- 20
(N)	n = 503	n =298	n = 274	n= 208	n = 90	n = 572	n = 120	n = 115	n = 194
Insomnia	66 (13)	47 (16)	43 (16)	31 (15)	10 (11)	84 (15)	25 (21)	16 (14)	19 (10)
Headache	84 (17)	75 (25)	32 (12)	20 (10)	18 (20)	70 (12)	25 (21)	5 (4)	27 (14)
Agitation	56 (11)	41 (14)	25 (10)	16 (8)	6 (7)	47 (8)	15 (13)	9 (8)	13 (7)
Somnolence*	11 (2)	15 (5)	25 (9)	13 (6)	3 (3)	41 (7)	5 (4)	2 (2)	11 (6)
Anxiety	45 (9)	31 (10)	19 (7)	11 (5)	10 (11)	40 (7)	16 (13)	7 (6)	9 (5)
Akathisia**	12 (2)	2 (1)	11 (4)	22 (11)	3 (3)	36 (6)	5 (4)	17 (15)	9 (5)
Nausea	47 (9)	22 (7)	18 (7)	12 (6)	6 (7)	36 (6)	10 (8)	3 (3)	11 (6)
Sedation*	23 (5)	6 (2)	17 (6)	13 (6)	5 (6)	35 (6)	8 (7)	4 (4)	25 (13)
Constipation	29 (6)	19 (6)	18 (7)	8 (4)	5 (6)	31 (5)	7 (6)	3 (3)	15 (8)
Hypoesthesia oral*	4 (1)	6 (2)	16 (6)	14 (7)	1 (1)	31 (5)	0	0	0
Vomiting	25 (5)	15 (5)	10 (4)	15 (7)	4 (4)	29 (5)	8 (7)	2 (2)	6 (3)
Dizziness*	25 (5)	28 (9)	18 (7)	7 (3)	1 (1)	26 (5)	14 (12)	2 (2)	11 (6)
Dyspepsia	25 (5)	26 (9)	12 (4)	8 (4)	5 (6)	25 (4)	13 (11)	4 (4)	13 (11)
Schizophrenia	28 (6)	29 (10)	6 (2)	13 (6)	3 (3)	22 (4)	5 (4)	8 (7)	1 (1)
Fatigue	13 (3)	9 (3)	12 (4)	6 (3)	2 (2)	20 (4)	10 (9)	0	7 (4)
Parkinsonism	8 (2)	0	9 (3)	7 (3)	1 (1)	17 (3)	0	16 (14)	1 (1)

Tremor	7 (1)	5 (2)	5 (2)	9 (4)	1 (1)	15 (3)	0	5 (4)	5 (3)
Weight gain	2 (<1)	0	6 (2)	4 (2)	5 (6)	15 (3)	4 (3)	1 (1)	13 (7)

*Drug-related: somnolence, akathisia, sedation, hypoesthesia (oral), dizziness, parkinsonism, tremor, weight gain

Adverse events in long-term Schizophrenia Studies (for AE n ≥ 2%) (Cohort B)

Adverse events in long-term Schizophrenia Studies (for AE n ≥ 2%) (Cohort B)		
Adverse event N (%)	**Asenapine flex-dose 10-20 mg/d (n = 908)**	**Olanzapine flex-dose 10-20 mg/d (n = 311)**
Schizophrenia/psychosis	229 (25)	62 (20)
Sedation/somnolence	170 (19)	63 (20)
Insomnia	170 (1()	45 (15)
Depression	141 (16)	40 (13)
Weight increased	125 (14)	95 (31)
Anxiety	118 (13)	22 (7)
Akathisia	89 (1)	11 (4)
Headache	83 (9)	27 (9)
Agitation	48 (5)	10 (3)
Nausea	38 (4)	11 (4)
Fatigue	35 (4)	20 (6)
Parkinsonism	34 (4)	6 (2)
Vomiting	28 (3)	5 (2)
Constipation	27 (3)	6 (2)
Dizziness	25 (3)	10 (3)
Tremor	23 (3)	3 (1)
Hypertension	23 (3)	5 (2)
Asthenia	22 (2)	7 (2)
Weight decreased	22 (2)	8 (3)
Tension	21 (2)	2 (1)

The table below summarizes the common adverse events reported in the controlled mania trials. The findings were quite similar to those in the Schizophrenia trials.

Cohort C (adverse events for n > 2%) in acute, 3-week mania trials

Cohort - AEs for n > 2%) in acute, 3-week mania trials			
Adverse event N (%)	Placebo (n= 203)	ASEN 10-20 mg (n = 379)	Olan 5-20 (n = 394)
Sedation/somnolence	13 (9)	91 (24)	101 (26)
Dizziness	6 (3)	42 (11)	29 (7)
Insomnia	11 (5)	23 (6)	28 (7)
Nausea	11 (5)	20 (5)	8 (2)
Mania	11 (5)	19 (5)	8 (2)
Weight increased	1 (1)	18 (5)	32 (8)
Agitation	8 (4)	17 (5)	18 (5)
Constipation	11 (5)	17 (5)	18 (5)
Hypoesthesia oral	1 (1)	17 (5)	2 (1)

Anxiety	4 (2)	16 (4)	6 (2)
Vomiting	8 (4)	16 (4)	6 (2)
Appetite increased	2 (1)	15 (4)	22 (6)
Akathisia	5 (3)	15 (4)	21 (5)
Dyspepsia	5 (3)	15 (4)	14 (4)
Fatigue	4 (2)	14 (4)	16 (4)
Dry mouth	2 (1)	13 (3)	37 (9)
Arthralgia	2 (1)	11 (3)	3 (1)
Dysguesia	1 (1)	10 (3)	0
Dystonia	2 (1)	10 (3)	4 (1)
Tremor	3 (2)	9 (2)	12 (3)
Back pain	7 (3)	9 (2)	8 (2)
Pain in extremity	1 (1)	9 (2)	6 (2)
Depression	3 (2)	8 (2)	1 (<1)

Adverse events in 12-week, Bipolar, Mania Study (for AE with N > 2%)

AE in 12-week Bipolar, Mania Study (for n ≥ 2%) (Cohort D)				
Adverse event N (%)	PLA/ASEN (wk data) 10-20 mg/d flexible dose	ASEN (12-wk data) 10-20 mg/d flexible dose	ASEN (all) 10-20 mg/d flexible dose	OLAN (12-week data) 5-20 mg/d Flexible dose
(N)	(N = 94)	(N = 181)	(N = 275)	(N = 229)
Mania	5 (5)	8 (4)	13 (5)	8 (4)
Parkinsonism	3 (3)	10 (6)	13 (5)	4 (2)
Hypoesthesia	5 (5)	7 (4)	12 (4)	3 (1)
Vomiting	1 (1)	11 (6)	12 (4)	1 (< 1)
Dyspepsia	0	10 (6)	10 (4)	9 (4)
Dystonia	3 (3)	6 (3)	9 (3)	5 (2)
Diarrhea	2 (2)	7 (4)	9 (3)	8 (4)
Dry mouth	2 (2)	7 (4)	9 (3)	25 (11)
Fatigue	1 (1)	8 (4)	9 (3)	12 (5)
Agitation	2 (2)	6 (3)	8 (3)	9 (4)
Dysgeusia	3 (3)	5 (3)	8 (3)	0
Arthralgia	2 (2)	5 (3)	7 (3)	3 (1)
Suicidal ideation	1 (1)	5 (3)	6 (2)	3 (1)
Salivary hypersecretion	0	6 (3)	6 (2)	3 (1)
Pain in extremity	0	6 (3)	6 (2)	2 (1)

Adverse events in clinical pharmacology studies (n > 2%) Cohort F- healthy subjects

Serious adverse events were reported for 1% of asenapine group and none in the placebo group. There were no deaths in healthy subjects in the clinical pharmacology studies. Adverse events that were probably drug-related included: somnolence, paresthesia oral, hypoesthesia oral, dizziness, dysgeusia, fatigue, headache, restless legs, dizziness postural, dry mouth, restlessness, insomnia, and paresthesia. Dose-related adverse events were: hypoesthesia oral, and dizziness postural.

Cohort F		
		ASENAPINE

Adverse Event N (%)	**Placebo** (N = 96)	< 10 mg/d (n = 657)	10 mg/d (n = 64)	20 mg/d (n = 18)	30 mg/d (n = 6)	All (n = 745)
Somnolence/sedation	6 (6)	358 (55)	29 (45)	9 (50)	6 (100)	402 (54)
Paresthesia oral	1 (1)	245 (37)	38 (59)	9 (50)	3 (50)	295 (40)
Hypoesthesia oral	1 (1)	205 (31)	22 (34)	12 (67)	0	239 (32)
Dizziness	6 (6)	140 (21)	12 (19)	3 (17)	3 (50)	158 (21)
Dysgeusia	0	127 (19)	5 (8)	1 (6)	0	133 (18)
Fatigue	1(1)	93 (14)	34 (53)	2 (11)	0	129 (17)
Headache	8 (8)	99 (15)	20 (31)	5 (28)	3 (50)	127 (17)
Restless legs syndrome	0	72 (11)	5 (8)	0	0	77 (10)
Nausea	4 (4)	61 (9)	10 (16)	2 (11)	0	73 (10)
Dizziness postural	2 (2)	52 (8)	5 (8)	5 (28)	1 (17)	63 (9)
Dry mouth	0	60 (9)	2 (3)	0	0	62 (8)
Restlessness	1 (1)	42 (6)	11 (17)	4 (22)	0	57 (8)
Insomnia	1 (1)	16 (2)	31 (48)	3 (17)	1 (17)	51 (7)
Paresthesia	0	26 (4)	6 (9)	3 (17)	2 (33)	37 (5)
Diarrhea	0	24 (4)	12 (19)	0	0	36 (5)
Akathisia	0	31 (5)	3 (5)	0	0	34 (5)
Oral discomfort	0	34 (5)	0	0	0	34 (5)
Hypotension	0	30 (5)	0	1 (6)	0	31 (4)
Bradycardia	0	27 (4)	0	0	0	27 (4)
Miosis	0	21 (3)	0	0	0	21 (3)
Tachycardia	0	21 (3)	0	0	0	21 (3)
Glossodynia	0	21 (3)	0	0	0	21 (3)
Abdominal pain	2 (2)	17 (3)	1 (6)	1 (6)	0	20 (3)
ALT increased	0	8 (1)	0	0	1 (17)	18 (2)
Dysarthria	0	10 (2)	0	0	0	17 (2)
Dyspnea	0	6 (1)	7 (11)	3 (17)	0	16 (2)
Nasopharyngitis	0	13 (2)	2 (3)	0	0	15 2)

Adverse Events (n > 2%) in Clinical Pharmacology Studies- Patients (Cohort G)

Cohort G							
Adverse event N (%)	Placebo (n = 61)	Asenapine					QUET (n = 37)
		< 10 mg (n = 66)	10 mg/d (n = 196)	20 mg/d (n = 37)	≥ 30 mg (n = 64)	All ASE (n = 363)	
Headache	12 (20)	20 (30)	11 (6)	7 (19)	7 (11)	45 (12)	4 (11)
Insomnia	10 (16)	10 (15)	17 (9)	10 (27)	7 (11)	44 (12)	7 (19)
Agitation	7 (11)	7 (11)	24 (12)	3 (8)	3 (5)	37 (10)	6 (16)
Sedation	5 (8)	5 (8)	13 (7)	7 (19)	11 (17)	36 (10)	4 (11)
Anxiety	6 (10)	17 (26)	5 (3)	2 (5)	9 (14)	33 (9)	1 (3)
Somnolence	9 (15)	3 (5)	9 (5)	9 (24)	9 (14)	30 (8)	3 (8)
Dizziness	4 (7)	10 (15)	5 (3)	6 (16)	4 (6)	25 (7)	1 (3)
Dysgeusia	4 (7)	3 (5)	5 (3)	9 (24)	8 (13)	25 (7)	1 (3)
Restlessness	1 (2)	4 (6)	5 (3)	8 (22)	4 (6)	21 (6)	1 (3)
Hypoesthesia, oral	0	2 (3)	4 (2)	8 (22)	7 (11)	21 (6)	0
Dyspepsia	10 (16)	5 (8)	1 (1)	2 (5)	9 (14)	17 (5)	7 (19)
Nausea	5 (8)	13 (20)	2 (1)	2 (5)	0	17 (5)	2 (5)
Constipation	4 (7)	2 (3)	2 (1)	4 (11)	7 (11)	15 (4)	3 (8)
Fatigue	4 (7)	5 (8)	2 (1)	4 (11)	2 (3)	13 (4)	1 (3)
Extrapyramidal d/o	2 (3)	1 (2)	6 (3)	0	3 (5)	10 (3)	0
Tachycardia	2 (3)	6 (9)	2 (1)	1 (3)	1 (2)	10 (3)	2 (5)

Dermatitis, contact	4 (7)	10 (15)	0	0	0	10 (3)	0
Irritability	2 (3)	8 (12)	0	1 (3)	1 (2)	10 (3)	0
Diarrhea	2 (3)	4 (6)	1 (4)	2 (5)	1 (2)	9 (2)	0
Blood pressure ↑	1 (2)	2 (3)	6 (3)	0	1 (2)	9 (2)	0
Vomiting	5 (8)	7 (11)	0	3 (8)	0	8 (2)	4 (11)
Pruritus	5 (8)	7 (11)	0	1 (3)	0	8 (2)	0

8.1.6. VITAL SIGNS FINDINGS

Overall, treatment with asenapine had little effect on blood pressure and heart rate; however, there were cases of orthostatic cases without significant consequences. There was no significant effect on mean systolic, diastolic blood pressure, and heart rate; there were few subjects with clinically significant changes in blood pressure or heart rate. Treatment with asenapine was associated with a mean weight gain of approximately 1.1 kg, compared to a weight gain of 0.1 kg with placebo treatment. Approximately 5% of subjects in the asenapine group had weight gain of > 7%, compared to 2% in the placebo group.

8.1.7. ELECTROCARDIOGRAM (ECG) FINDINGS

At the intended therapeutic doses of 5 mg and 10 mg BID, treatment with asenapine resulted in a relatively small prolongation of the QTc interval. The magnitude was less than that observed with quetiapine treatment. There was no dose-response relationship; however, there was an exposure-response relationship. The point estimates of QTcF prolongation associated with mean steady state plasma asenapine Cmax values were less than 5 msec for all doses studied and were less than those for quetiapine (7-8 msec). In the controlled Schizophrenia and mania trials, there were no cases of QTc interval > 500 msec, and there were no cases of increases in QTcF > 60 msec.

8.1.8. CLINICAL LABORATORY FINDINGS

Overall, asenapine treatment had no significant effect on clinical laboratory parameters. However, there was a modest increase in mean transaminase concentrations, and there were a small number of cases of serum transaminase concentrations greater than three times the upper limit of normal. There were no serious adverse events associated with increases in transaminase concentration. Furthermore, there was no effect on bilirubin concentration, and there were no cases meeting criteria for Hy's law.

8.1.8.1 Hematology Laboratory Findings

<u>Hematologic Adverse Events in Cohort E</u>

Abnormalities in hematology parameters were reported as adverse events by less than 0.5% of subjects treated with asenapine. There were 5 (0.3%) cases of anemia; one was a serious adverse event. There was one (0.1%) case of neutropenia. (Currently, the details

of the case are unavailable). There was one (0.1%) case of thrombocytopenia. There were no hematologic adverse events in the placebo group. In the olanzapine group, there were 4 (0.4%) cases of anemia; one was a serious adverse event, and one led to discontinuation. There were 5 (0.6%) cases of neutropenia in the olanzapine group; one led to discontinuation. There were 2 (0.2%) cases of leukopenia in the olanzapine group; one led to discontinuation. In the haloperidol group, there were 5 (4.3%) cases of anemia, and one case (0.9%) of leukopenia. Few subjects reported adverse events related to hematology investigation results. Three subjects (0.2%) in the asenapine 5-10 mg BID group had hemoglobin decreased (0 placebo), 2 (0.1%) reported hematocrit decreased (0 placebo), and 1 (0.1%) reported hemoglobin increased (0 placebo).

Hematology laboratory abnormalities reported as adverse events (phase 2/3 studies)

Adverse Event SOC/ Preferred Term n (%)	Placebo (N=706)	Asenapine			Risp 3 mg BID (N=120)	Halo 4 mg BID (N=115)	Olan 5-20 mg QD (N=899)
		<5 mg BID (N=298)	5-10 mg[a] BID (N=1953)	All (N=2251)			
Blood and lymphatic disorders							
Anaemia	0	0	5 (0.3)	5 (0.2)	0	5 (4)	4 (0.4)
Hypochromic anaemia	0	0	0	0	0	1 (1)	1 (0.1)
Thrombocytopaenia	0	0	1 (0.1)	1 (0.04)	0	0	0
Leukocytosis	2 (0.3)	0	3 (0.2)	3 (0.1)	0	1 (1)	1 (0.1)
Leukopenia	0	0	0	0	0	1 (1)	2 (0.2)
Neutropenia	0	0	1 (0.1)	1 (0.04)	0	0	5 (0.6)
Investigations							
Haematocrit decreased	0	0	2 (0.1)	2 (0.1)	0	0	1 (0.1)
Haematocrit increased	0	0	0	0	0	1 (0.9)	1 (0.1)
Haemoglobin decreased	0	0	3 (0.2)	3 (0.1)	0	0	1 (0.1)
Haemoglobin increased	0	0	1 (0.1)	1 (0.04)	0	0	1 (0.1)
Monocyte count incr	0	1 (0.3)	0	1 (0.04)	0	0	0
Neutrophil count decr	1 (0.1)	1 (0.3)	1 (0.1)	2 (0.1)	0	0	0
Neutrophil count incr	1 (0.1)	3 (1.0)	2 (0.1)	5 (0.2)	0	0	1 (0.1)
Platelet count decreased	1 (0.1)	0	0	0	0	0	0
WBC count decreased	0	1 (0.3)	1 (0.1)	2 (0.1)	0	0	2 (0.2)
WBC count increased	2 (0.3)	2 (0.7)	2 (0.1)	4 (0.2)	0	0	2 (0.2)

Hematologic Laboratory Parameters in Cohort E

Mean values: no significant changes in mean values
Specifically, no significant changes in absolute neutrophil counts in controlled studies

Central Tendency in Controlled Schizophrenia and Mania Trials:

Asenapine < 5 mg BID: neutrophil ↑1.67%
Asenapine 5 mg BID: neutrophil ↑8.95%
Asenapine 10 mg BID neutrophil ↑8.26%
Asenapine 5-10 mg BID flexible: neutrophil ↑7.32%

Asenapine all 5-10 BID: neutrophil ↑8.46%
Risperidone 6 mg: Neutrophil ↑3.45

Olanzapine neutrophil ↓−0.3

Haloperidol 8 mg: neutrophil ↑2.29

Central Tendency in Controlled Mania:

Placebo: ↑1.8

Asenapine: ↑2%

Olanzapine: ↓4.88%

Outlier Analysis

A larger proportion of subjects in the asenapine 5-10 mg BID group had decreases in hemoglobin (9.6%) compared to the placebo group (5.4%). The proportion in the asenapine group was less than that observed in the olanzapine group (12.9%). The proportion of subjects with decreases in red blood cell count was comparable between the asenapine and placebo groups (7.5% and 6.7% , respectively).

A larger proportion of subjects in the asenapine 5-10 mg BID group had decreases in white blood cell count (7.1%) compared to the placebo group (2.7%). The proportion was comparable to the olanzapine group (8.0%). A greater proportion of subjects had increases in white blood cell count (15.1%, asenapine 5-10 mg BID) compared to decreases for all treatment groups.

A greater proportion of subjects in the asenapine 5-10 mg BID group had decreases in platelet counts (2.7%) compared to the placebo group (0.7%) for the assessment of shifts at any time point. However, this was less than the proportion observed in the olanzapine group (4.0%).

Hematology test	Placebo (N=706)	Asenapine <5 mg BID (N=298)	Asenapine 5-10 mg[a] BID (N=1953)	Asenapine All (N=2251)	Risp 3 mg BID (N=120)	Halo 4 mg BID (N=115)	Olan 5-20 mg QD (N=899)
Hemoglobin (g/dL) N	617	283	1825	2108	117	102	829
Baseline mean	144.1	145.3	144.9	144.9	145.4	141.8	145.0
Change from baseline[b]	-0.3	1.5	-0.2	0.0	-2.9	-1.5	-1.0
n (%) L/N to High[c]	8 (1.3)	4 (1.4)	40 (2.2)	44 (2.1)	1 (0.9)	2 (2.0)	16 (2.0)
n (%) H/N to Low[c]	31 (5.4)	18 (6.6)	159 (9.6)	177 (9.2)	12 (10.6)	7 (7.2)	95 (12.9)
<80 (F), <100 g/L (M)	1 (0.2)	1 (0.4)	8 (0.4)	9 (0.4)	1 (0.9)	0	4 (0.5)
Hematocrit (%) N	615	283	931	1214	117	101	523
Baseline mean	43.7	44.1	44.1	43.9	43.4	43.7	44.0
Change from baseline[b]	-0.0	0.6	-0.5	-0.3	-1.1	-0.5	-0.9
n (%) L/N to High[c]	19 (3.2)	2 (0.7)	54 (3.0)	56 (2.7)	0	3 (3.1)	23 (2.8)
n (%) H/N to Low[c]	34 (5.8)	19 (7.1)	111 (6.4)	130 (6.5)	17 (15.0)	7 (7.3)	60 (7.8)
White Blood Cells ($x10^9$/L) N	617	283	1822	2105	117	102	827
Baseline mean	7.4	7.8	7.2	7.3	7.9	7.2	7.3
Change from baseline[b]	0.1	0.3	0.3	0.3	0.0	0.1	-0.0
n (%) L/N to High[c]	68 (12.1)	50(19.9)	256(15.1)	306 (15.7)	19 (19.2)	10(10.8)	89 (11.7)
n (%) H/N to Low[c]	16 (2.7)	9 (3.2)	124 (7.1)	133 (6.6)	7 (6.0)	1 (1.0)	63 (8.0)
>16 x 10^9/L	7 (1.1)	6 (2.1)	27 (1.5)	33 (1.6)	1 (0.9)	0	7 (0.8)
<2 x 10^9/L	0	1 (0.4)	2 (0.1)	3 (0.1)	0	0	1 (0.1)
Platelet count ($x10^9$/L) N	606	281	1809	2090	117	98	824
Baseline mean	276.0	252.2	262.3	261.0	270.5	285.0	266.6
Change from baseline[b]	7.3	9.4	11.9	11.5	-5.5	1.5	3.5
n (%) L/N to High[c]	30 (5.3)	17 (6.1)	105 (6.0)	122 (6.0)	3 (2.8)	5 (5.4)	25 (3.2)
n (%) H/N to Low[c]	4 (0.7)	6 (2.2)	48 (2.7)	54 (2.6)	3 (2.6)	2 (2.1)	32 (4.0)
>700 x 10^9/L	1 (0.2)	0	3 (0.2)	3 (0.1)	1 (0.9)	0	0
<50 x 10^9/L	0	1 (0.4)	3 (0.2)	4 (0.2)	0	0	2 (0.2)

An analysis of subjects with shifts to a low absolute count is presented in the table below. Among all of the controlled Schizophrenia trials, there were 18 (2.07%) subjects with shifts to low absolute neutrophil counts. For one subject, neutropenia was reported as an adverse event. By comparison, there were 8 (1.8%) subjects in the placebo group with shifts to a low absolute neutrophil count.

Shifts to low absolute neutrophil count in Controlled Schizophrenia Trials

PLA	ASEN <5 BID	ASEN 5 BID	ASEN 10 BID	ASEN 5-10 BID FLEX	ASEN 5-10 ALL	RIS 6 MG	OLAN 10-20	HAL 8 MG
N= 503	N= 298	N= 274	N= 208	N= 90	N= 572	N= 120	N= 194	N= 115
8 (1.8)	7 (2.5)	7 (2.9)	3 (1.6)	1 (1.4)	11 (2.2)	3 (2.7)	5(3)	1(1)

In the controlled mania trials, there were 6 (2.1%) subjects with shifts to a low absolute neutrophil count. In the placebo group, there was 1 (0.7%) subject and in the olanzapine group, there were 5 (1.6%) subjects with shifts to low absolute neutrophil counts.

Table. Shifts to low absolute neutrophil count in Controlled Mania Trials

PLA	ASEN 5-10 BID	OLAN 5-20
N= 203	N= 379	N= 394
1 (0.7)	6 (2.1)	5 (1.6)

8.9.1.2 Chemistry Laboratory Findings

The mean serum chemistry findings are presented in the tables below.

Schizophrenia Controlled Trials: Mean Changes in Chemistry Parameters from Baseline to Last Assessment

Chemistry Parameter	PLAC	ASEN <5 BID	ASEN 5 BID	ASEN 10 BID	ASEN 5-10 BID FLEX	RIS 6 MG	OLAN 10-20 MG	HAL 8 MG
CPK	+39%		+40%	+30%	+19%		+2%	+2%
Creatinine	+2.1%	−.02%	+1%	+8%	+1%	+2%	+0.3%	+0.2%
Bilirubin Total	+18%	+5%	+6%	+5%	+14%	−2	−3%	+8%
ASAT	+2%	+7%	+6%	+9%	+6%	+4%	+8%	−9%
ALAT	−2%	+12%	+4.2%	+10%	+2%	+9%	+14%	−8%
Cholesterol Total	−2	+0.1%	−1%	+2%	+1%	+0.4%	+4%	−1%
HDL Cholesterol	1%		+1%	+2%	−0.4%		+2%	+1%
LDL Cholesterol	+0.1%		−0.2%	+2%	+2%		+2%	−1%
Triglyceride Fasting	−9%	−12%	−1%	+0.1%	+19%		+13%	−6%
Glucose Fasting	−2%	+0.4%	+4%	+1%	+7%	+7%	+4%	+2%
Prolactin	−42%	−51%	−26	−28	+19%	+173%	−12%	+6%

Mania Controlled Trials: Mean Changes in Chemistry Parameters from Baseline to Last Assessment

Chemistry Parameter	PLAC	ASEN 5-10 MG BID FLEX	OLAN 10-20 MG QD
CPK	−1%	+75%	+39%
Creatinine	--	+1%	−0.3%
Bilirubin Total	+12%	−7%	−6%
ASAT	−7%	+24	+25%
ALAT	−14%	+28	+46%
Cholesterol Total	−1%	+1%	+7%
HDL Cholesterol		+2%	+2%
LDL Cholesterol	−2%	+2%	+6%
Triglyceride Fasting	−11%	−2%	+21
Glucose Fasting	−1%	−6	+1%
Prolactin			

The serum prolactin findings are presented in the table below.

Prolactin	**Placebo (N=706)**	**Asenapine**			**Risp 3 mg BID (N=120)**	**Halo 4 mg BID (N=115)**	**Olan 5-20 mg QD (N=899)**
		<5 mg BID (N=298)	**5-10 mg[a] BID (N=1953)**	**All (N=2251)**			
Prolactin (ug/L) N	465	283	535	818	116	106	180
Baseline median	14.3	16.4	15.8	15.9	12.8	25.3	13.3
Change from baseline[b]	-3.4	-5.9	-2.3	-3.2	21.2	2.5	0.4
Prolactin (U/L) N	151		1280	1280			648
Baseline median	0.3		0.4	0.4			0.4
Change from baseline[b]	-0.0		-0.1	-0.1			0.0
n (%) L/N to High[c]	80 (19.3)	35(21.7)	452 (44.4)	487 (41.3)	70 (97.2)	33 (71.7)	254(50.6)
n (%) H/N to Low[c]	5 (0.8)	2 (0.7)	99 (5.6)	101 (4.9)	0	0	8 (1.1)
n (%) L/N to High (last)	45 (10.9)	15 (9.3)	238 (23.4)	253 (21.5)	56 (77.8)	25 (54.4)	16 (32.9)
n (%) H/N to Low (last)	4 (0.7)	1 (0.4)	46 (2.6)	47 (2.3)	0	0	4 (0.7)
N	627	285	1831	2116	116	106	833
>4 x ULN	6 (1.0)	1 (0.4)	114 (6.2)	115 (5.4)	32 (27.6)	11 (10.4)	33 (4.0)
>2 x ULN	30 (4.8)	14 (4.9)	351 (19.2)	365 (17.2)	83 (71.6)	37 (34.9)	148(17.8)
>1 x ULN	114(18.2)	49(17.2)	709 (38.7)	758 (35.8)	109 (94)	55 (51.9)	379(45.5)

8.2 DRUG DISCONTINUATION PHENOMENA

Drug discontinuation signs and symptoms were not formally or prospectively studied in a directed manner in any of the asenapine studies. There were no patterns of signs or

symptoms suggesting that there is a discontinuation syndrome associated with discontinuing treatment with asenapine.

8.3 ABUSE POTENTIAL

There were no systematic clinical studies with asenapine to assess the potential for abuse, tolerance or dependence. There is no evidence that subjects self-administered asenapine in a pattern consistent with misuse or abuse.

8.4 HUMAN REPRODUCTION AND PREGNANCY DATA

Studies to assess the effects of asenapine on human reproduction and development have not been conducted. There were cases of pregnancy in the clinical studies. Nine female subjects became pregnant while participating in a clinical study with asenapine as did 3 female partners of 3 male subjects participating in the asenapine trials. Of the participating female subjects, 1 subject was receiving asenapine, 3 were receiving olanzapine, and for 5 subjects, the study medication is still blinded because they are participating in ongoing studies. The one subject with known exposure to asenapine was included in study A751006; she was treated with 10 mg BID for 4 wks, when a pregnancy test was positive. Study medication was discontinued and an abortion was induced. One subject, in an ongoing blinded study, included in Table 126, reported she was pregnant after completing the study but never had a positive pregnancy test and later claimed she was never pregnant. This subject is listed but not counted in the 9 subjects. Of the 3 male subjects, all received asenapine (2 participated in a drug interaction study and one participated in the bipolar mania study A7501005). The known information on these subjects is summarized in Table 126.

8.5 OVERDOSE EXPERIENCE

Experience with asenapine overdose is limited. Based on the limited amount of experience, it appears that overdose with asenapine is not associated with a high degree of toxicity. This might be related to the extremely low oral bioavailability of asenapine when the drug product is completely swallowed.

In premarketing clinical studies, there were 3 subjects who had an accidental or intentional acute overdosage of asenapine. Two cases involved large overdoses of 100 and 400 mg asenapine and one case involved an overdose of 50 mg asenapine.

A 45 year old subject in the asenapine 5 mg BID group (study041021, short-term schizophrenia study) attempted suicide by means of an overdose on Day 29 of the study. He ingested 30 placebo tablets and 20 asenapine (5 mg) tablets in combination with cocaine and alcohol. He was hospitalized the next day and tested positive for cocaine. Adverse events reported during the hospitalization included decreased serum potassium and mild anemia. Anxiety was also reported and he was treated with lorazepam and quetiapine. He recovered and was discharged seven days later. The event was not considered related to study drug.

A 19 year old male [111005] in the asenapine 5 to 10 mg BID group (study 25517, long-term schizophrenia study) attempted suicide by means of an overdose on Day 73 of the study. He ingested 30 to 40 asenapine (10 mg) tablets and was hospitalized. He also had symptoms of agitation and confusion. His stomach was emptied and he recovered and was discharged the same day. Laboratory assessments performed three days later did not show any abnormality. The events were considered possibly related to study drug.

A 29 year old Caucasian female [41271007] in the asenapine 5 to 10 mg BID group (study A7501004, 3-week bipolar mania study) unintentionally took five extra doses of asenapine 10 mg during his second week in the study. There were no adverse events reported from this overdose. In addition, there was a 32 year old Black male [138010] who took two extra doses of asenapine 5 mg (study 041021) and the ECG showed bradycardia, supraventricular complexes, and intraventricular conduction; his blood pressure was 128/83 mmHg and heart rate was 47 beats/min. The SAEs of bradycardia and bundle branch block were recorded for this subject; however, the subject denied any symptoms. Asenapine 10 mg is not considered an overdose since the effective dose of asenapine is 5 to 10 mg BID; however, the subject took more than his prescribed dose for this protocol.

Overdoses with asenapine consisted of ingestion of 50 mg, 100 mg, and 400 mg; doses that are 2.5 to 20 times the maximum tolerated dose (20 mg BID) used in the clinical study program. Except for agitation and confusion seen with the highest overdose (400 mg), no major adverse events occurred. Asenapine administration sublingually has a bioavailability of 35% and the absorption is not linear. It is probable that any excessive doses of the drug will be ingested orally and the oral route of administration of asenapine has an even lower bioavailability (< 2%).

Management of Overdose

No specific information is available on the treatment of overdose with asenapine. There is no specific antidote. The possibility of multiple drug involvement should be considered. An electrocardiogram should be obtained and the management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulations may worsen hypotension in the setting of asenapine-induced alpha blockade). In case of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

8.6 POSTMARKETING SAFETY DATA

There are no postmarketing safety data, because asenapine has not been marketed in any country.

9. ADDITIONAL CLINICAL ISSUES

9.1 DOSING REGIMEN AND ADMINISTRATION

9.1.1 Schizophrenia

The recommended dose for the acute treatment of Schizophrenia is 5 mg BID administered sublingually. Efficacy was not clearly demonstrated for the 10 mg BID dose level. Furthermore, there were some important dose-related adverse drug reactions (akathisia, extrapyramidal symptoms).

9.1.2 Acute Mania associated with Bipolar Disorder

For the acute treatment of Mania associated with Bipolar Disorder, the recommended starting dose is 10 mg SL BID. The dose can be decreased within the dose range of 5-10 mg BID as needed, if patients experience adverse events.

9.1.3 Hepatic Impairment

Adjustment of the dose may be necessary for patients with moderate hepatic impairment. Currently, asenapine is contraindicated in patients with severe hepatic impairment.

9.2. DRUG-DRUG INTERACTIONS

One should use caution in the coadministration of asenapine with drugs that inhibit the isoenzyme CYP1A2 (such as fluvoxamine). Inhibition of CYP1A2 by fluvoxamine increased asenapine exposure by approximately 30%. One should also use caution when co-administering asenapine with drugs that induce CYP1A2, such as carbamazepine. Coadministration with carbamazepine decreased asenapine exposure by approximately 35%. Asenapine has inhibitory effects on the isoenzyme CYP2D6. Exposure to paroxetine increased two-fold when co-administered with asenapine. Thus, one should use caution when co-administered with drugs that are metabolized significantly by CYP2D6.

One should use caution when co-administering asenapine with other drugs that have sedative and CNS-depressant effects.

9.3 SPECIAL POPULATIONS

9.3.1 Hepatic Impairment

Severe hepatic impairment can increase asenapine exposure up to 7-fold, compared to exposure in the presence of normal hepatic function. With moderate hepatic impairment, asenapine exposure can increase up to two-fold.

9.3.2 Renal Impairment

Based on limited pharmacokinetic data in patients with various degrees of renal impairment, dosage adjustment based on renal impairment does not appear to be necessary.

9.3.3 Elderly

Asenapine pharmacokinetics and pharmacodynamics were not studied in elderly patients to any significant degree. As with many drugs, one should use caution when administering asenapine in the elderly, since the elderly are at increased risk of hepatic and renal impairment.

9.4.4 Gender

There were no dedicated clinical pharmacology studies investigating potential differences in asenapine pharmacokinetics between male and female subjects. Among the 346 subjects in the population pharmacokinetic analysis, 15% of subjects were female. In the analysis, gender was assessed as a potential covariate on clearance, but no significant difference was observed. In addition, plasma protein binding studies indicated that there was no difference between plasma from male and female subjects. Based on the limited data, there is no evidence of gender-related differences in the pharmacokinetics of asenapine. There is no recommendation for asenapine dose adjustment based on gender.

9.3.5 Pregnancy and Lactation

Studies to assess the effects of asenapine on human reproduction and development have not been conducted. Treatment with asenapine is not recommended for use during pregnancy, unless it is clearly necessary. It is not known whether asenapine or its metabolites are excreted in human milk. However, animal data indicate that asenapine does cross the placenta in rats and rabbits, and it is present in the milk of lactating rats. It is recommended that women treated with asenapine should not breast-feed.

9.3.6 Pediatrics

A single, small study in adolescents suggested that the pharmacokinetics of asenapine were similar between adolescents and adults. The study demonstrated that, compared to adults, adolescents swallowed a higher proportion of the asenapine dose. Asenapine has not been studied in children below the age of 13.

9.4 LITERATURE REVIEW

The sponsor provided journal articles as well as brief synopsis. I have reviewed the articles. The review is included in Appendix 4. In summary, a review of the literature on asenapine does not contribute significantly to the review of the NDA.

9.6 POSTMARKETING RISK MANAGEMENT PLAN

The company submitted a synopsis of a Risk Management Plan that consisted of routine pharmacovigilance activities. The items included the types of adverse events that are commonly associated with atypical antipsychotic drugs. There are no safety findings of specific concern with asenapine. Reviewers from the Office of Surveillance and Epidemiology have reviewed the proposed Risk Management Plan, and they have concluded that a specific RMP for asenapine is not necessary. I concur with their conclusions.

10. OVERALL ASSESSMENT

10.1 CONCLUSIONS

10.1.1 EFFICACY

The primary objective of the controlled, short-term Schizophrenia trials was to evaluate the efficacy of asenapine (5-10 mg BID) compared to placebo, as measured by the Positive and Negative Syndrome Scale (PANSS). Two of these studies (004 and 023) demonstrated the efficacy of asenapine 5 mg BID SL. However, 10 mg BID was not demonstrated to be efficacious in Study 023, as measured by the pre-specified primary statistical analysis plan (last observation carried forward). However, the results of a non-primary statistical analysis plan (mixed-model repeated measure) suggested that the 10 mg BID dose was efficacious in the treatment of Schizophrenia. In two other similarly designed studies (021 and 022), asenapine was not efficacious in either fixed doses of 5 mg BID or 10 mg BID or as flexible doses of 5-10 mg BID.

In the controlled, short-term mania trials, the primary objective was to evaluate the efficacy of asenapine compared with placebo in the treatment of subjects with manic or mixed episodes associated with Bipolar I Disorder, as measured by the Young-Mania Rating Scale. In both trials, asenapine 5-10 mg BID was demonstrated to be efficacious in the acute treatment of mania.

10.1.2 SAFETY

Generally, asenapine 5-10 mg BID, administered sublingually, was reasonably safe and well tolerated in clinical programs for Schizophrenia and Mania. There were no new or unexpected adverse events compared to what one would expect with other atypical antipsychotic medications.

The deaths in both programs were not related to treatment with asenapine; they were associated with the illnesses under treatment or with other medical conditions. The majority of the deaths were suicides (8 of 15), and the suicide rates in the studies were similar to those in other studies of Schizophrenia and Mania. Furthermore, the suicide rates adjusted for duration of exposure were similar among treatments (asenapine, placebo, and active-control drugs).

The majority of serious adverse events were related to the illnesses under treatment (psychotic and manic symptoms). The relatively few serious adverse events that were possibly or probably related to treatment with asenapine were: syncope, akathisia, somnolence, rhabdomyolysis, bradycardia, and dystonia. Similarly, the majority of adverse events associated with discontinuation were related to the illnesses under treatment (psychotic and manic symptoms). Adverse events leading to discontinuation related to asenapine treatment were: transaminase elevation, akathisia, convulsion, sedation, oral hypoesthesia, dystonia, tremor, dizziness, weight gain

Common, drug-related adverse events were: extrapyramidal symptoms, akathisia, sedation, dizziness, weight gain, and oral hypoesthesia. Dose-related adverse events included extrapyramidal symptoms and akathisia. Extrapyramidal symptoms included dystonia, parkinsonism, dyskinesia, extrapyramidal disorder, and movement disorder. Specific cases of dystonia included: oculogyration, torticollis, blepharospasm, and macroglossia. Dyskinesia cases included tardive dyskinesia. Specific adverse reactions included under 'parkinsonism' were rigidity, cogwheel rigidity, hypertonia, gait disturbance, tremor, blunted affect, and masked facies. Generally, the extent of extrapyramidal symptoms related to asenapine was considerably less than that with risperidone and haloperidol.

Overall, treatment with asenapine had little effect on blood pressure and heart rate; however, there were cases of orthostatic cases without significant consequences. Treatment with asenapine was associated with a mean weight gain of approximately 1.1 kg, compared to a weight gain of 0.1 kg with placebo treatment. In a dedicated QT study, asenapine treatment was associated with a modest degree of QT prolongation which was exposure-related but not dose-related. Overall, asenapine treatment had no significant effect on clinical laboratory parameters. However, there was a modest increase in mean transaminase concentrations, and there were a small number of cases of serum transaminase concentrations greater than three times the upper limit of normal. There were no serious adverse events associated with increases in transaminase concentration. Furthermore, there was no effect on bilirubin concentration, and there were no cases meeting criteria for Hy's law.

10.2 RECOMMENDATION ON REGULATORY ACTION

I recommend that the Division take an approvable action for the two indications sought:

1. Asenapine for the treatment of Schizophrenia in adults
2. Asenapine for the treatment of acute mania associated with Bipolar Disorder in adults.

For each indication, two adequate and well controlled trials demonstrated the efficacy of asenapine. Furthermore asenapine was reasonably safe and well tolerated in subjects with a diagnosis of Schizophrenia or Bipolar Disorder, Acute Manic or Mixed Episode.

10.3 RECOMMENDATION ON POSTMARKETING ACTION

10.3.1 Risk Management Activity

I recommend that the Division discuss with the sponsor specific plans for pharmacovigilance regarding the potential adverse reaction, agranulocytosis. For the safety data for asenapine reviewed to date, there is not a signal for agranulocytosis. However, agranulocytosis is associated with other atypical antipsychotics, particularly with drugs that have structural similarities with asenapine (clozapine, quetiapine and olanzapine). In my opinion, it would be helpful to have further discussion internally and with the DPP safety team about monitoring and managing the potential risk of agranulocytosis.

10.3.2 Required Phase 4 Commitments

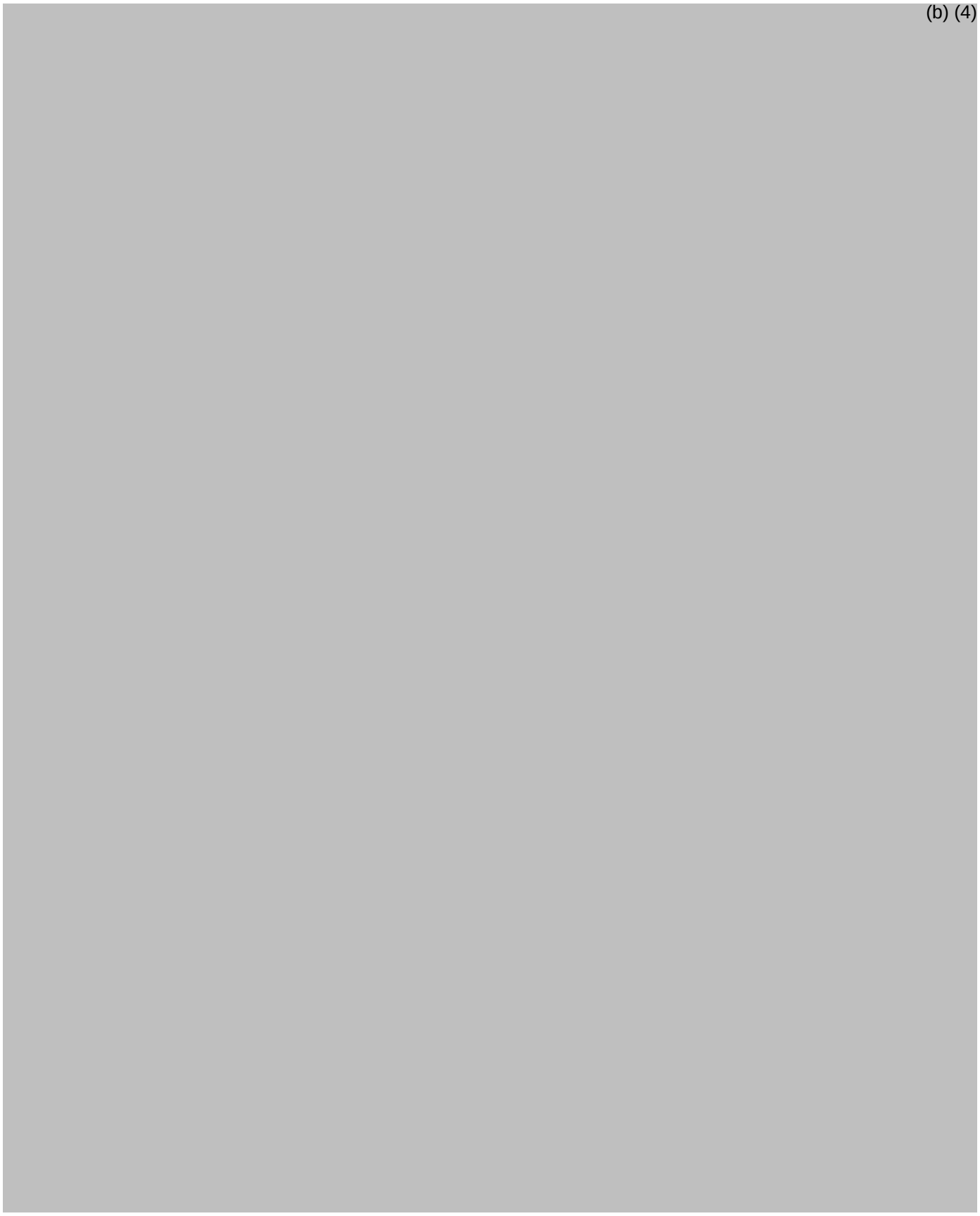
I recommend that the Division request that the sponsor conduct adequate and well controlled long-term maintenance studies in Schizophrenia and Bipolar Disorder. For Bipolar Disorder, the maintenance study should be appropriately designed to assess the efficacy of asenapine in preventing all types of mood episodes associated with Bipolar Disorder (depression, mania, and mixed episodes).

In addition, I recommend that we discuss internally and with the Pediatrics division, the types of pediatric studies that would be indicated. This would partially depend on an assessment of the postmarketing safety profile of asenapine in adults.

10.3.3 Other Phase 4 Requests

Currently, I do not recommend additional Phase 4 requests.

11 LABELING REVIEW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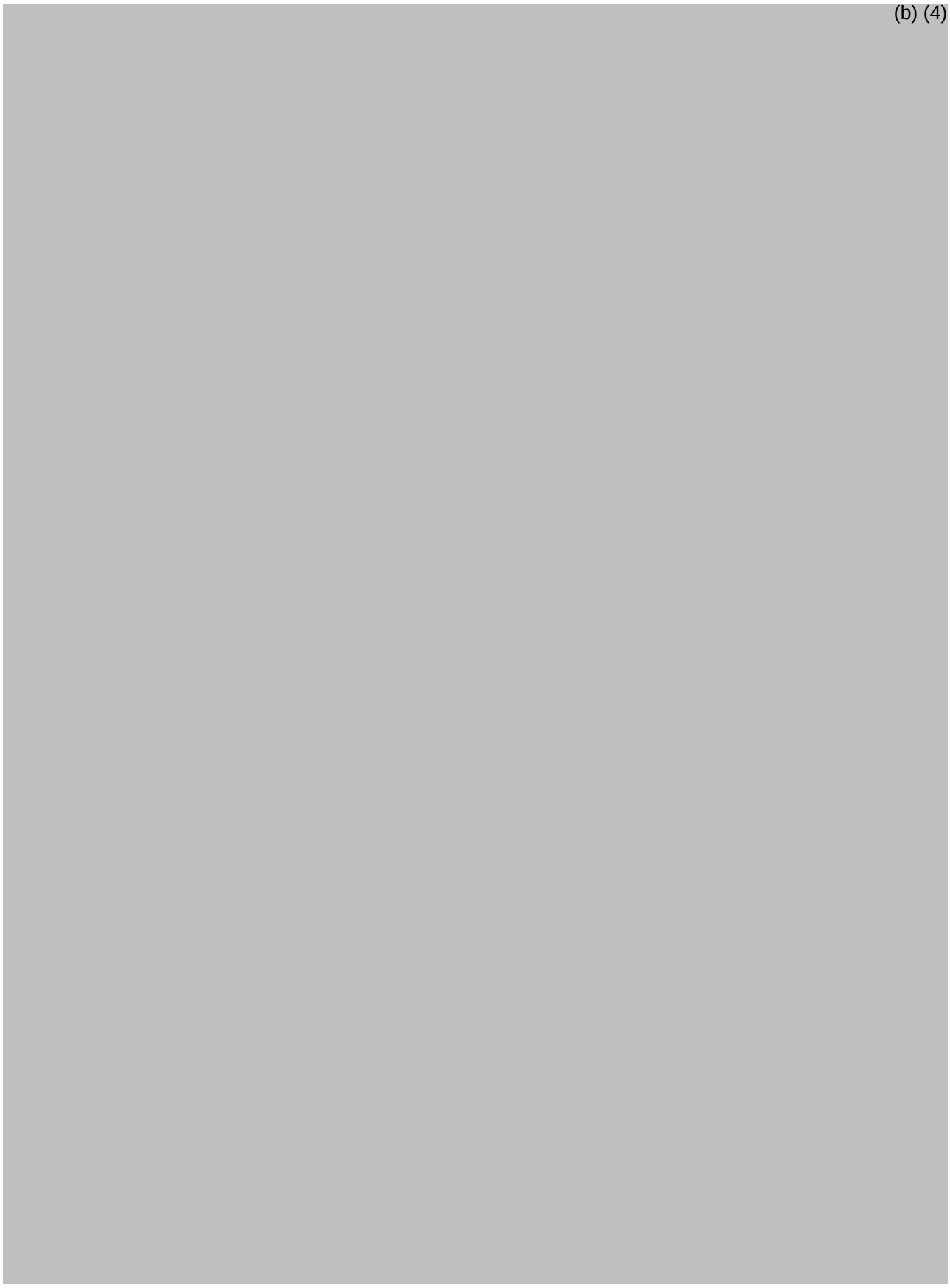
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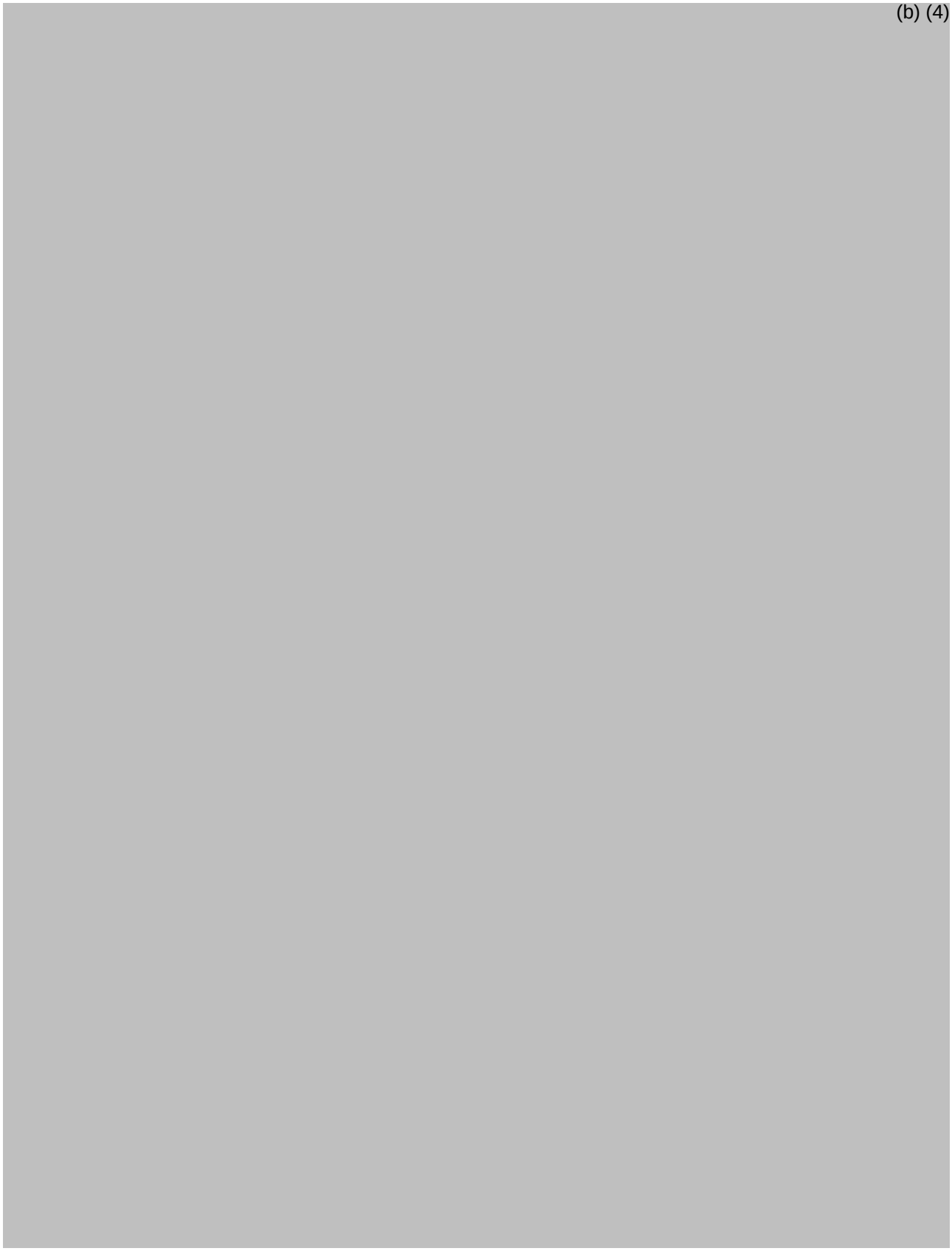
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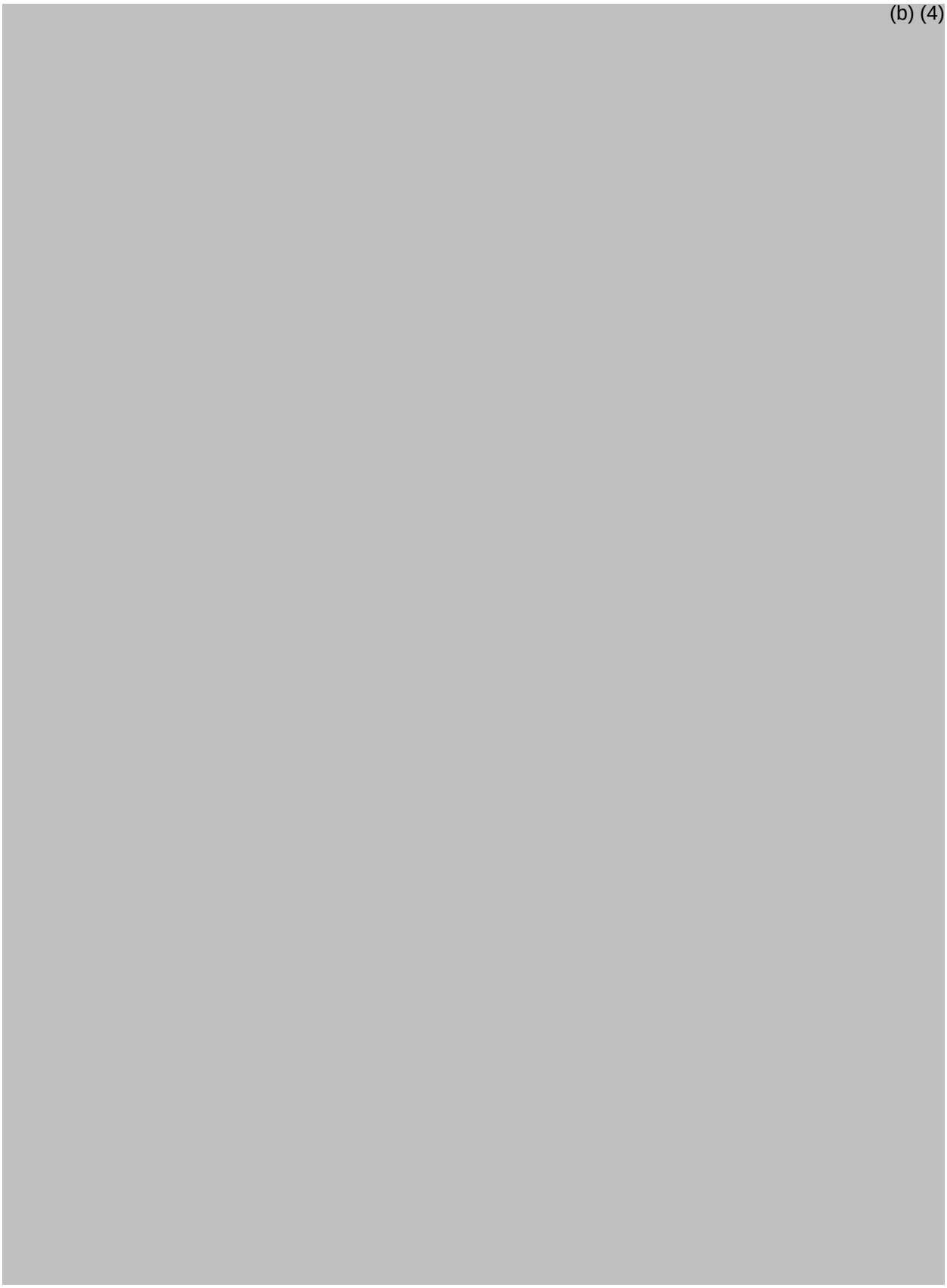
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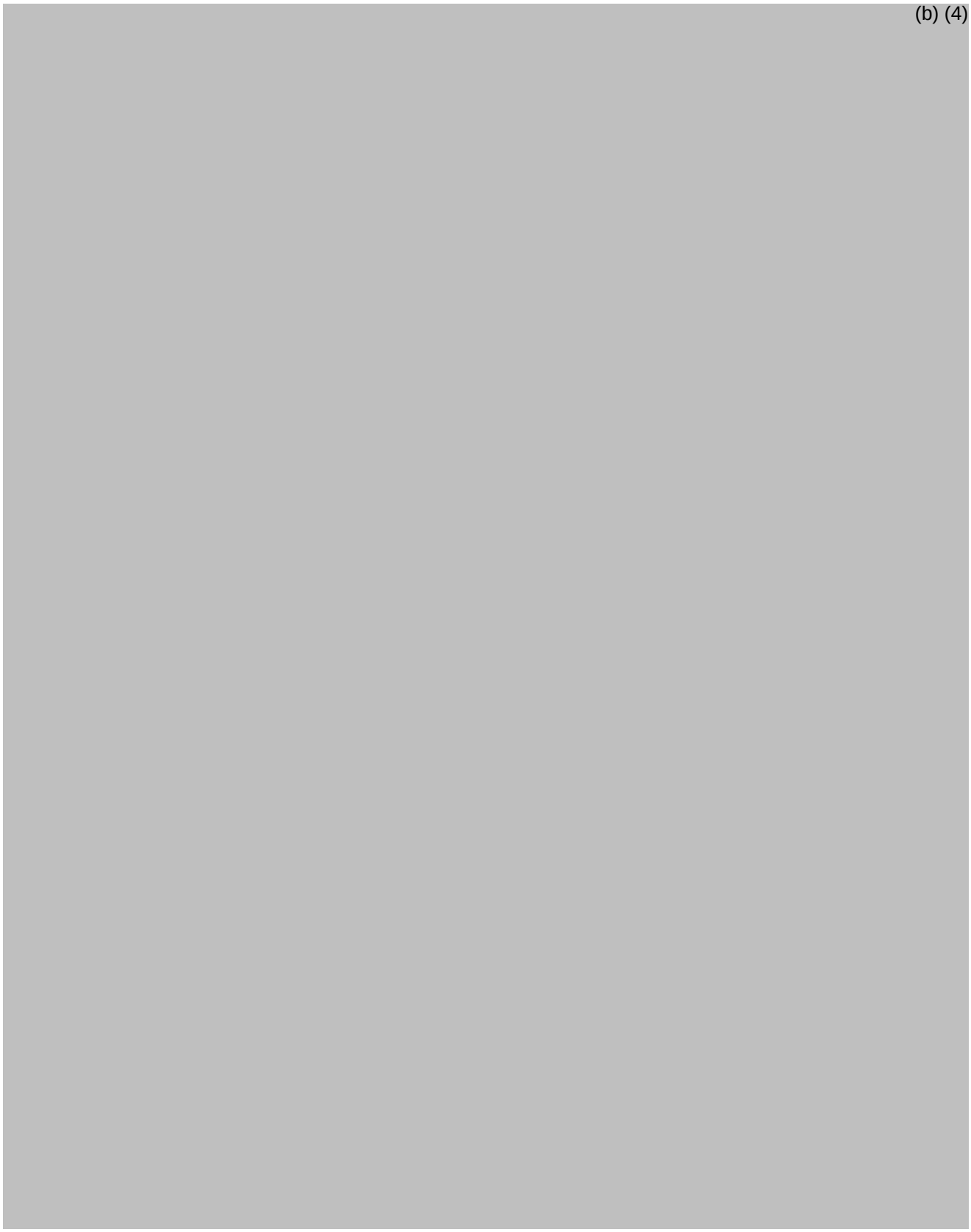
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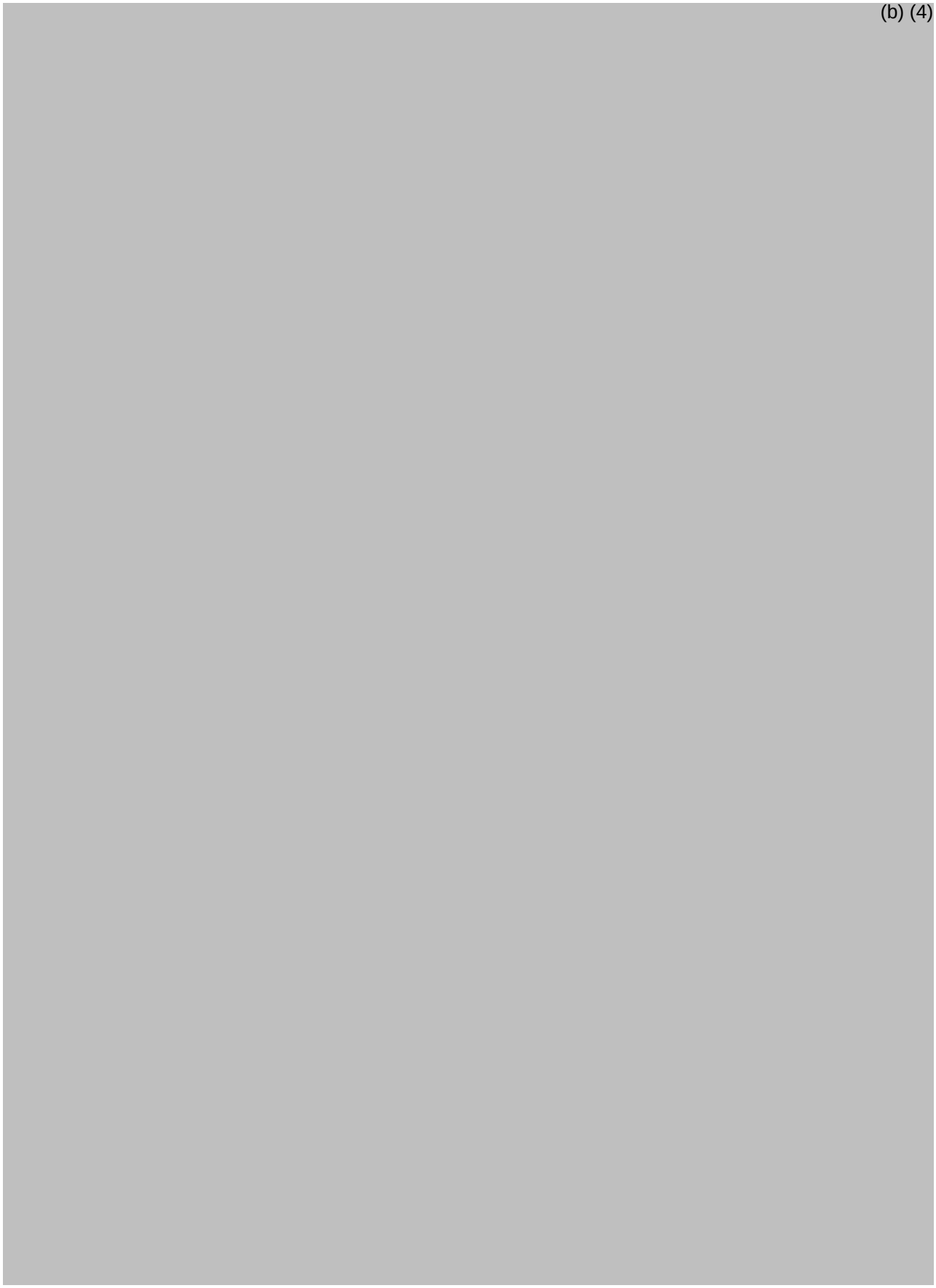
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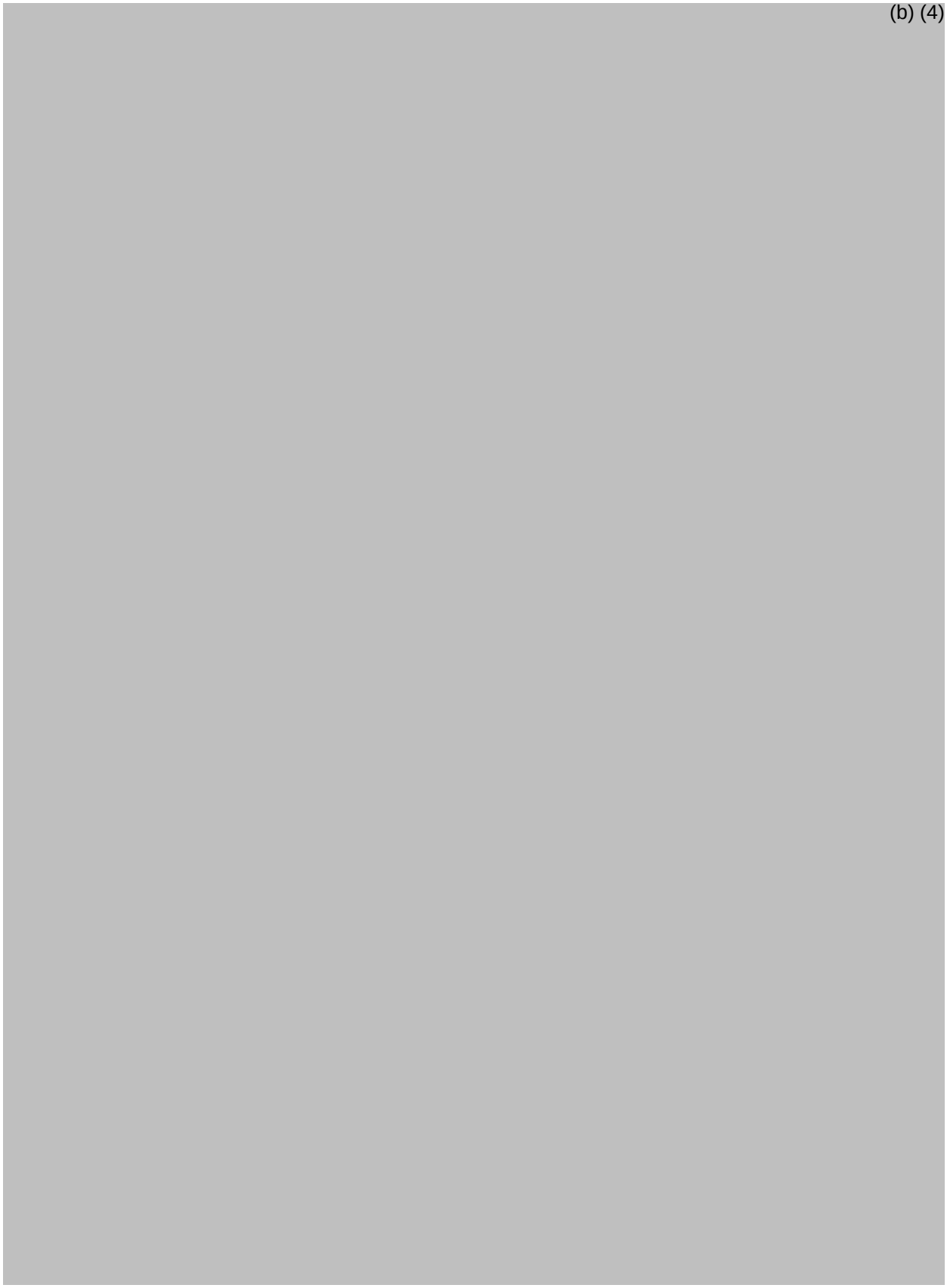
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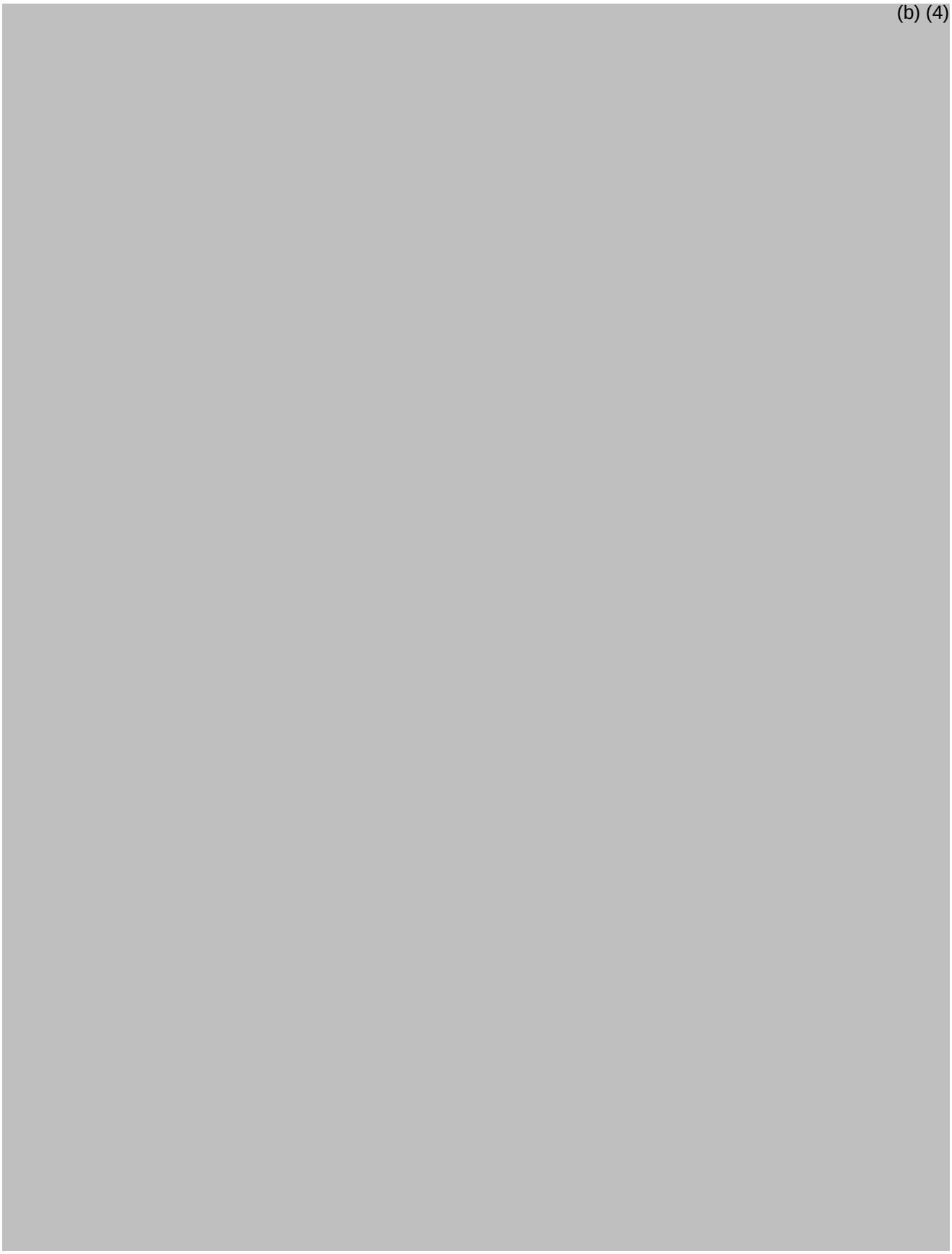
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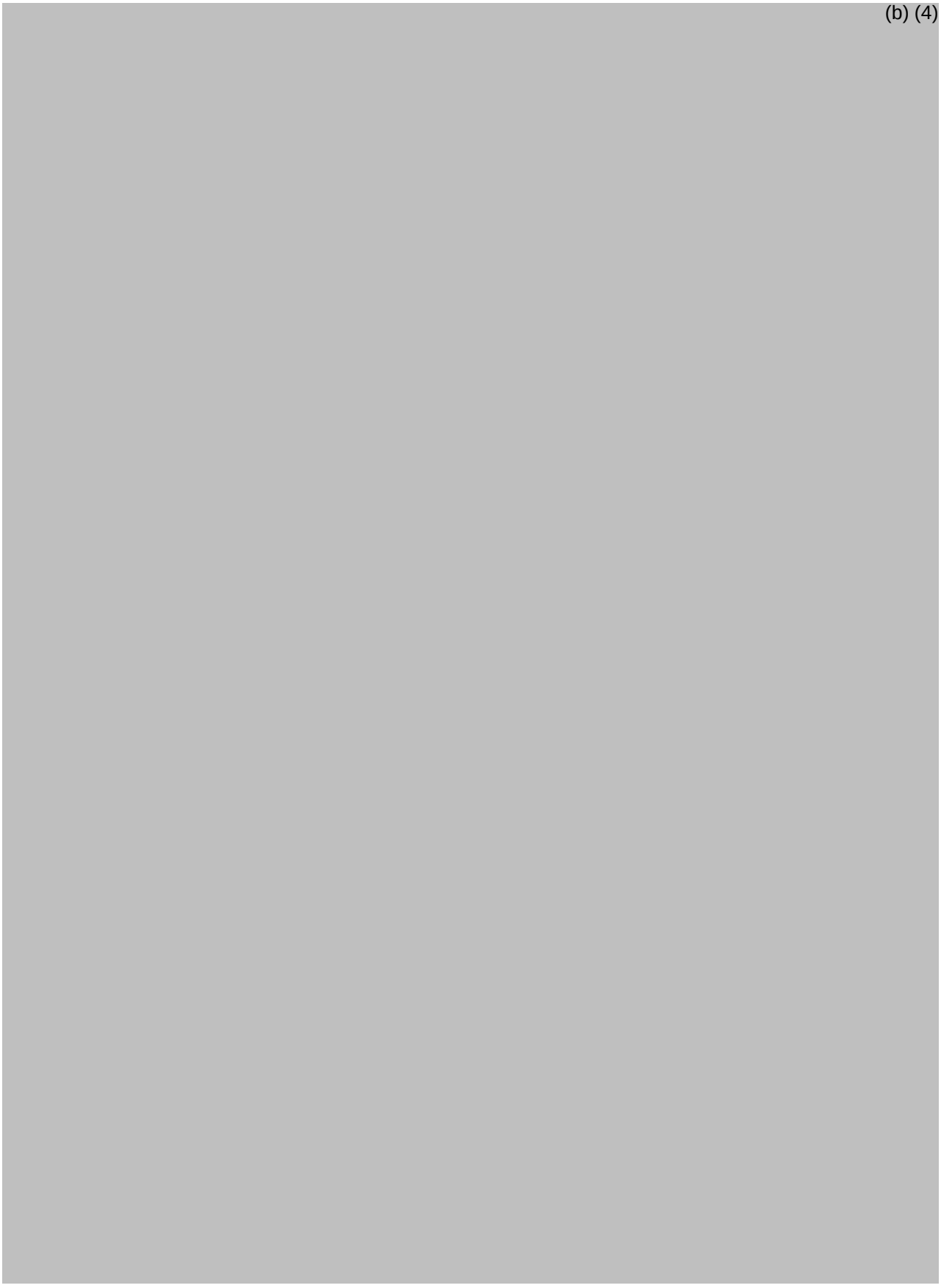
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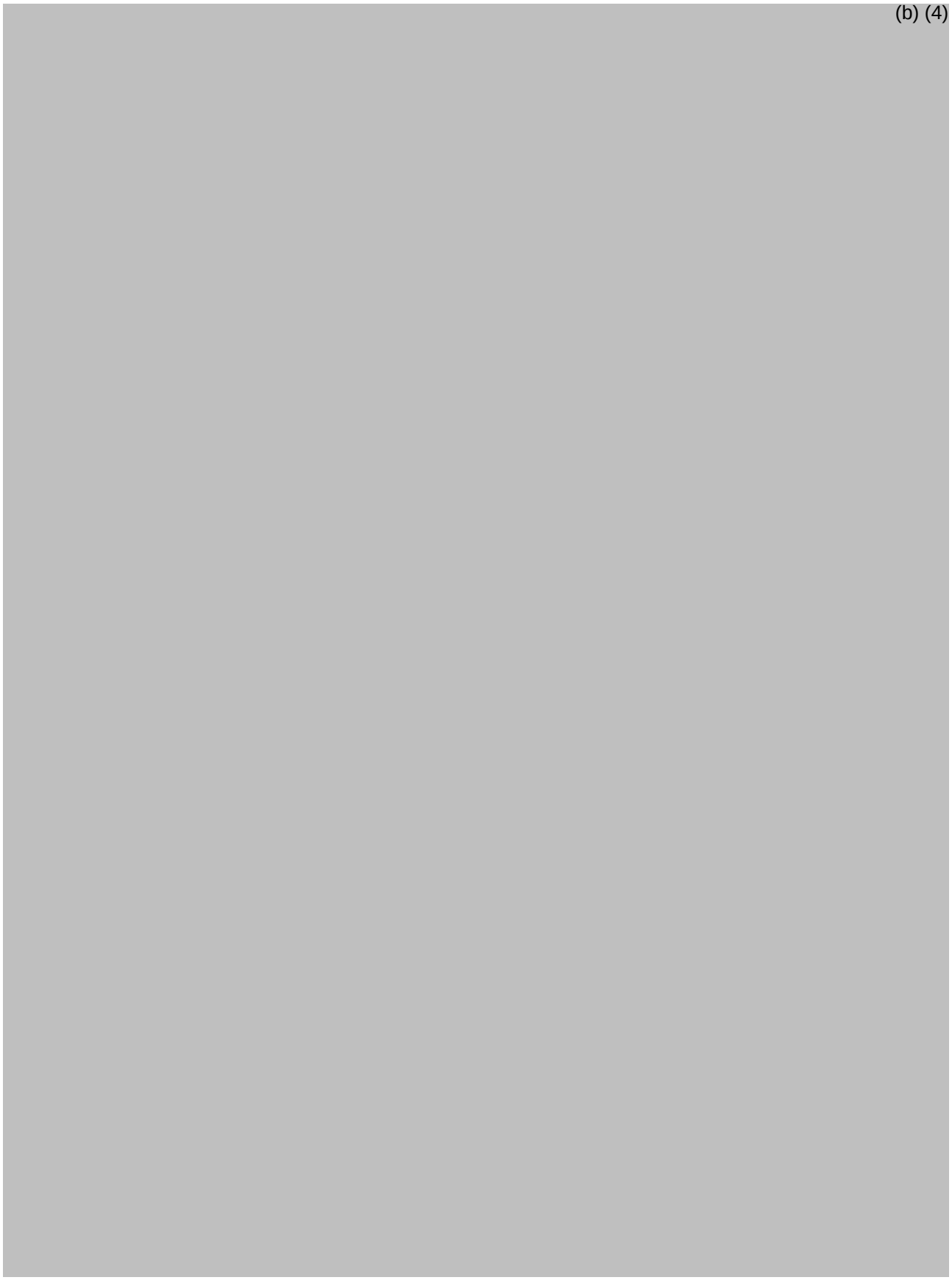
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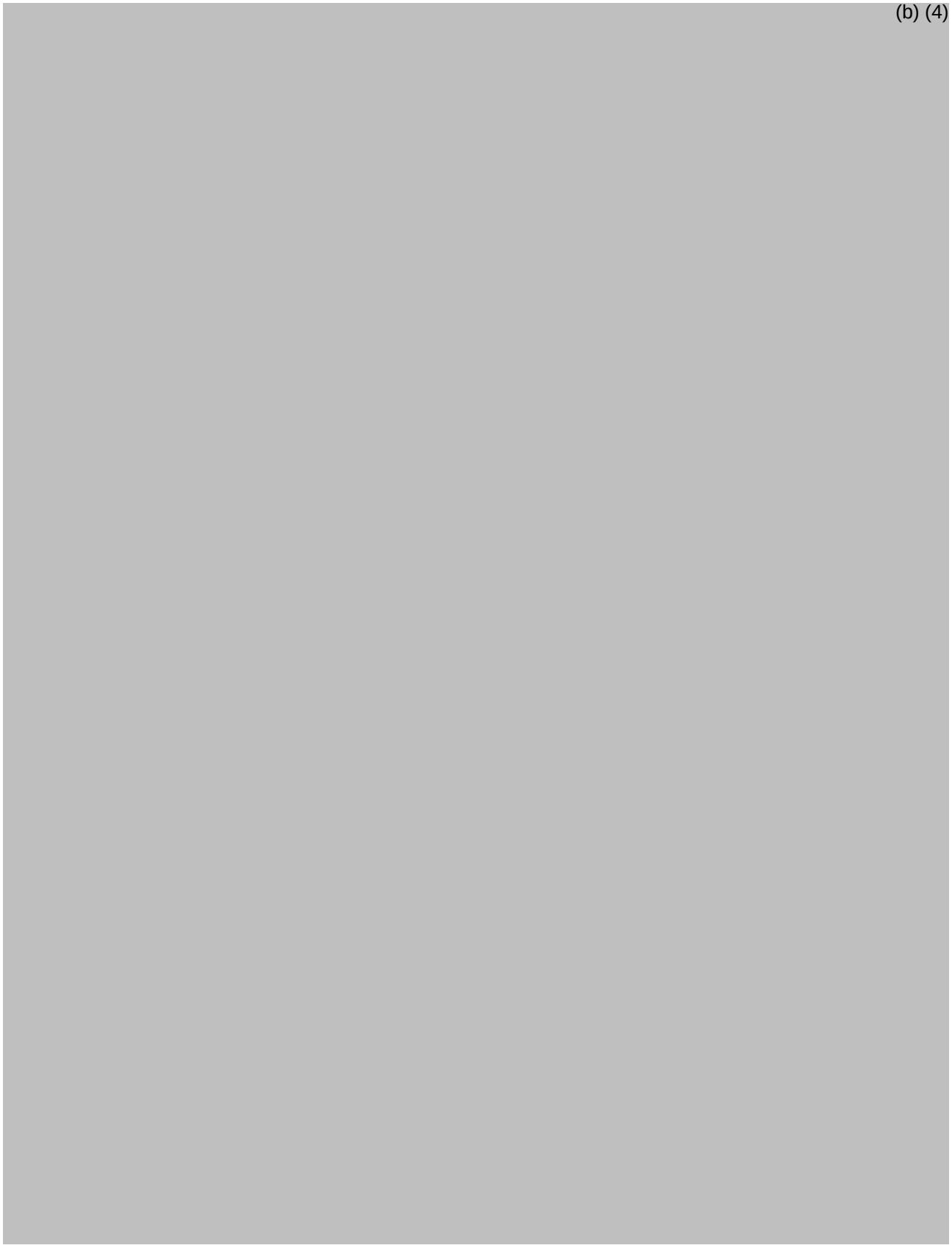
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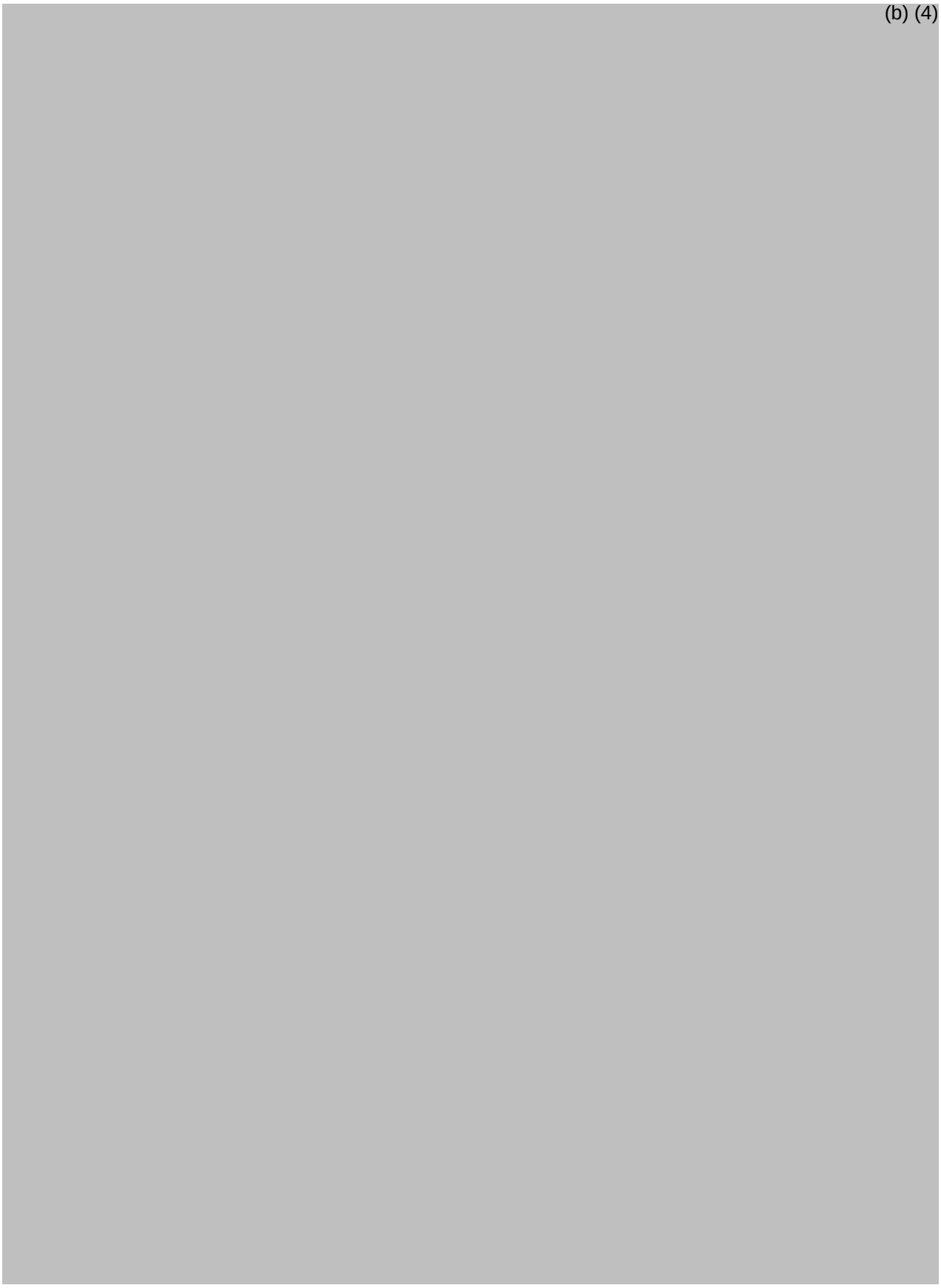
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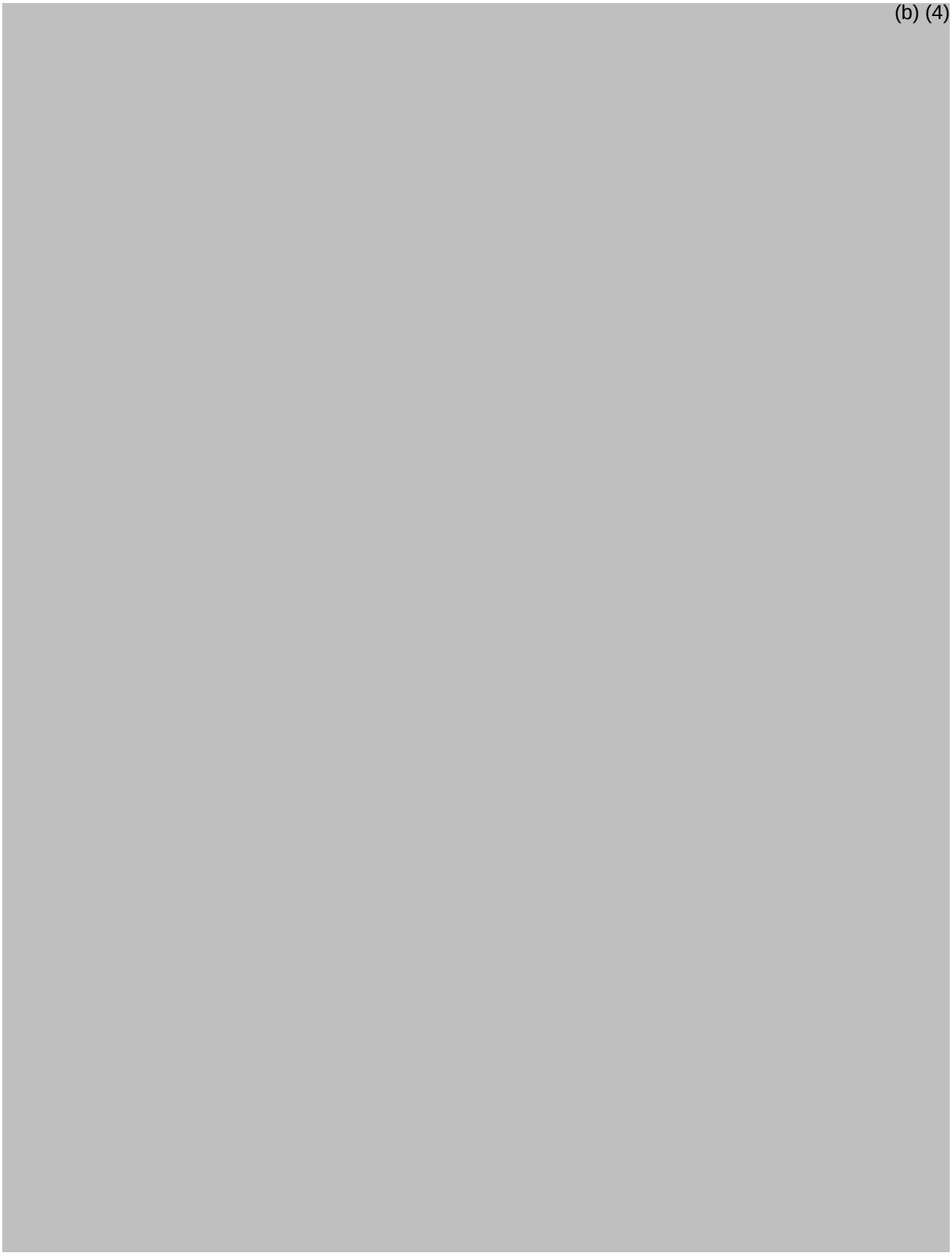
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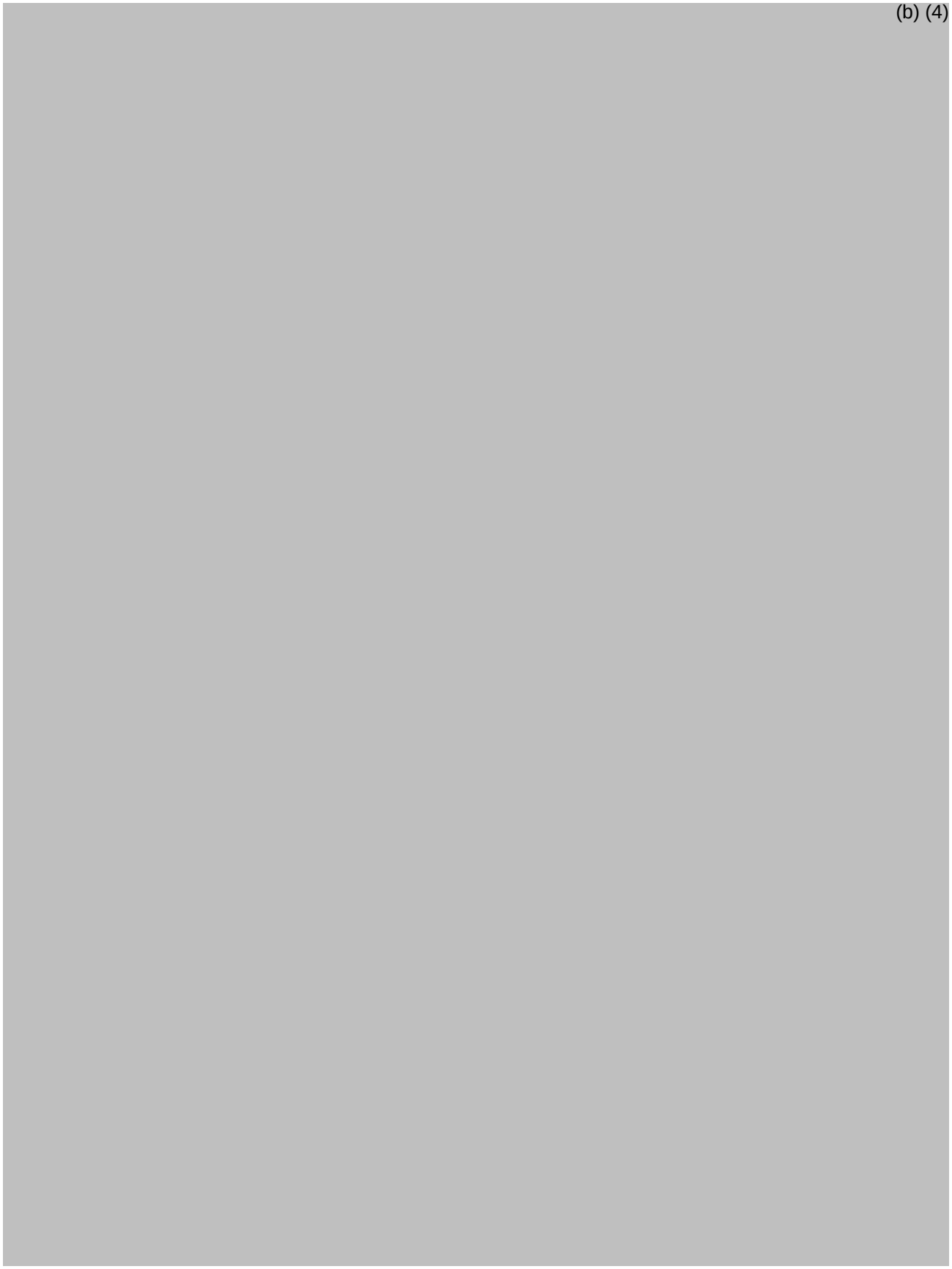
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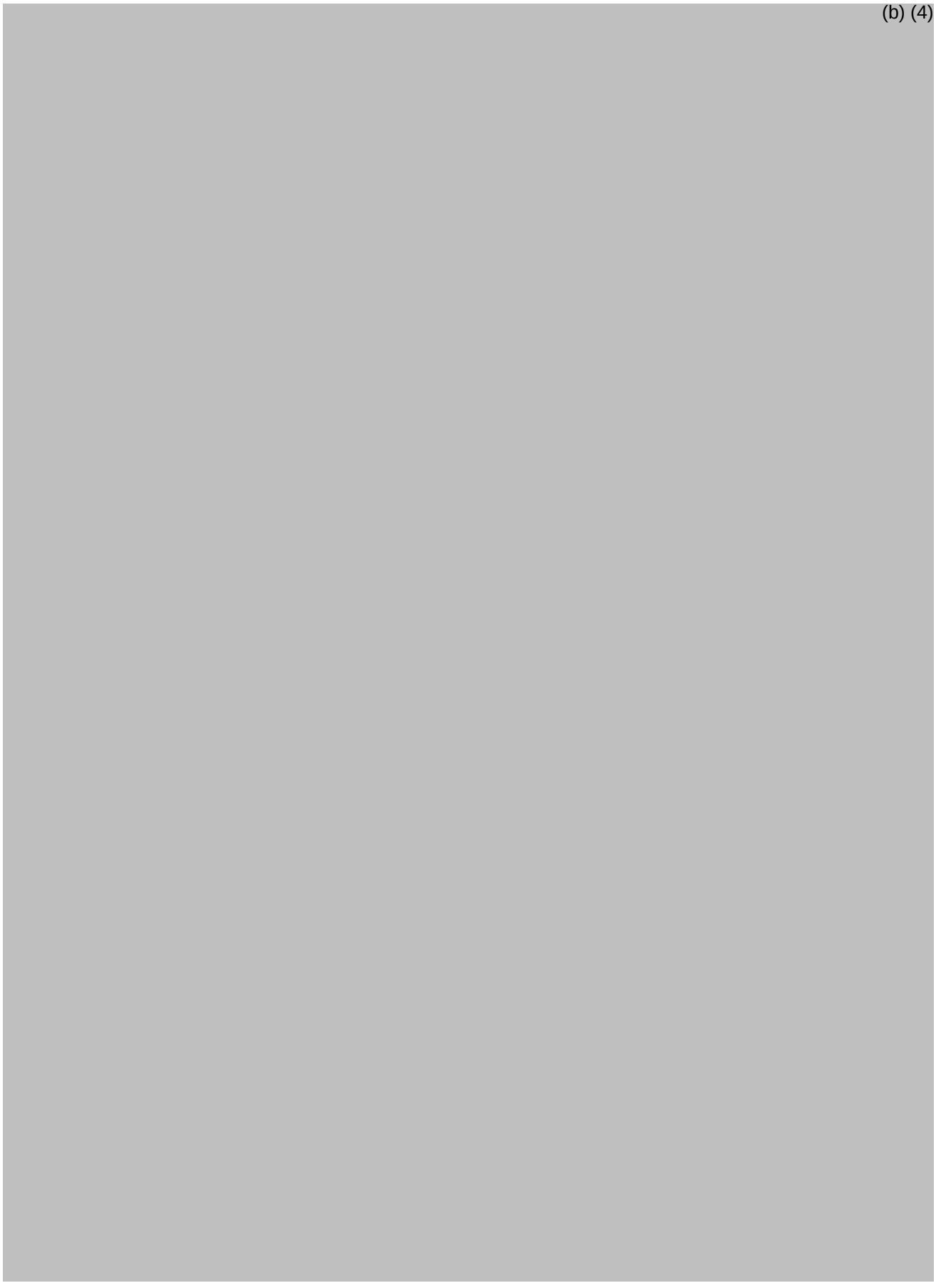
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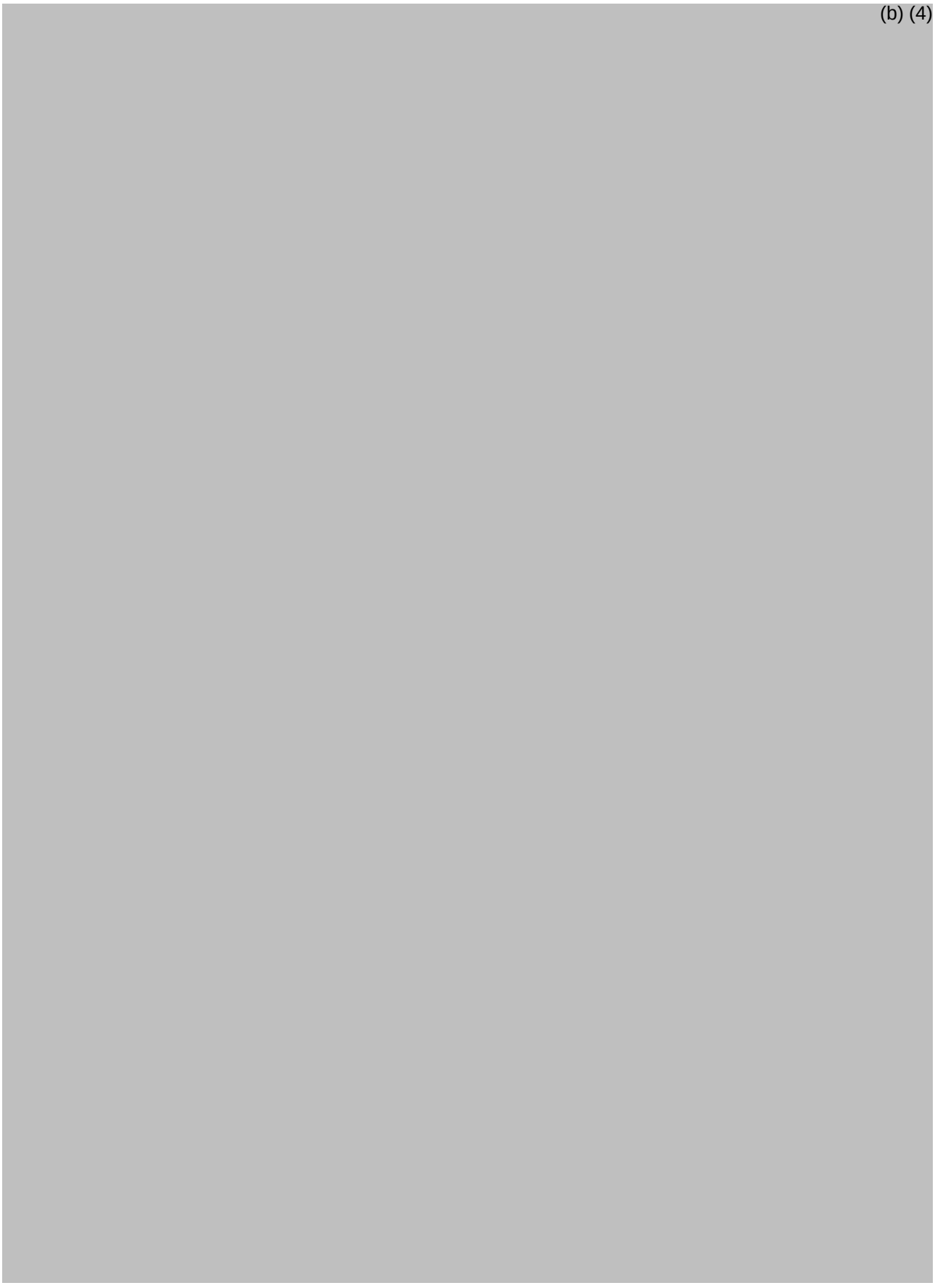
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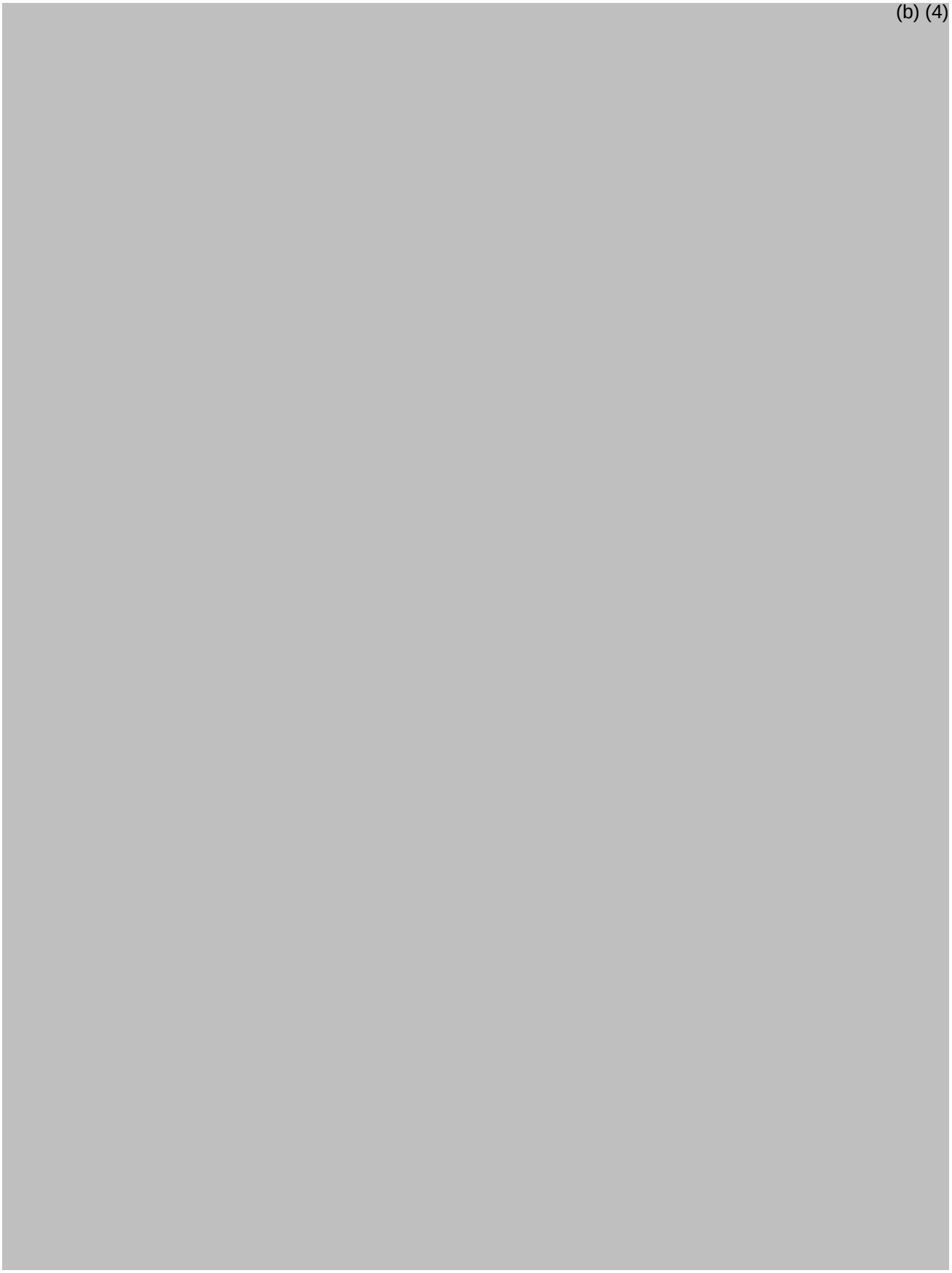
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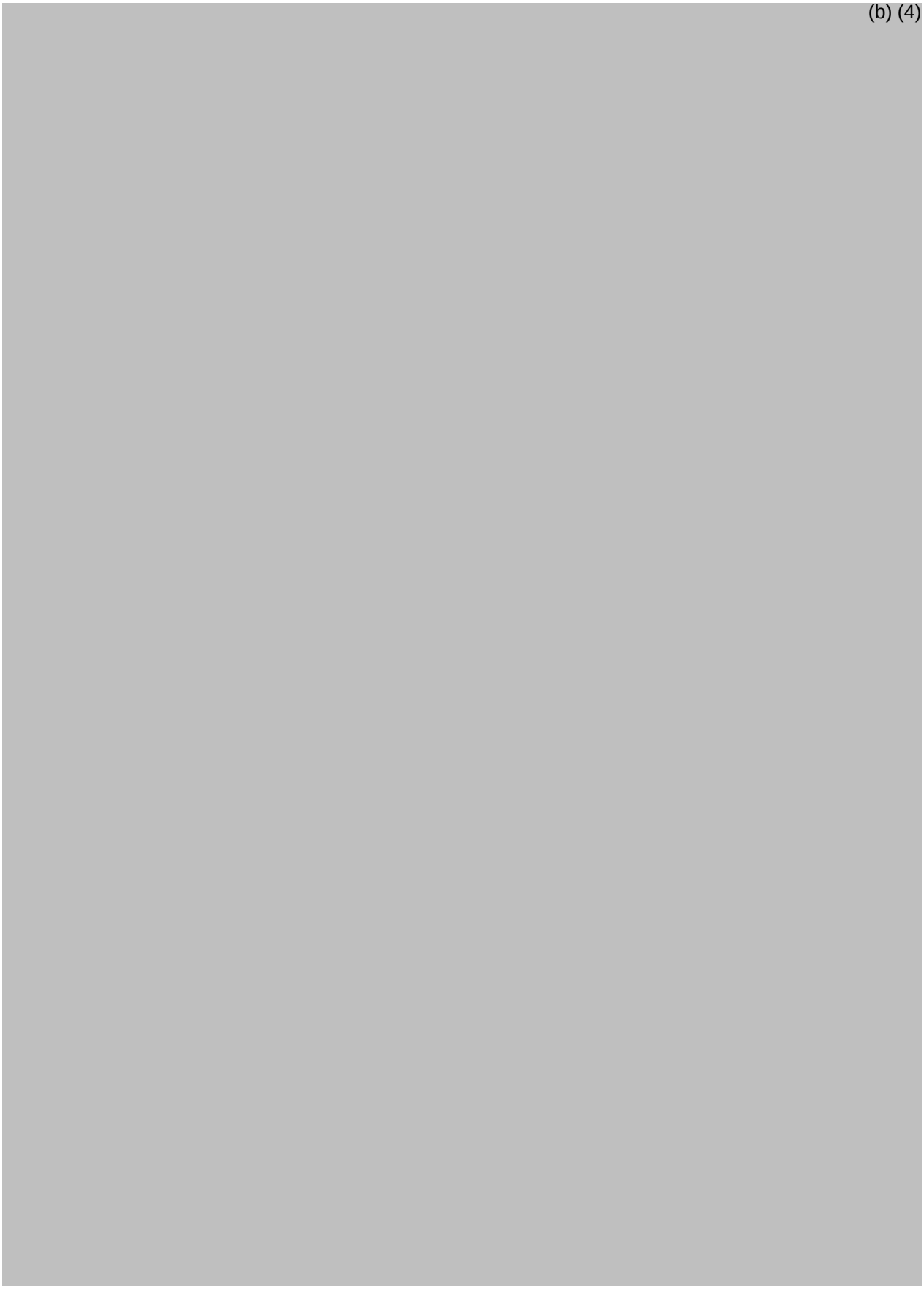
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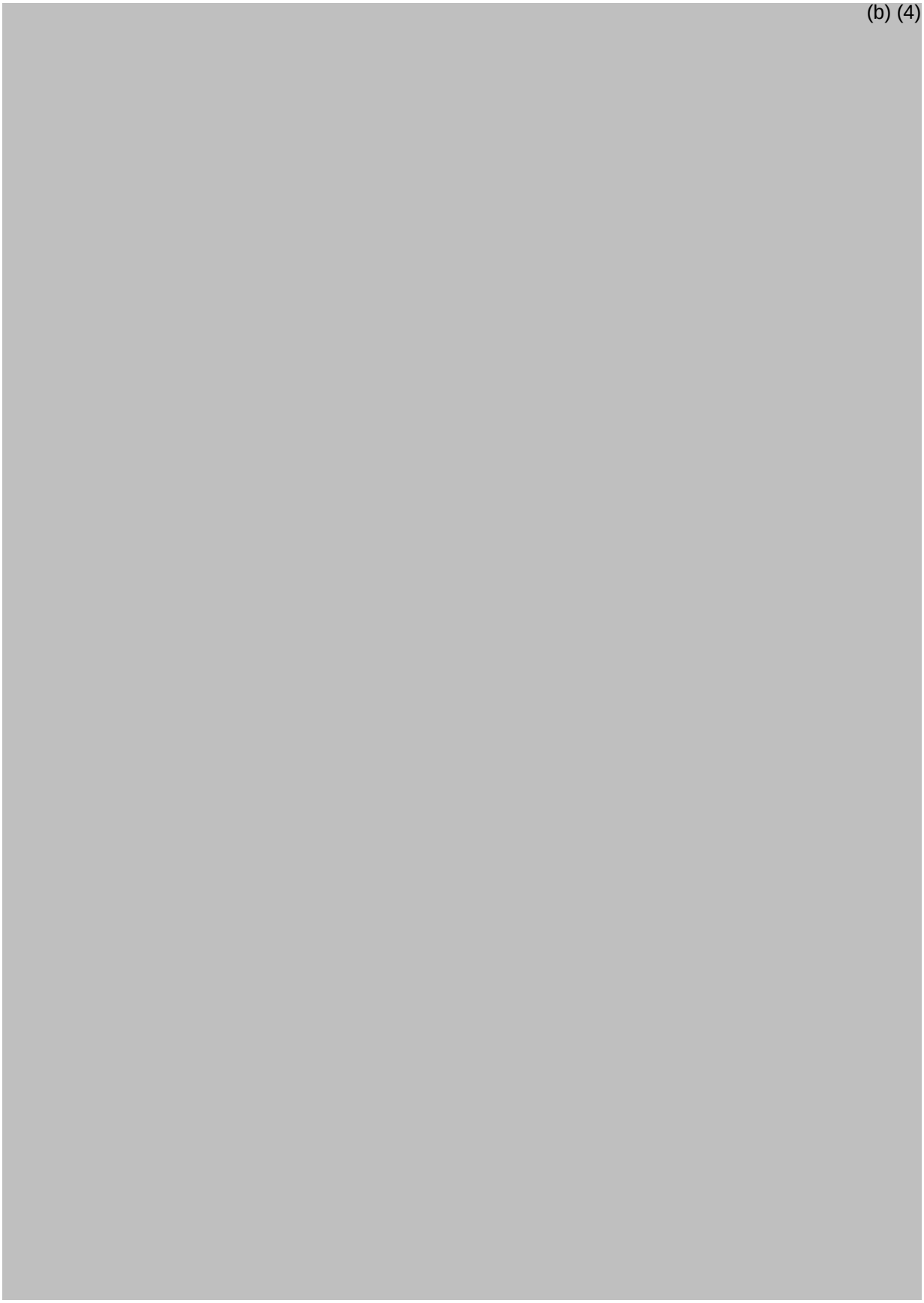
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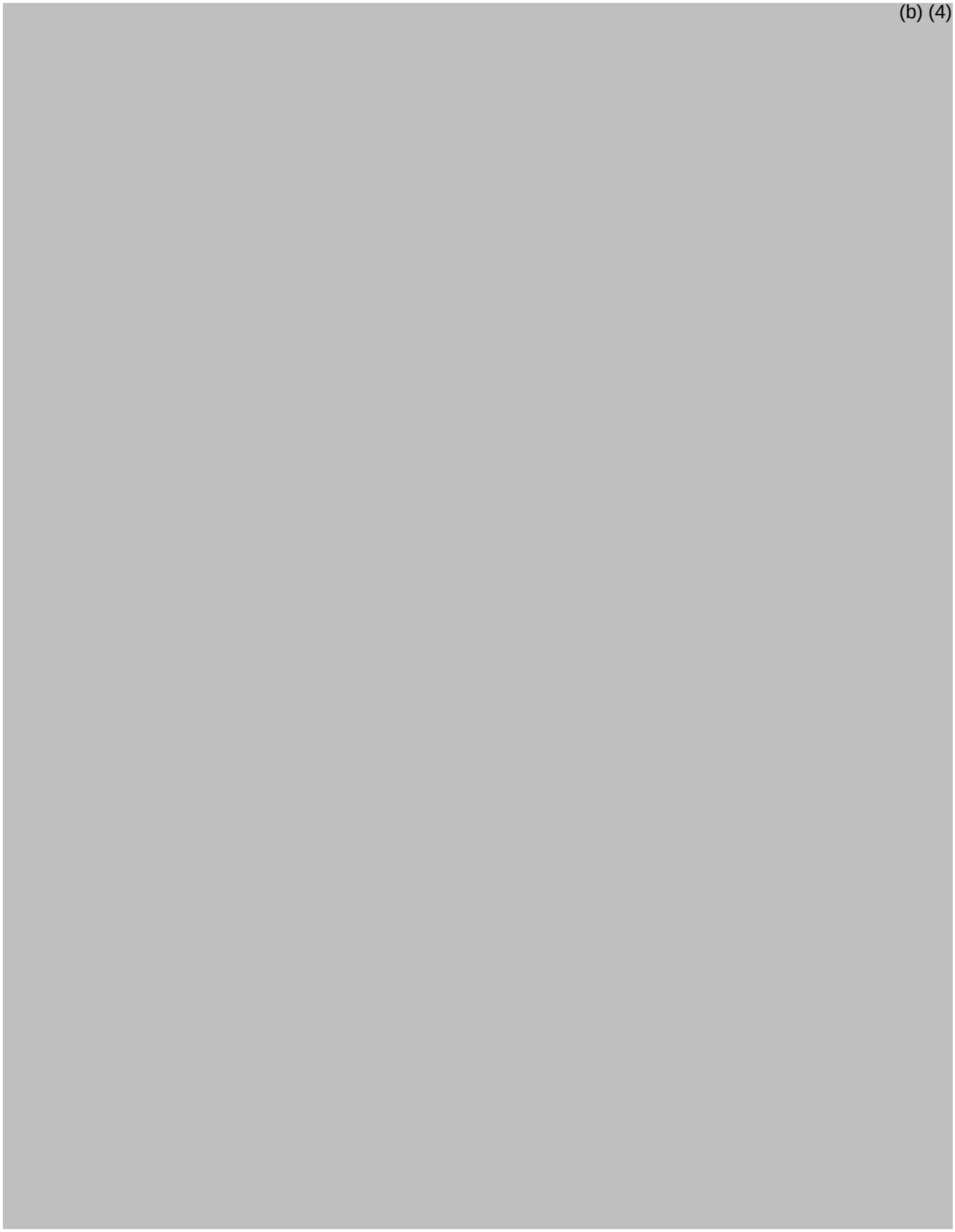
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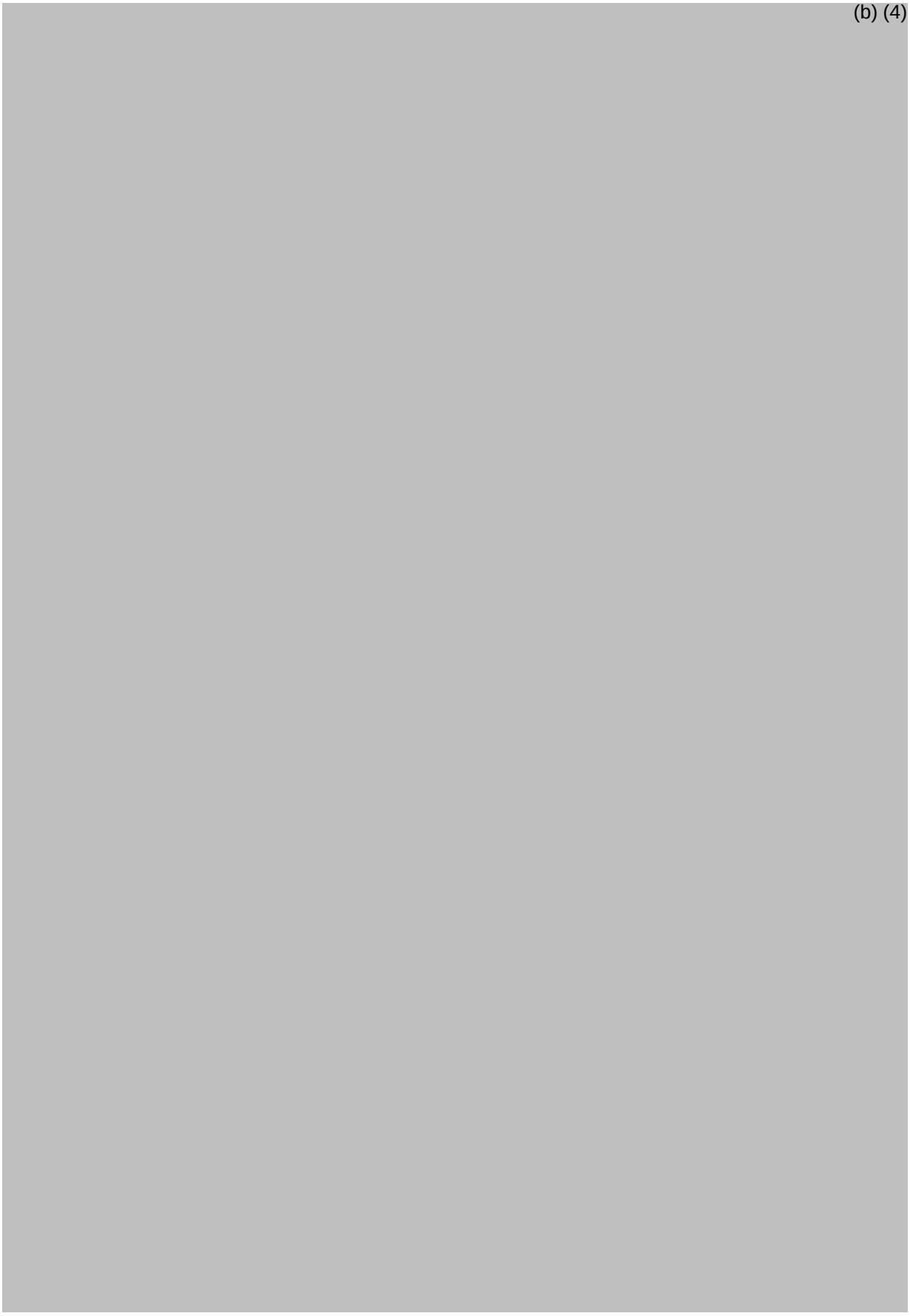
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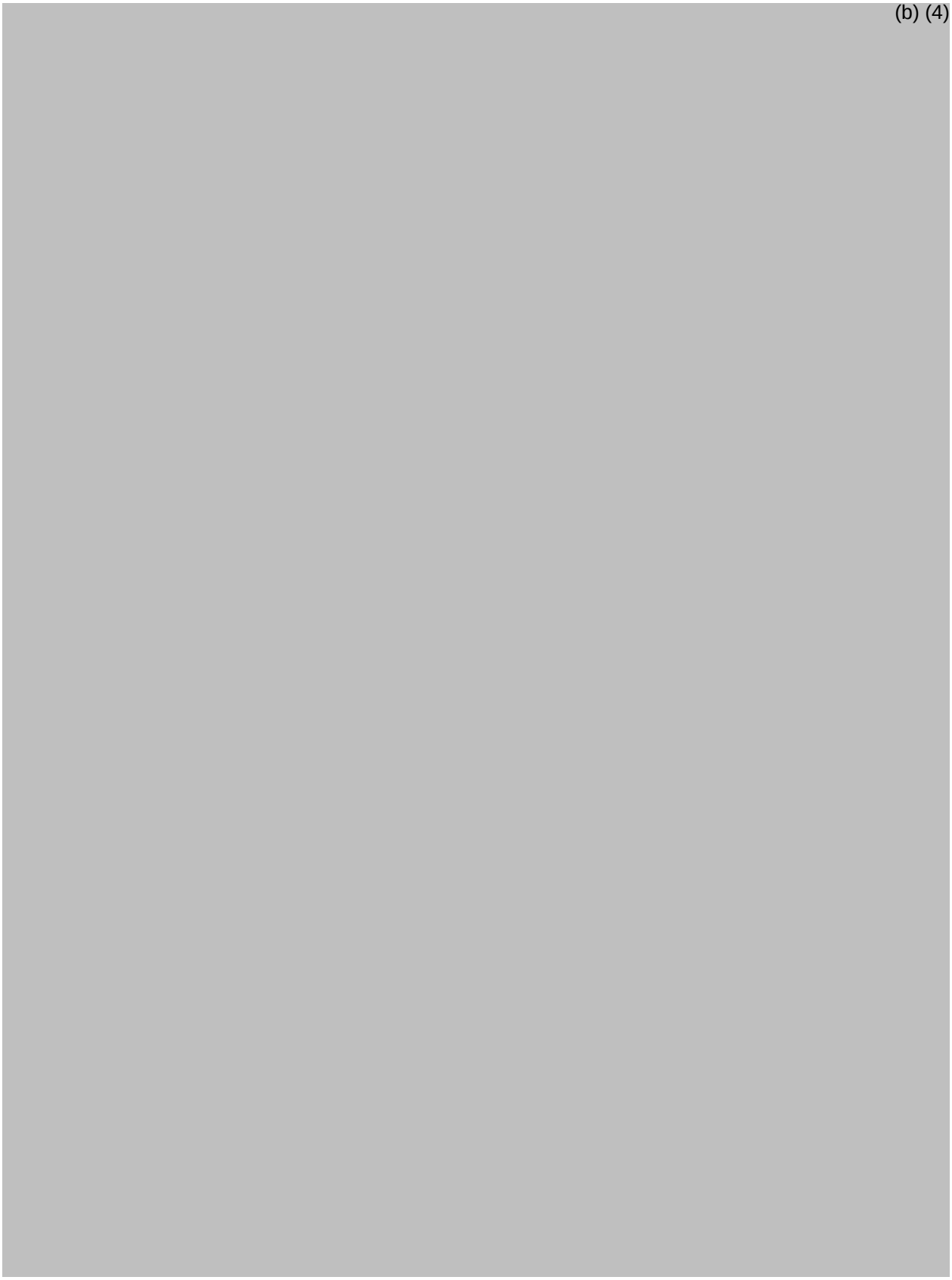
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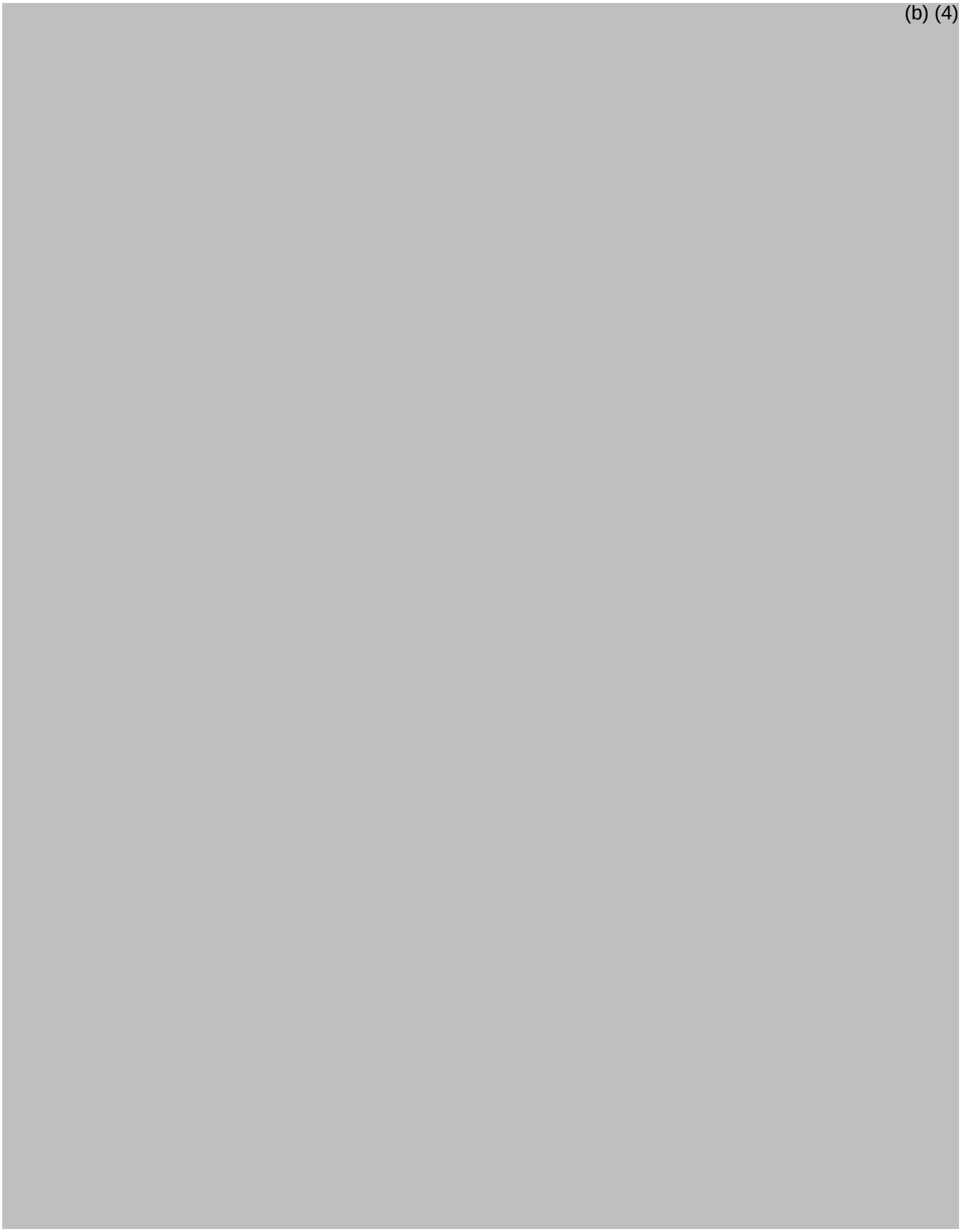
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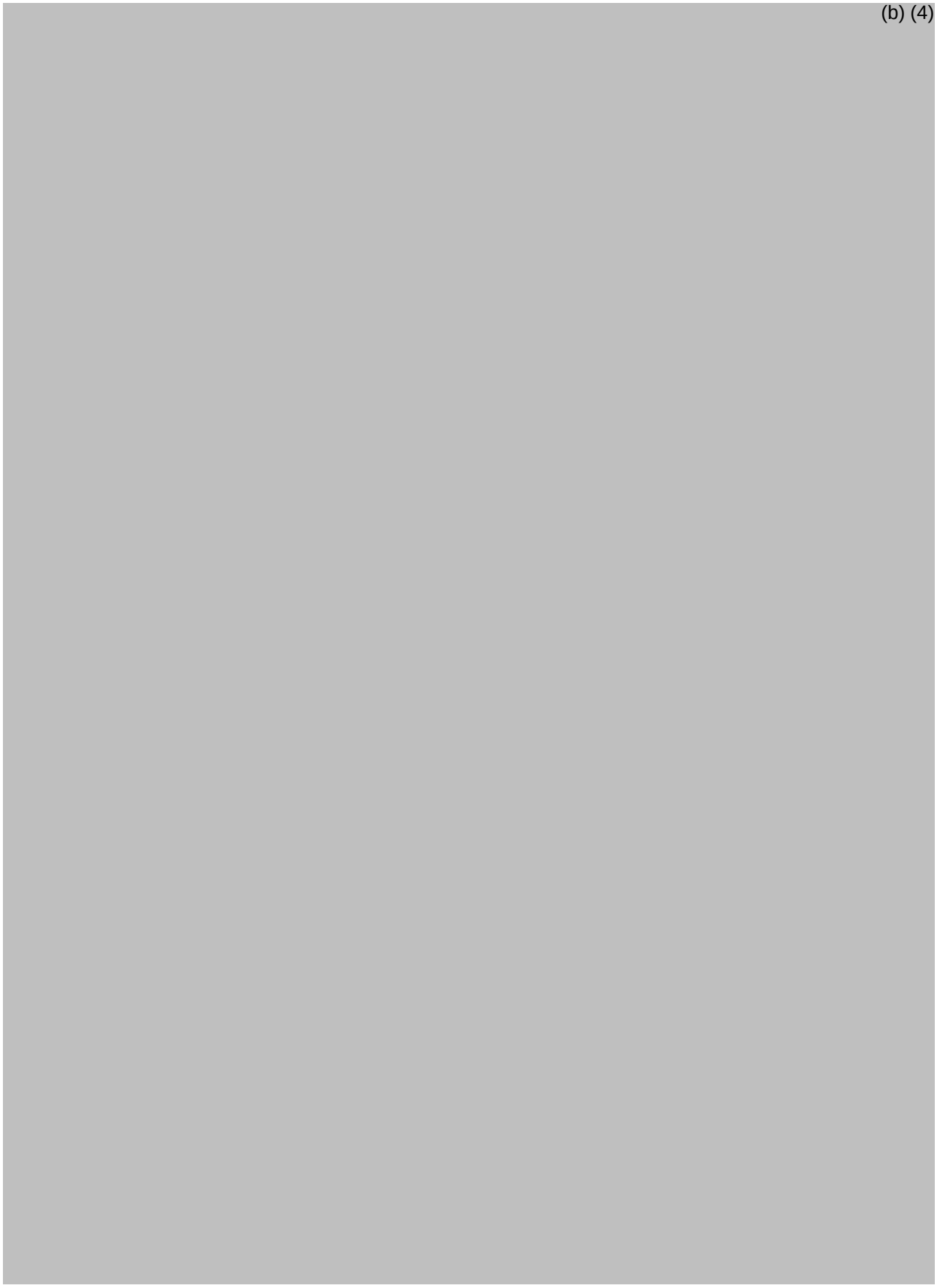
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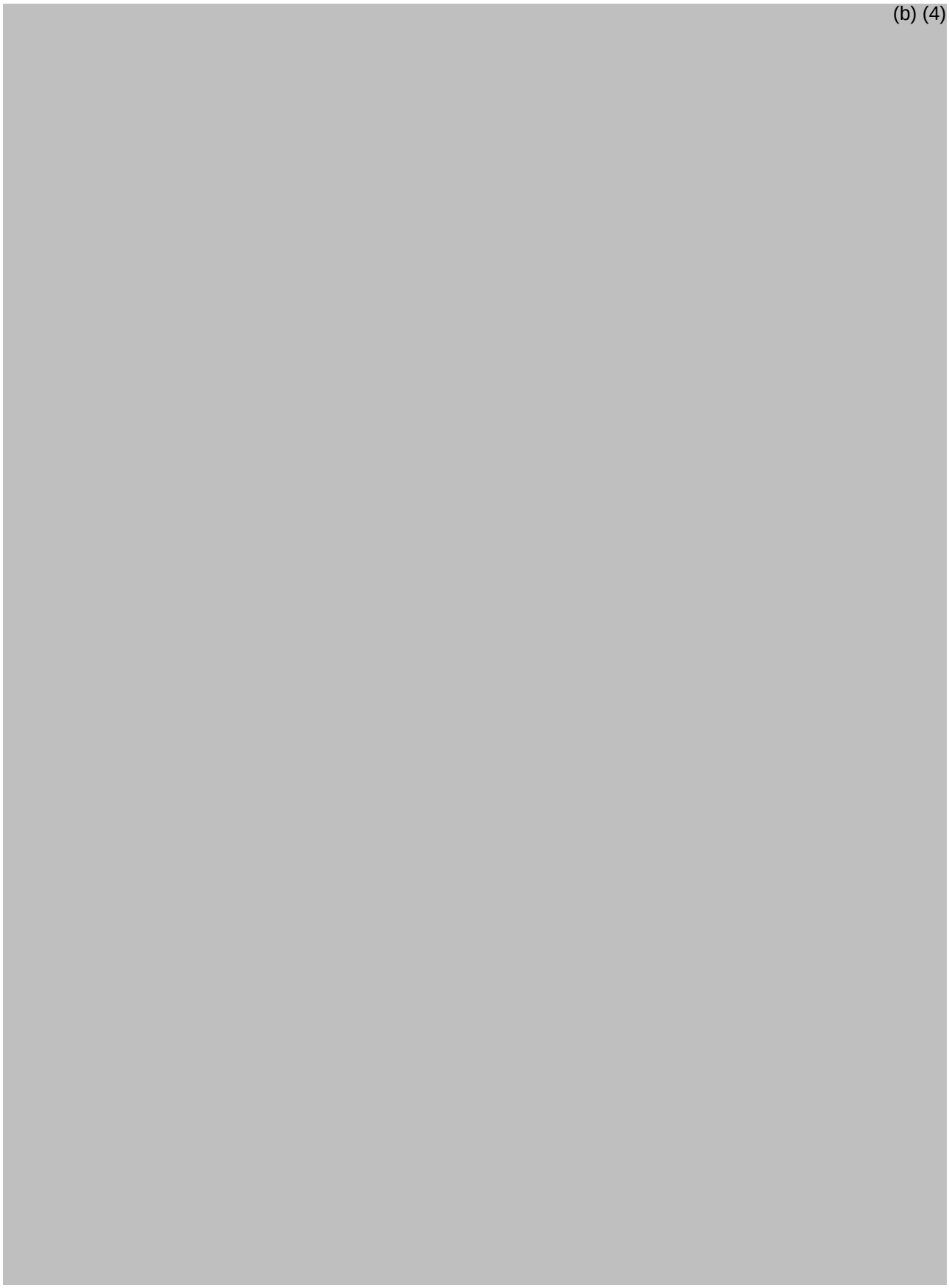
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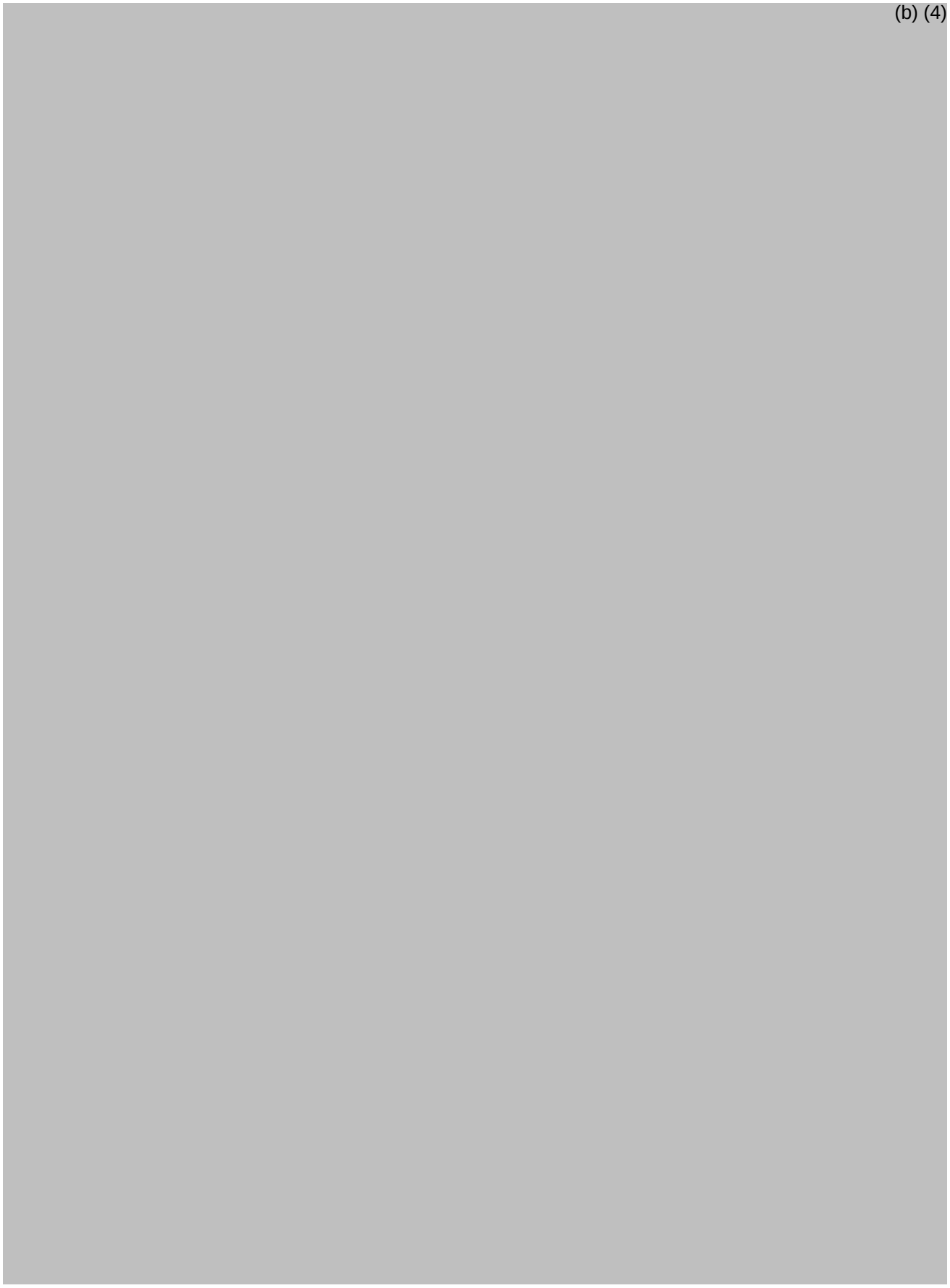
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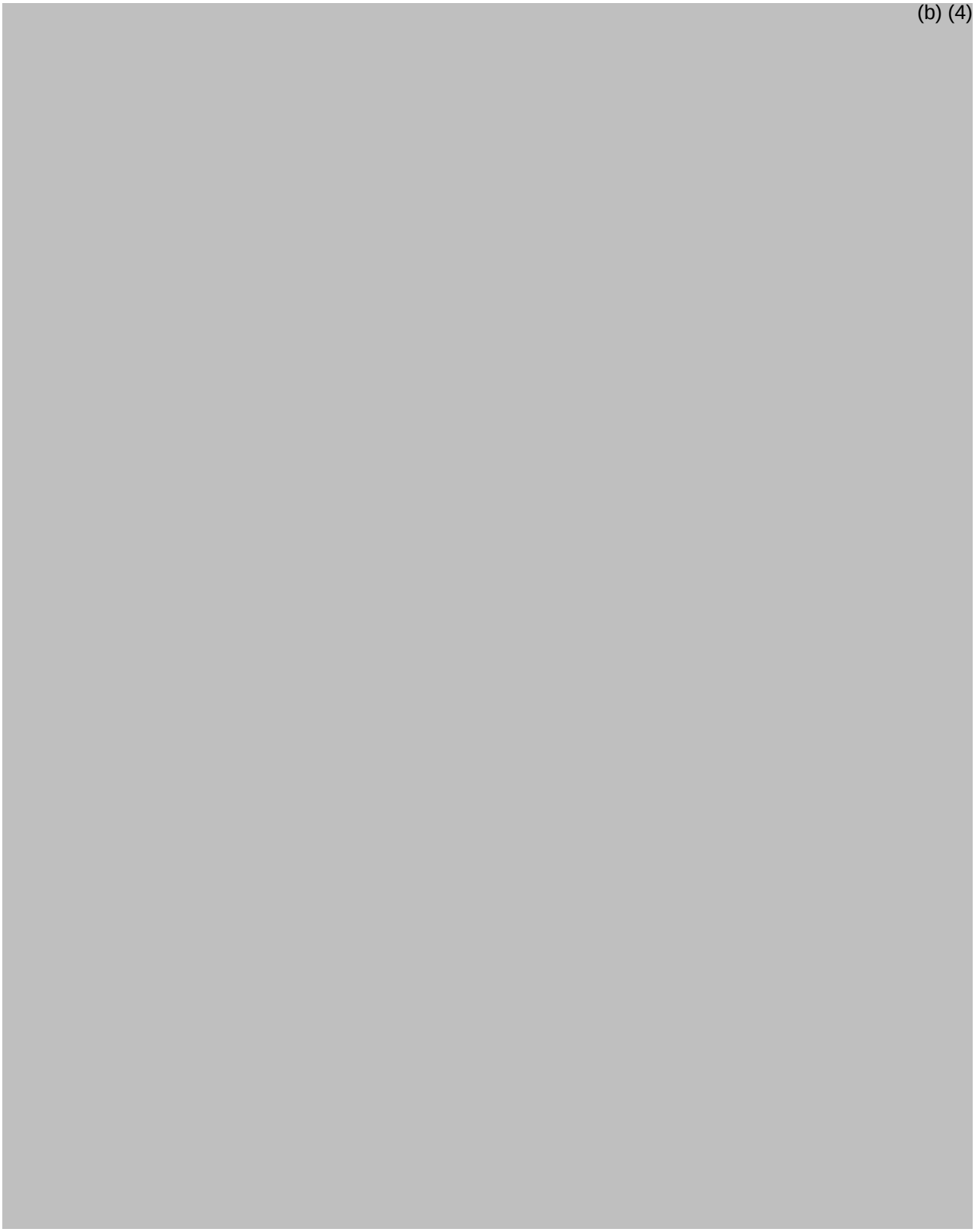
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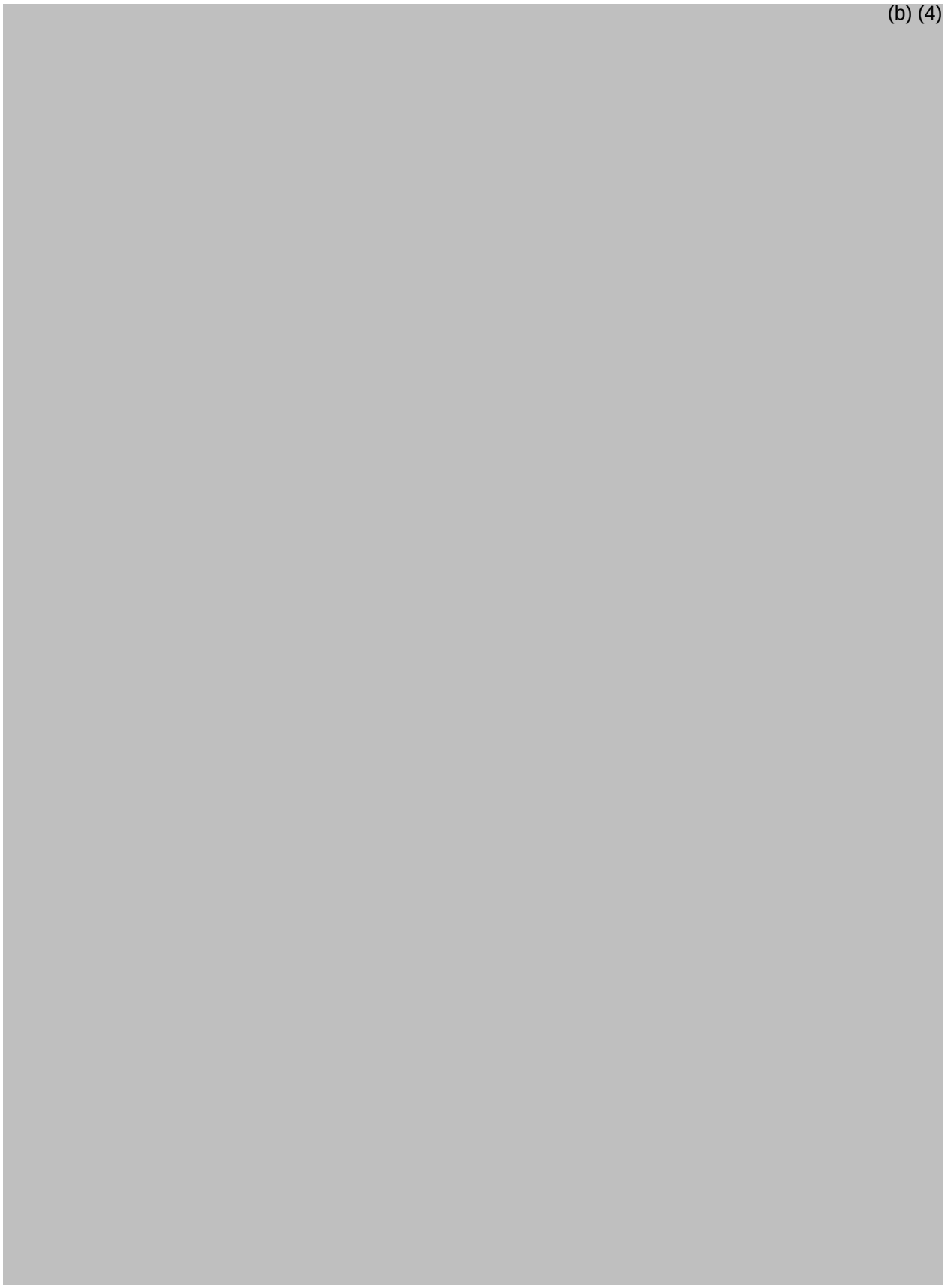
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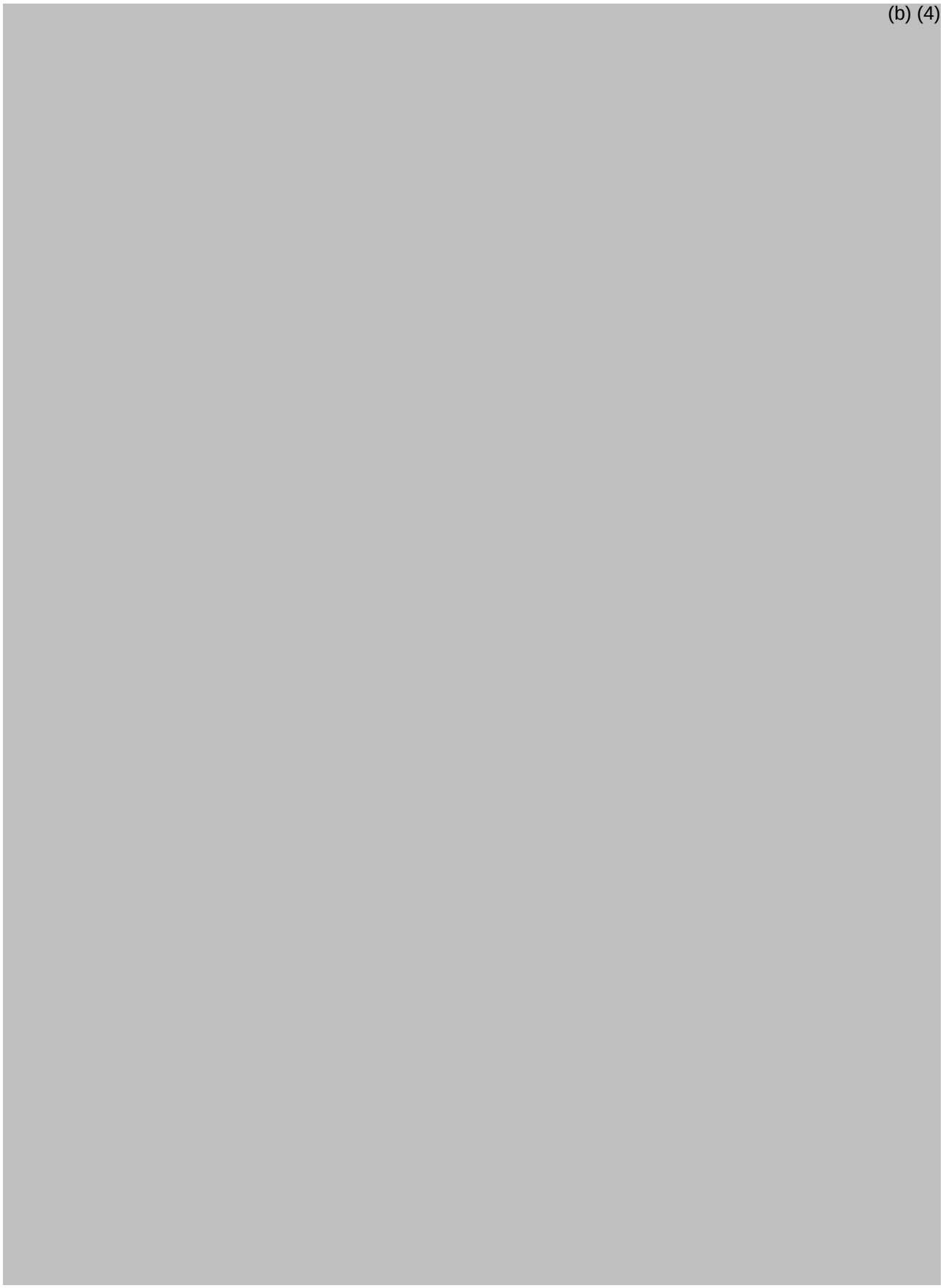
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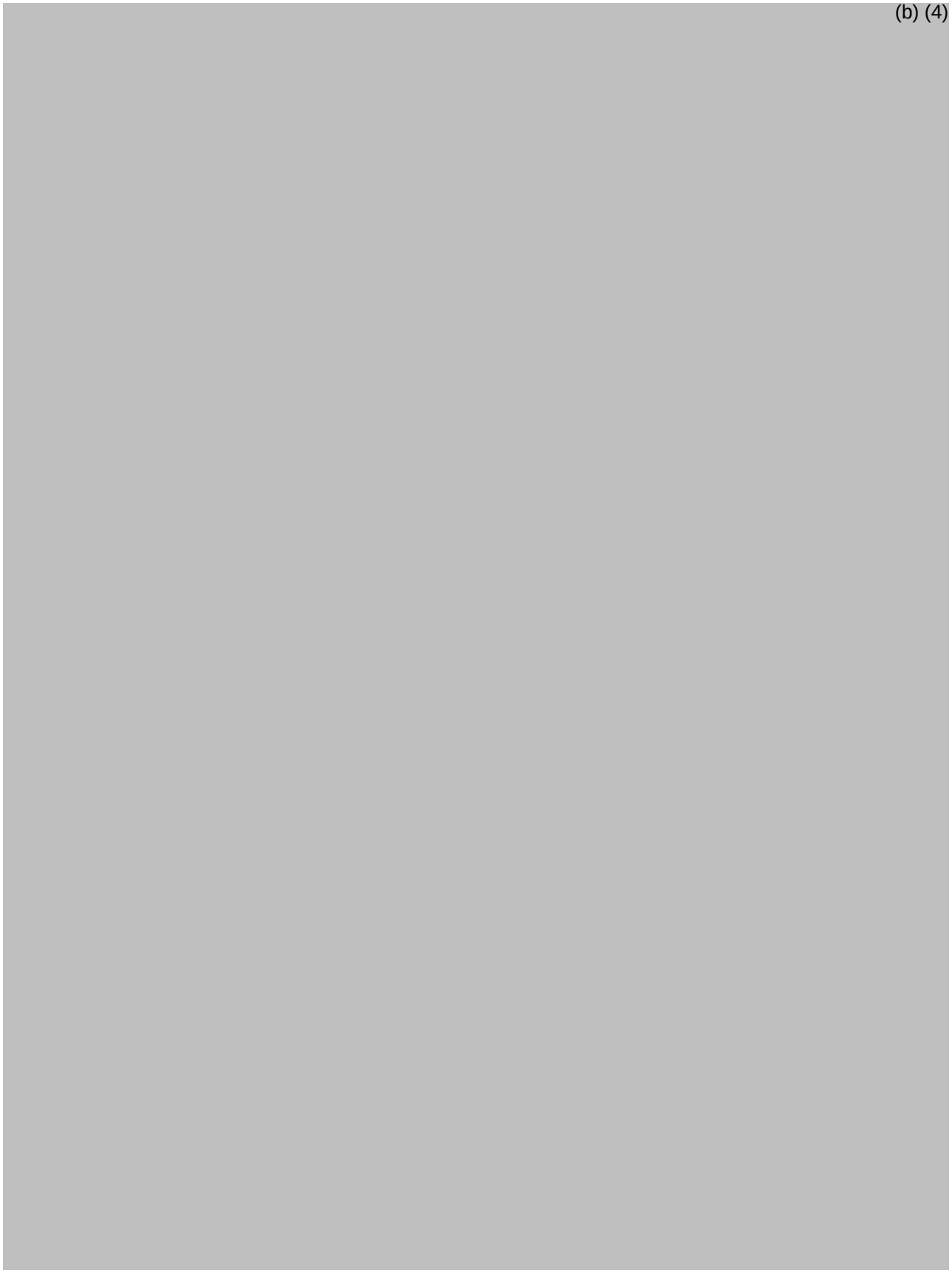
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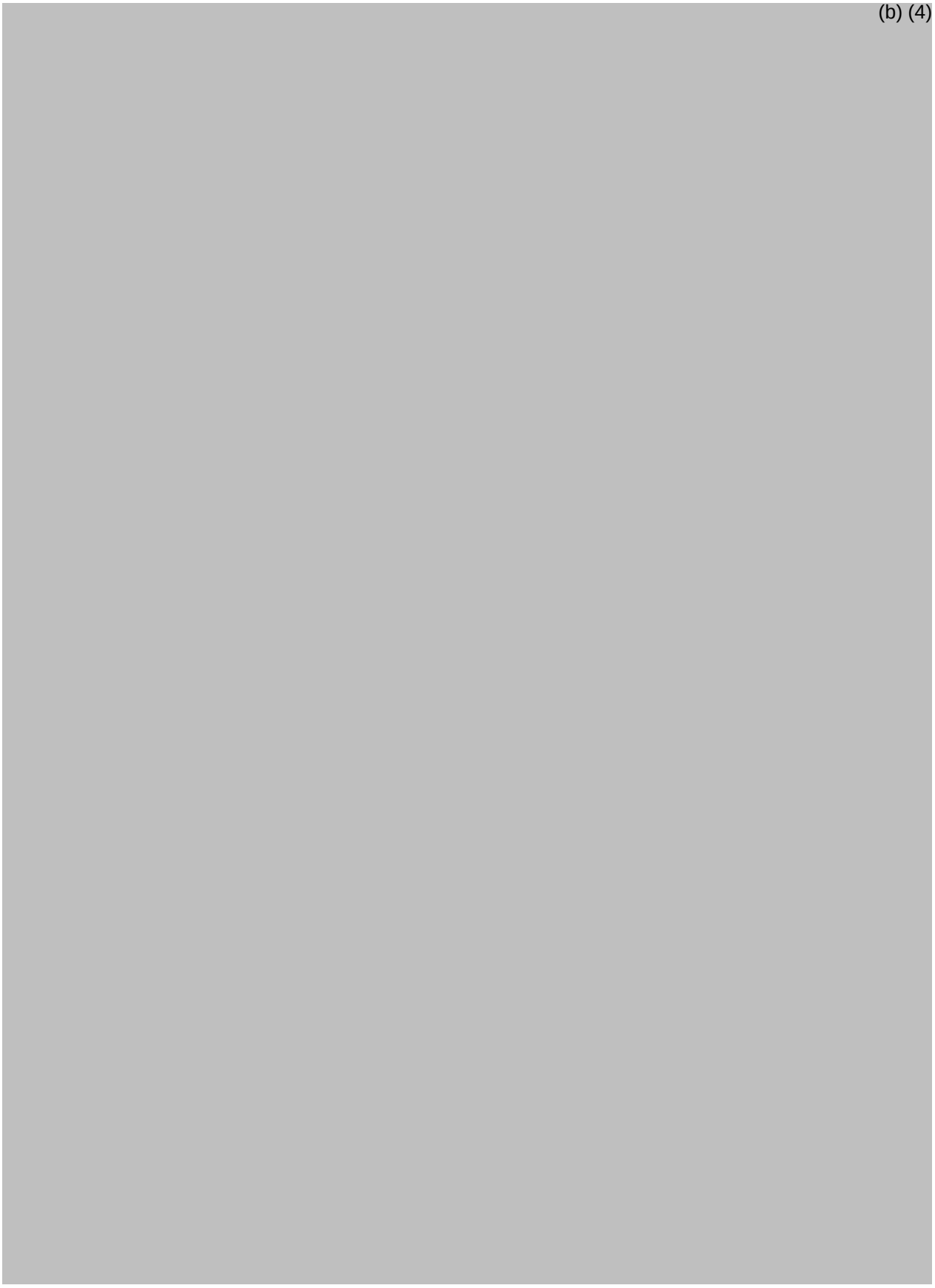
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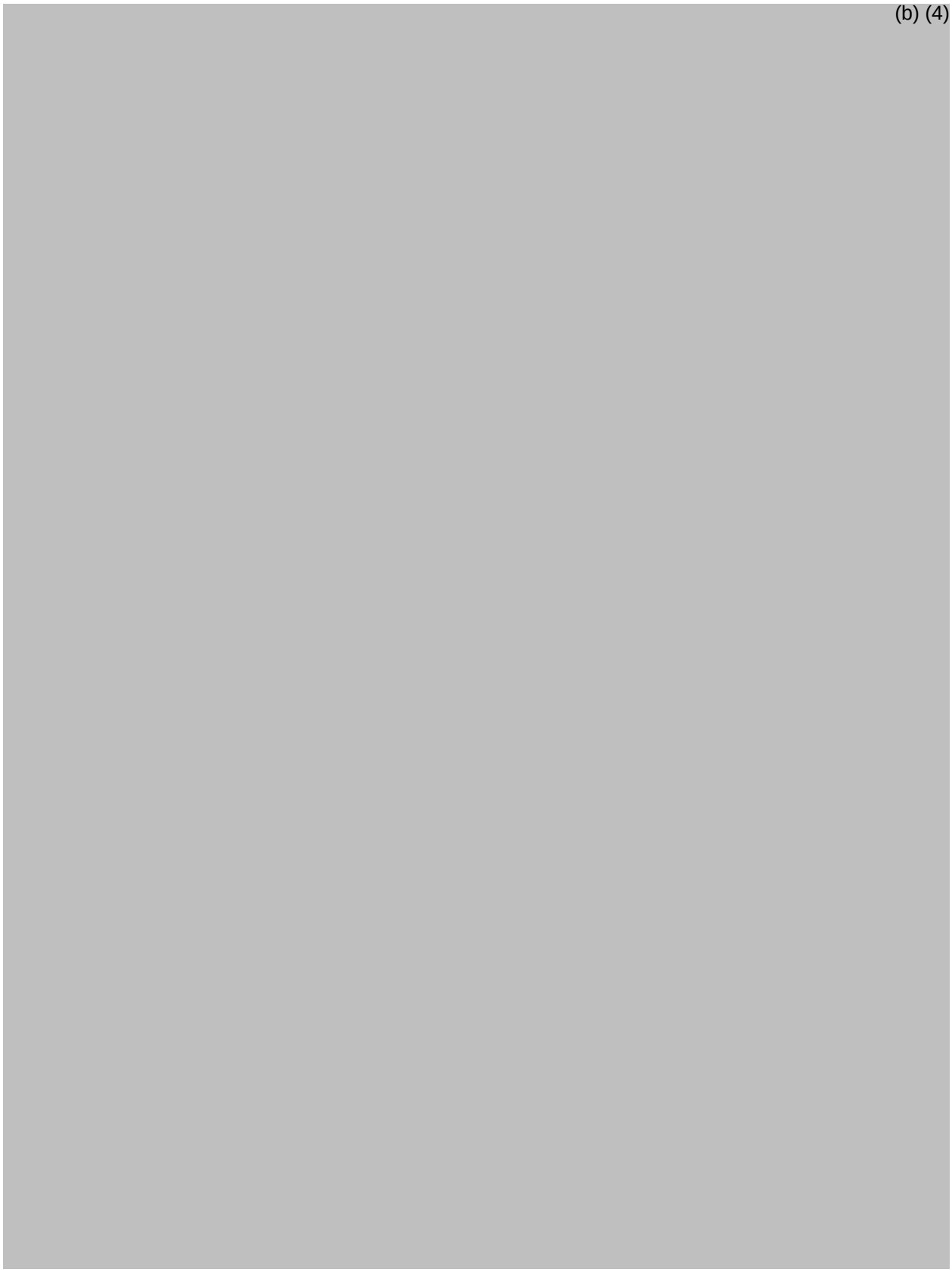
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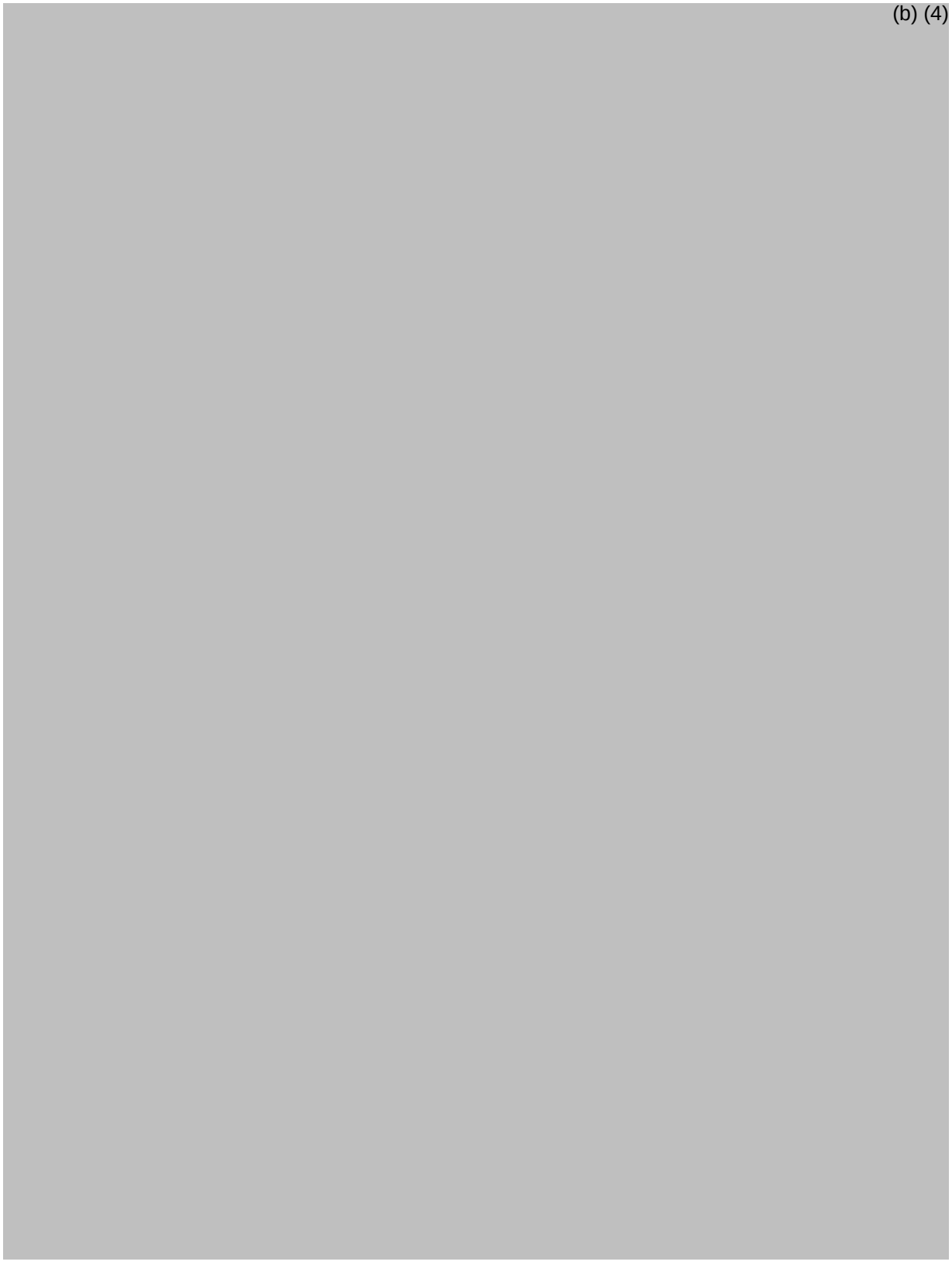
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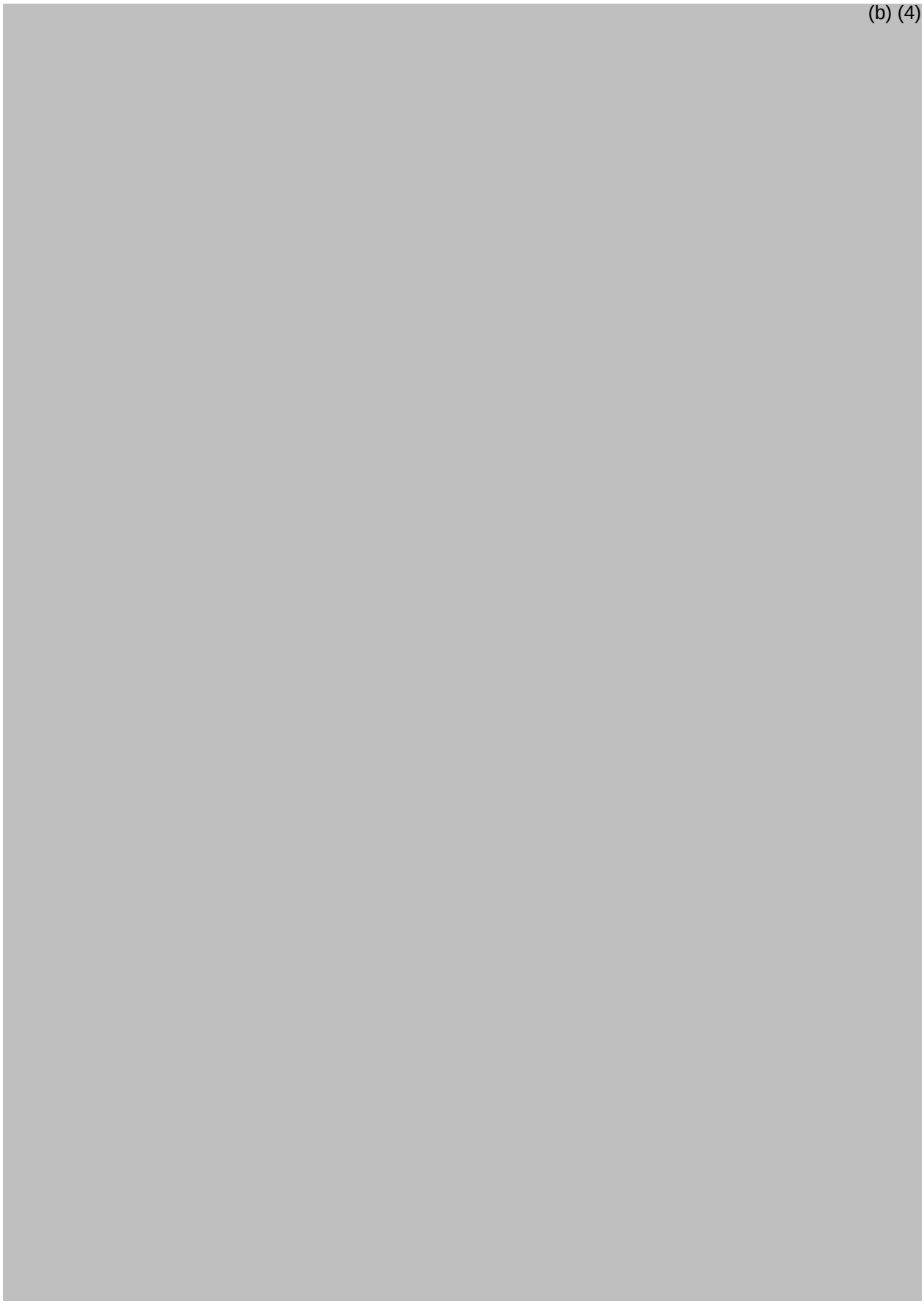
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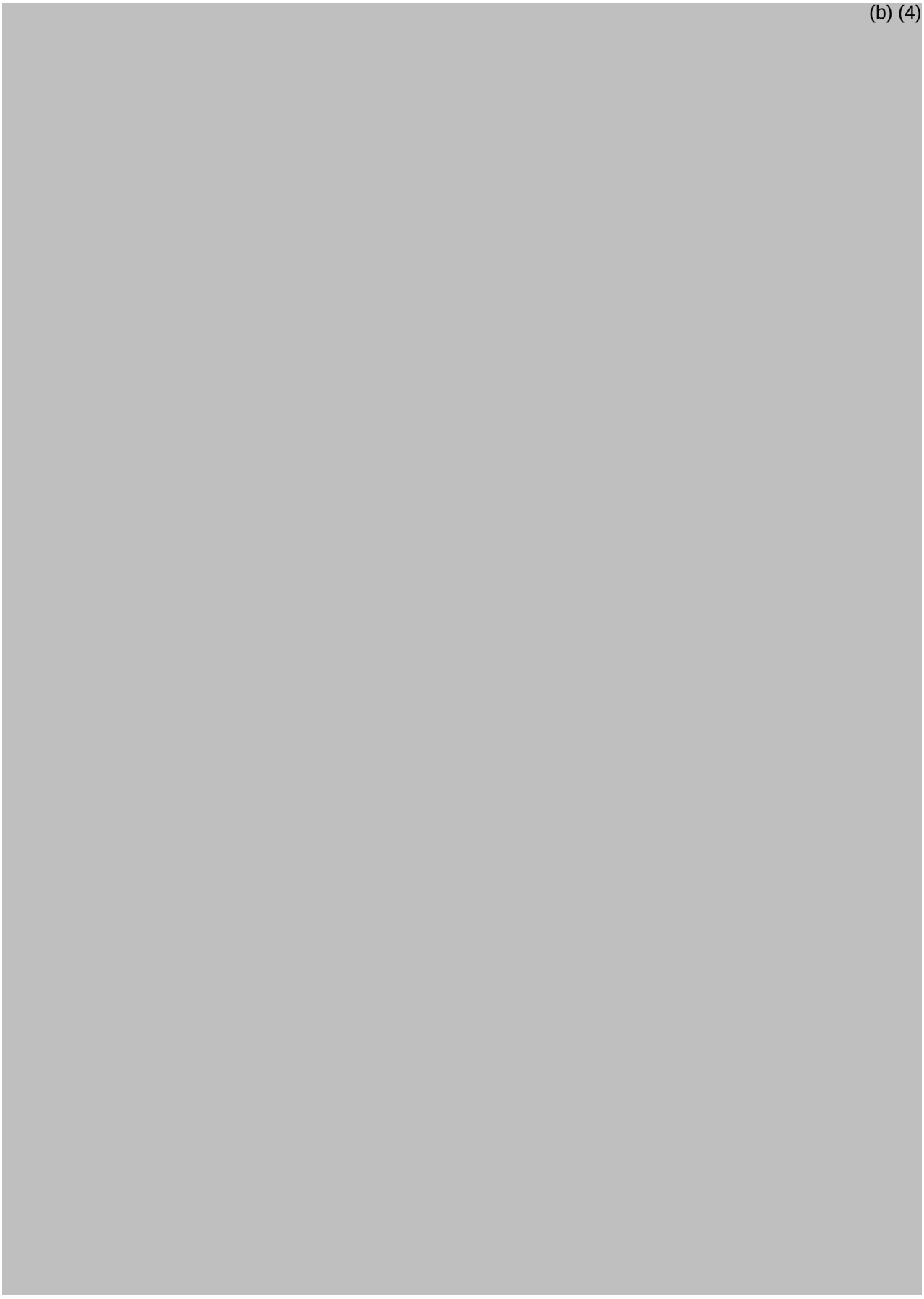
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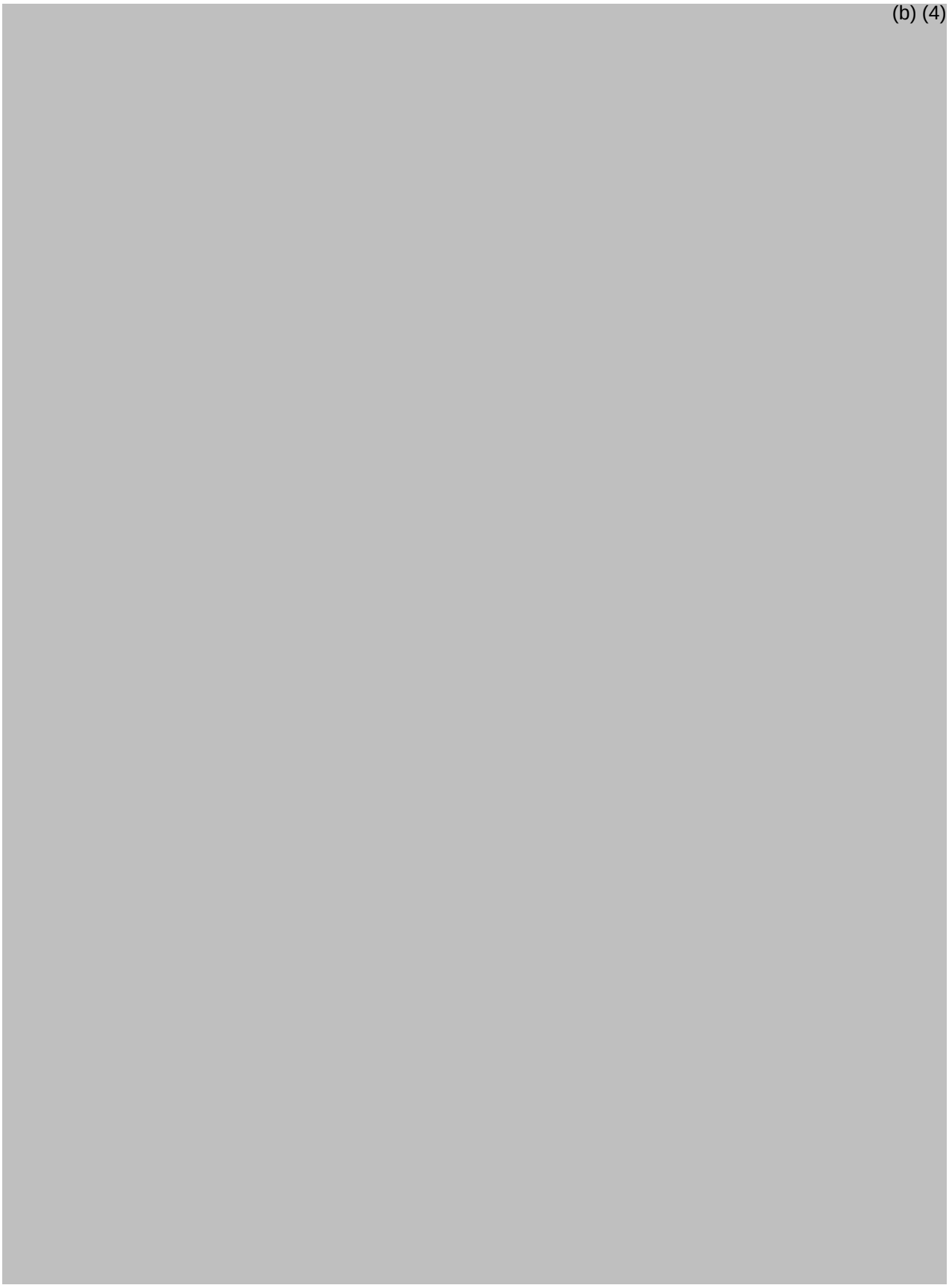
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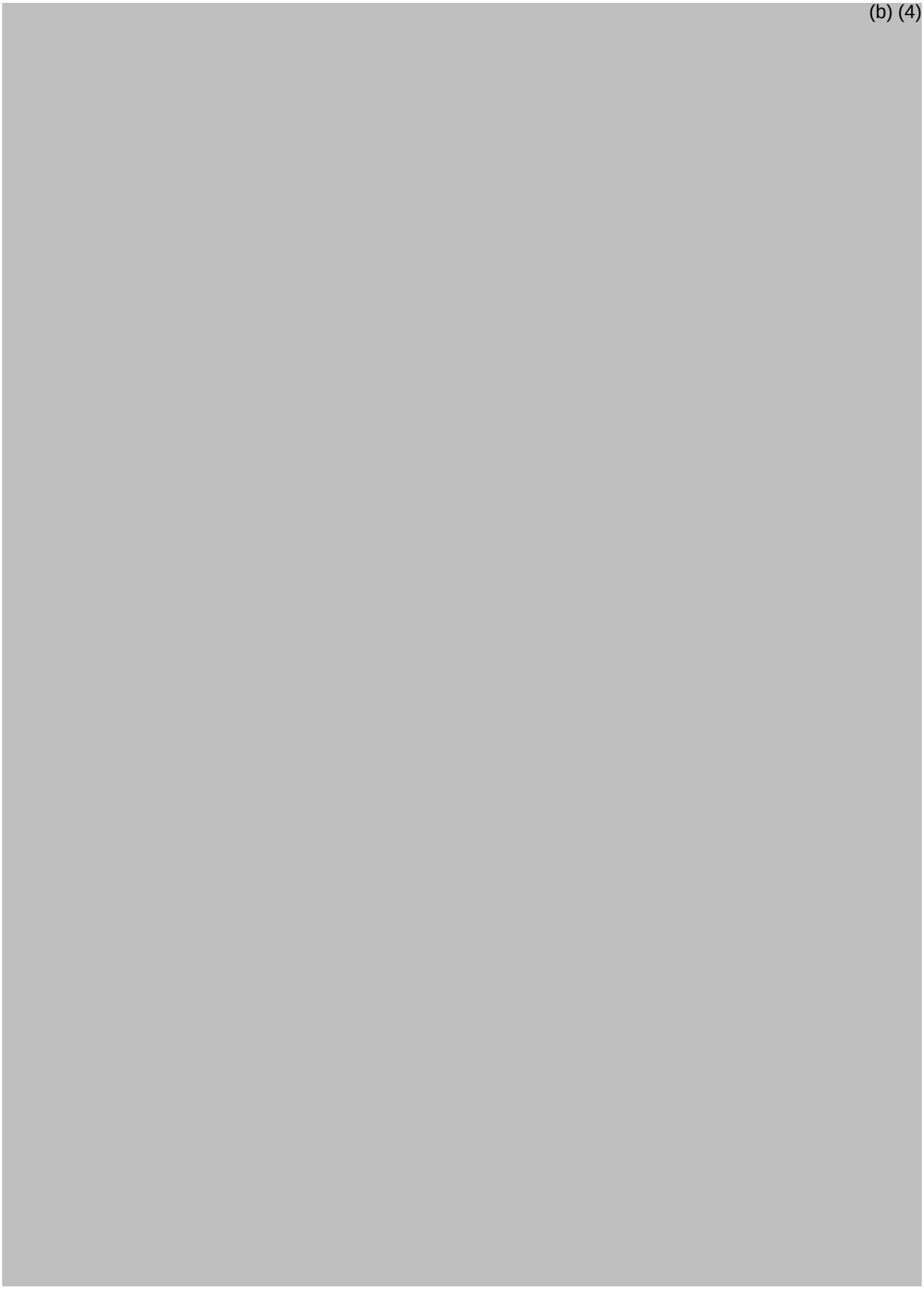
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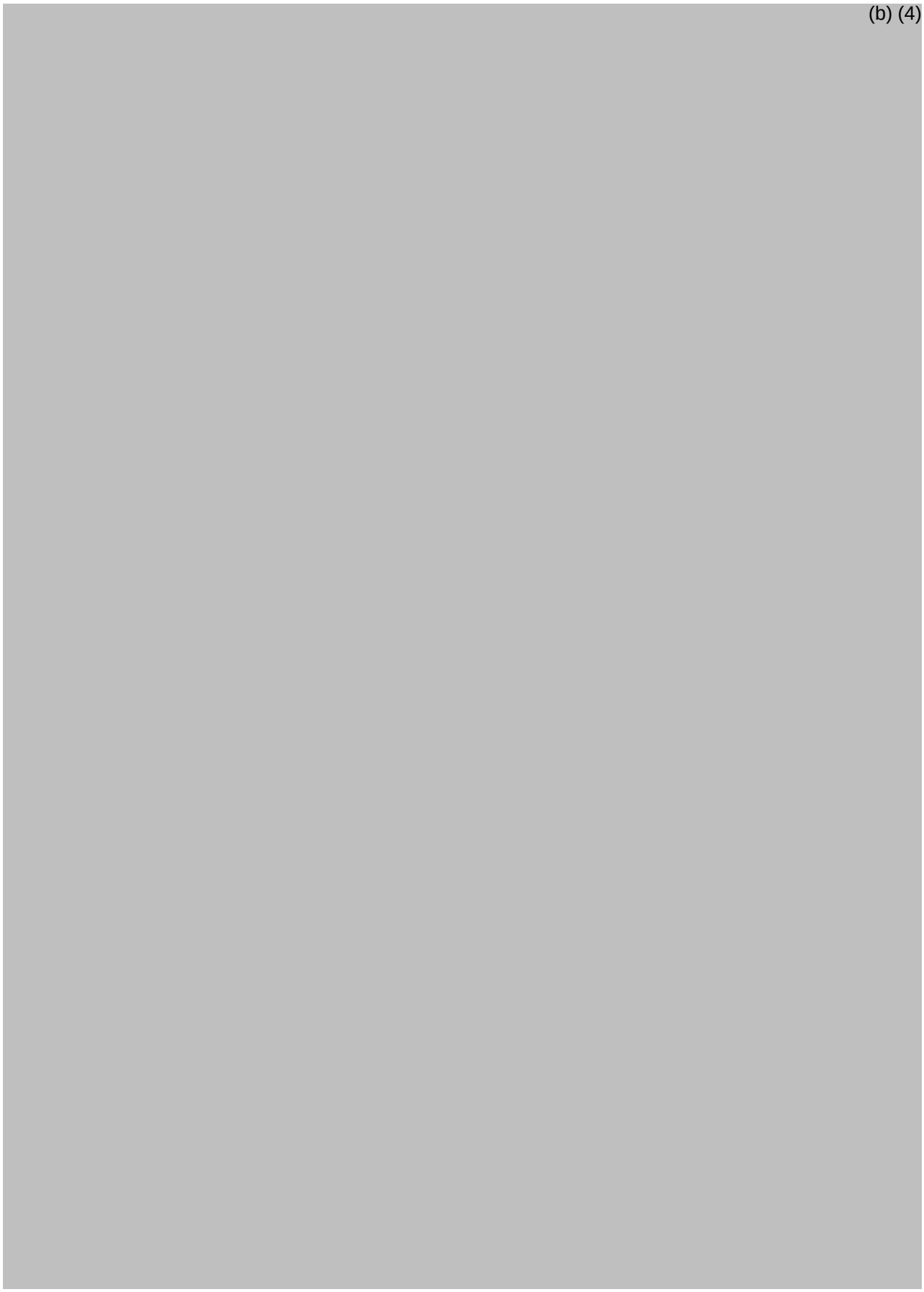
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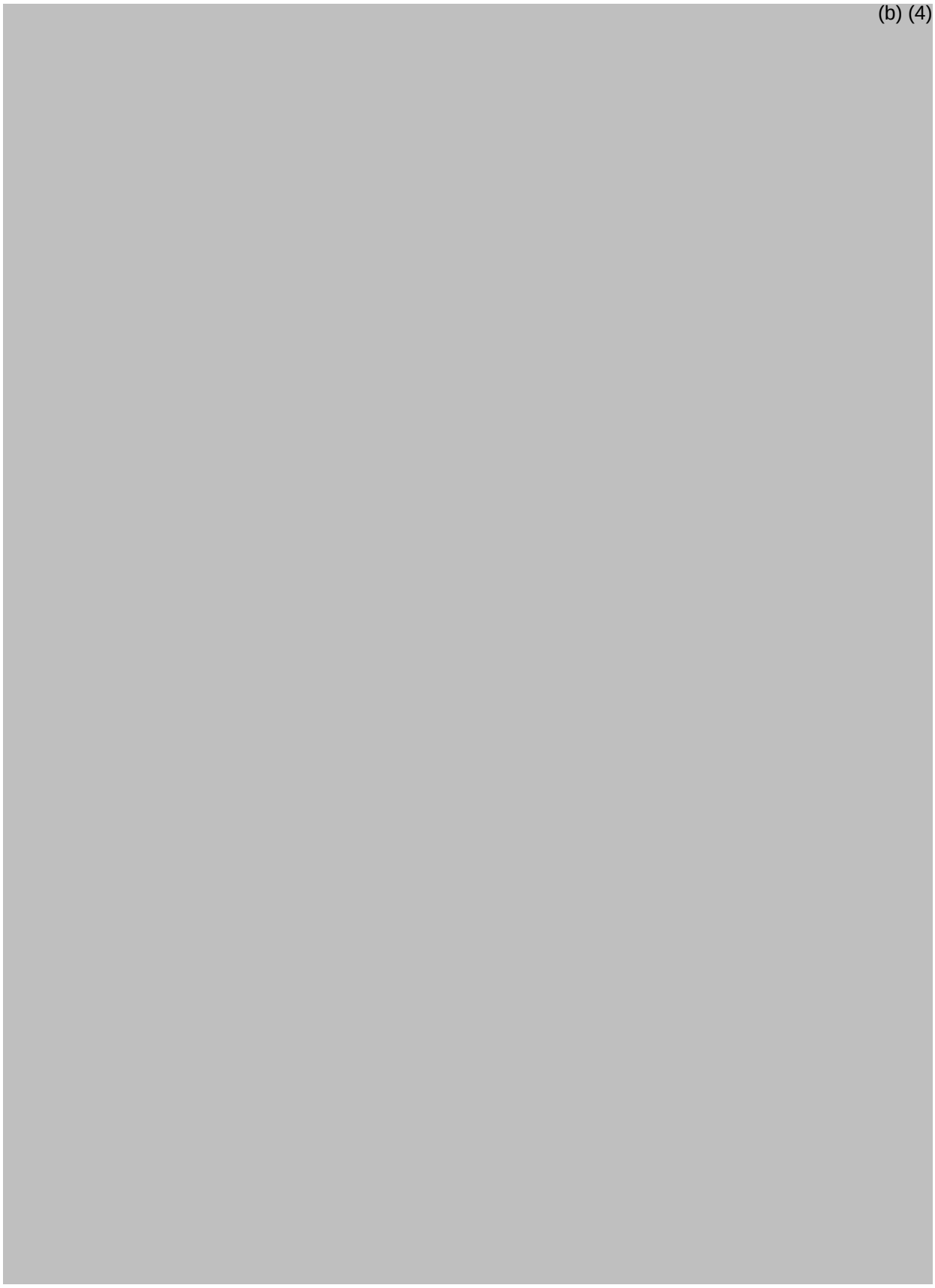
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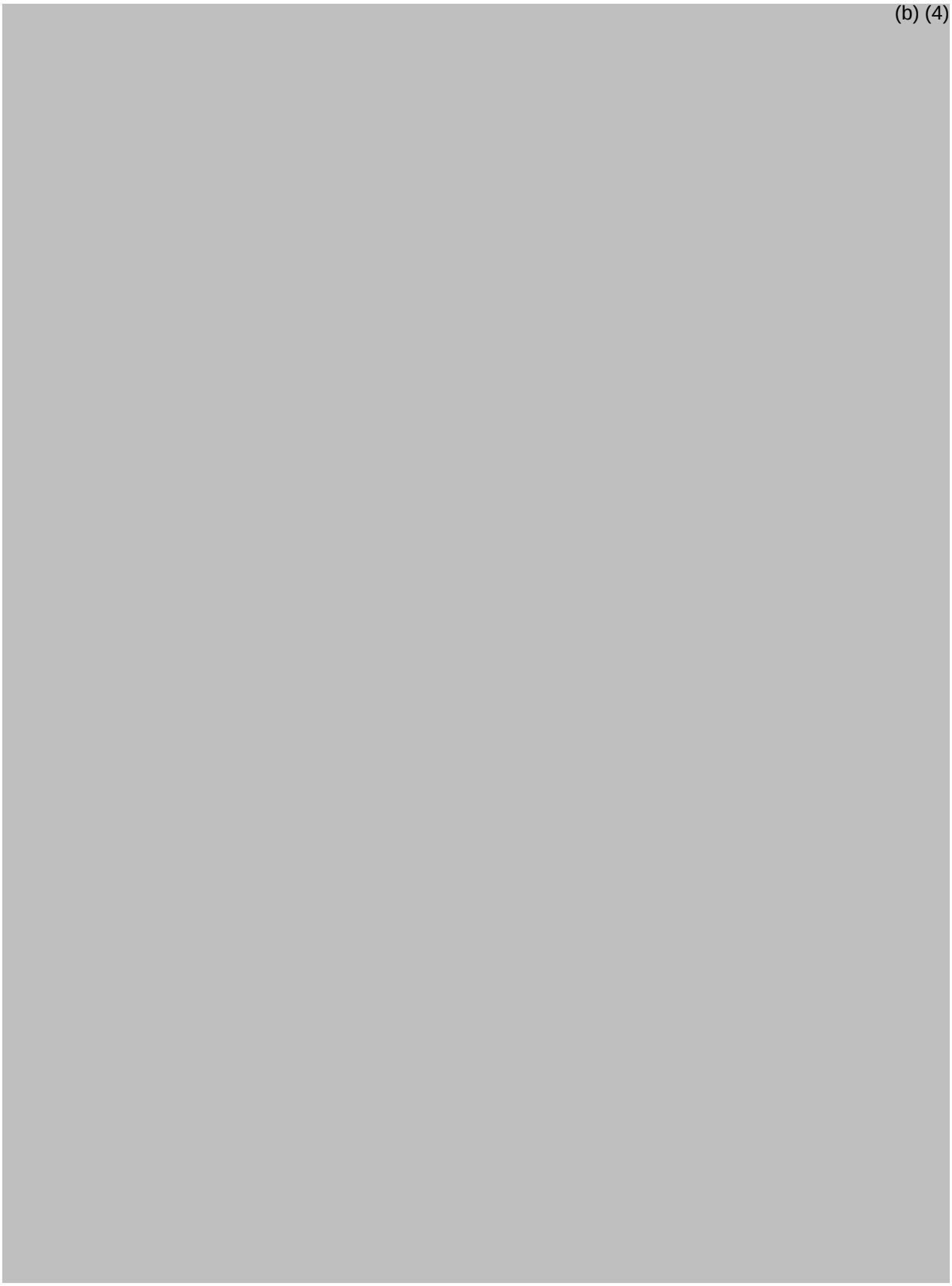
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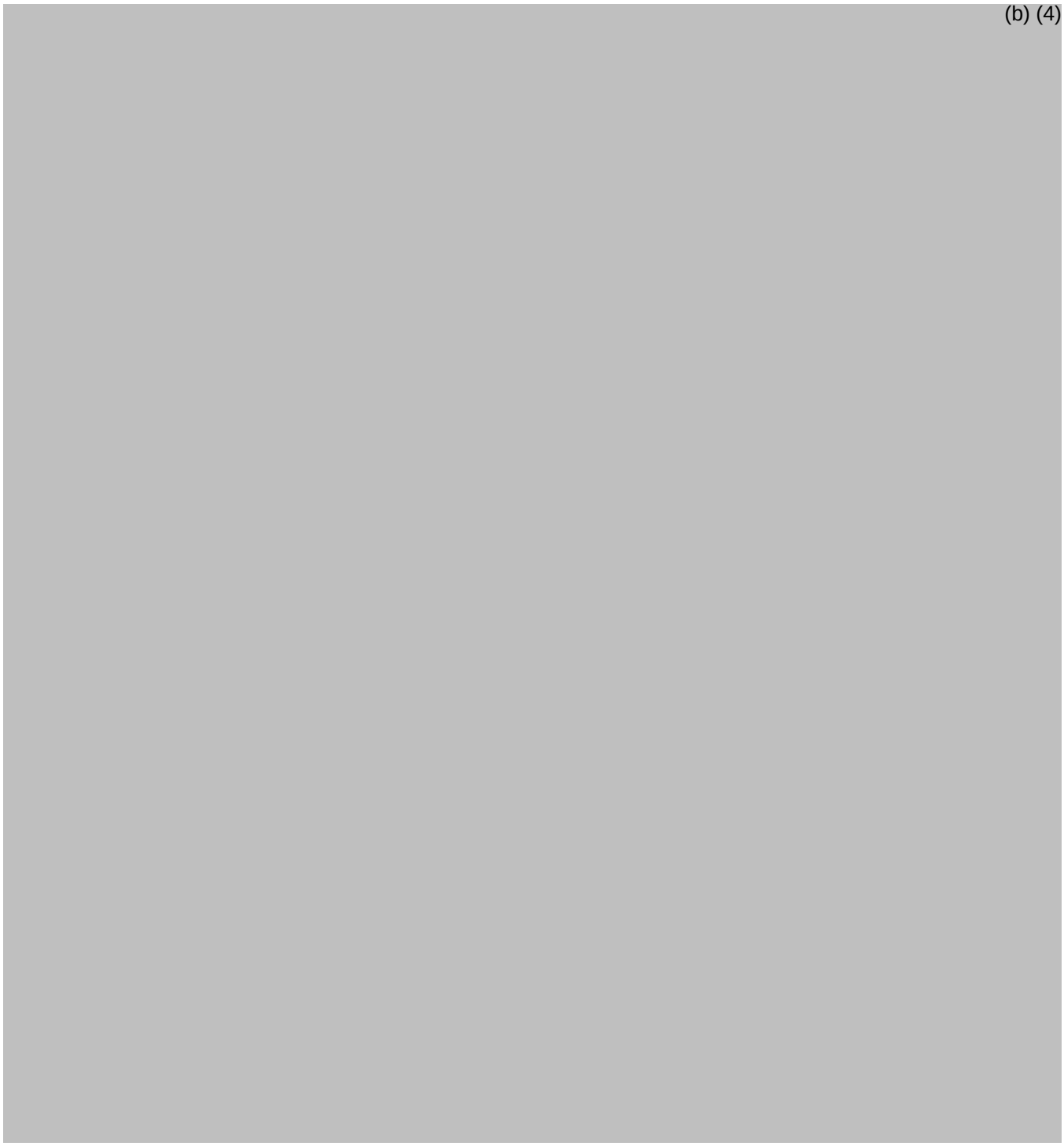
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12 APPENDIX

Sections and Appendices

Appendix 1: regulatory history
Appendix 2: table of studies
Appendix 3: literature review
Appendix 4: list of investigators and clinical sites
Appendices:

APPENDIX 12.1 Regulatory History for Asenapine: NDA #22-117

51-641: Asenapine in the treatment of Schizophrenia
70-329: Asenapine in the treatment of Mania associated with Bipolar Disorder

IND 51-641: asenapine in the treatment of Schizophrenia

- On September 30, 1996, Organon submitted IND 51-641: ORG-5222 sublingual tablets for the treatment of Schizophrenia

- The initial study conducted under IND 51-641 was protocol 041-001, entitled: a double-blind, placebo-controlled, titration study with sublingual ORG-5222 to establish the maximum tolerated dose in subjects with Schizophrenia.

ORG-5222 was investigated initially in Europe and Japan as intravenous and oral formulations. Due to low bioavailability and high first-pass metabolism of the oral formulation, a sublingual dosage form was developed.

IND 70-329: asenapine in the treatment of Mania associated with Bipolar Disorder

- On August 3, 2004, Organon submitted IND 70-329: ORG-5222 sublingual tablets for the treatment of acute mania associated with Bipolar Disorder

- Protocols A7501004 and A7501005 were both entitled: a Phase 3 multicenter, multinational, randomized, placebo-controlled, double-blind, 3-week study to evaluate the efficacy and safety of sublingual asenapine vs. olanzapine and placebo in patients with an acute manic episode.

Highlights of Regulatory Meetings and Communications between FDA and Organon

November 20, 2002 End of Phase 2 Meeting

- Discussed the design and acceptability of the two pivotal trials in Schizophrenia (fixed-dose studies 041-004 and 041-005). On face, the design appears to be acceptable.

- Discussed the establishment of the minimum effective dose of asenapine in Schizophrenia (dose ranging studies were adequately designed). Data appear to support that 5 mg BID was the minimum effective dose.

- Discussion of studies of asenapine in subjects with renal and hepatic impairment as well as ADME studies in healthy subjects.

- Discussion of drug-drug interaction studies of medications commonly used in the treatment of Schizophrenia and with drugs that interact significantly with the CYP450 enzyme system. Organon proposed studying interactions with cimetidine, carbamazepine, paroxetine, and imipramine. The Division discussed the fact that asenapine is metabolized primarily by CYP1A2 and recommended a drug interaction study with omeprazole. The Division also inquired about studies with the primary metabolites d-methyl-asenapine and n-oxide-asenapine. Organon planned to consider these points and discuss them further with the Division.

- Pediatric studies: Organon requested a deferral of pediatric studies until after the NDA is filed and additional safety data are collected for adults.

- Rationale for developing the racemate: asenapine is a racemic mixture of stereoisomers. The in vivo and in vitro pharmacological profiles are similar for both stereoisomers, and the physical chemical properties are similar. Modeling of both enantiomers demonstrates that they are superimposable, which supports the low chiral recognition. The Division agreed.

- PK/PD- dose proportionality demonstration. Organon proposed a pooled NONMEM analysis of a number of relevant clinical studies. The Division agreed, but requested that Organon study the relevant metabolites as well.

- The Division and the sponsor held a preliminary discussion about the plan to conduct a population PK analysis through sparse sampling within several pivotal studies. The objectives would be to assess the pharmacokinetic variability among the population and to determine the effects of age, gender, smoking, and concomitant medication treatment on the PK profile of asenapine and its metabolites.

- Discussed the planned extent of exposure, the number of subjects to be exposed to asenapine, as well as the doses and duration of exposure in the studies. The Division agreed that the planned exposure appears to be adequate for fulfilling ICH requirements.

- Division requested that Organon adequately study the potential for withdrawal phenomena upon discontinuation of treatment with asenapine beginning immediately upon discontinuation of treatment.

- Food effect study: Organon contended that such a study was not necessary, since asenapine is a fast-dissolving tablet that would be administered sublingually. Furthermore, Organon stated that asenapine is readily absorbed by the sublingual, supralingual, and buccal mucosa; therefore, food absorption should not significantly affect the availability of asenapine. The Division questioned whether any swallowed portion of asenapine would be absorbed lower in the gastrointestinal tract and whether the sublingual formulation could be absorbed more extensively than the oral formulation. Of there is no significant absorption of asenapine in the lower GI tract, then the Division would not require a food effect study. Organon replied that they would need to investigate these points further.

- Organon discussed the proposed designs for two pivotal trials of asenapine in subjects with Bipolar Disorder, Acute Manic or Mixed Manic Episodes with or without psychotic features, including rapid cycling Bipolar Disorder. The Division agreed that the proposed design would be acceptable for potentially submitting an NDA for the indication of acute mania.

- Organon discussed a proposed one-year, placebo-controlled, relapse prevention trial of asenapine in Schizophrenia. They proposed a short stabilization phase of only six weeks. The Division requested that Organon conduct a stabilization phase of six months, since this is a clinically meaningful period of stabilization. We emphasized that clinicians would not discontinue effective therapy after only six weeks of acute treatment. We also held a preliminary discussion about the proposed primary endpoint and potential definitions of relapse.

- We held preliminary discussions about Organon's plan to study negative symptoms and cognitive impairment associated with Schizophrenia. We agreed that these were extremely complex topics and that we would need to have considerable discussion in order to determine the details about how to proceed with these two new proposed indications. In principle, the Division agreed that both entities had the potential to be the subject of regulatory claims, as both are important clinical entities that constitute an unmet clinical need.

<u>April 27, 2004 Meeting Minutes: second End of Phase 2 Meeting</u>

- Negative Symptoms
- Maintenance relapse prevention
- Bipolar Disorder, Mania adjunctive studies (lithium and valproic acid)
- Pediatric indications

<u>July 22, 2005 Meeting Minutes: QT Evaluation and Thorough QT Study</u>

- Preclinical data: hERG assay; Purkinje fiber assay; dog studies
- Phase 1 and Phase 2 data: agreed that these data are not useful
- Thorough QT Study: Protocol A7501001: asenapine, quetiapine, placebo
- ECG monitoring in Phase 3 trials
- Metabolites: further study: CYP1A2 and CYP3A4 and others

July 18, 2006: Pre-NDA Meeting

- Adequacy of asenapine clinical programs for Schizophrenia and Mania
- Efficacy and Safety data bases
- Narratives for safety
- Presentation of QT data
- 4-month safety
- Content and format of electronic submission
- IND Annual Reports
- Suitability for filing

February 22, 2007 Meeting

- Adequacy of Pivotal Trials in Schizophrenia
- Adequacy of Pivotal Trials in Mania associated with Bipolar Disorder
- Adequacy of Safety data base
- Maintenance study randomized withdrawal- time to relapse

August 30, 2007

Submission of NDA 22-117 asenapine in the treatment of Schizophrenia and acute mania associated with Bipolar Disorder

Tables. Details of Organon Submissions and Communications (51-641; 70-329; and 22-117)

Topic/Issue	Correspondence			Regulatory History	
	Date	Ser. No.			Descriptio
Original IND 51,641: Clinical Hold	09/30/96	000	Letter to FDA		
	11/05/06		Letter from FDA	DPP Notifies Organon of Clinical Hold (communicated via phone on 10/20/96) 1. Identifies concerns about cardiovascular risk 2. Notes deficiencies in Investigator Brochure 3. Requests increased frequency of liver function testing In proposed protocol 4. Indicates that toxicity studies submitted support clinical trials of 2-weeks duration 5. Requests histopathology data	

	01/31/97	002	Letter to FDA	Organon responds to Clinical Hold
	03/14/97		Letter from FDA	DPP lifts Clinical Hold (communicated via phone on 03/04/97) 1. Significant cardiovascular (CV) AEs (syncope and asystole) should be reported as an IND Telephone Safety Report 2. Requests Investigator Brochure revisions 3. States that a recommendation for duration of clinical trials supported by preclinical data would be forthcoming
Reporting of CV AEs (syncope and asystole) as IND Telephone Safety Reports	04/18/97	003	Letter to FDA	Organon proposes definitions for reportable events (for syncope and asystole)
	06/26/97		Letter from FDA	DPP concurs with Organon's proposed definitions for reportable events for syncope and asystole with one addition
Recommended duration of clinical trials as supported by preclinical data	06/23/97		Letter from FDA	DPP states that preclinical data support clinical trials of up to 13-weeks duration 1. 52-week studies in rat and dog are inadequate 2. Requests summary table of available PK/ toxicokinetic data in rat, Dog and human 3. States Ames test in *Salmonella typhimurium* strains should be repeated 4. States *in vivo* micronucleus assay in rats should be repeated 5. Requests Investigator Brochure revisions

Topic/Issue	**Correspondence**		**Regulatory History**		
	Date	**Ser. No.**			**Descriptio**
Recommended duration of clinical trials as supported by preclinical data	07/10/97	006	Letter to FDA	Organon responds to FDA Letter dated 06/23/97 and requests teleconference to discuss choice of dose used in 52-week dog study and chromosomal aberration assay	
	08/27/97	008	Letter to FDA	In follow up to a 08/12/97 teleconference, Organon provides the following proposals for DPP comment: 1. Protocol for study in dogs 2. Revision to Investigator Brochure pertaining to chromosomal aberration assay	
	03/04/98	016	Letter to FDA	Organon requests permission to implement humanitarian extension protocol in which the maximum duration of treatment is not limited to 13 weeks	
	03/27/98		Fax from FDA	DPP requests information for review of Serial No. 016	
	04/16/98	018	Letter to FDA	Organon provides information requested in 03/27/98 fax	
	06/04/98		Letter from FDA	DPP states that case-by-case requests can be made for extensions of exposure beyond 13 weeks until preclinical requirements are satisfied	
	06/23/98	024	Letter to FDA	Organon proposes content of case-by-case requests for extensions of exposure beyond 13 weeks	
	06/14/99	046	Letter to FDA	Organon provides report for 39-week toxicity/toxicokinetic study in dogs and requests opinion on necessity for continued case-by-case requests for extension of exposure beyond 13 weeks	

	10/15/99	052	Letter to FDA	Organon repeats request – opinion on necessity for continued case-by-case requests for extension of exposure beyond 13 weeks
	02/11/00		Telephone contact	DPP notifies the sponsor that the requirement for prior approval for treatment beyond 13 weeks is no longer required
Embryofetal development studies	02/11/98		Letter from FDA	DPP raises concern about the adequacy of the embryofetal development studies (sensitivity of the methods used to assess fetal effects) conducted in rat and rabbit Requests individual line listings for all fetuses included in

Topic/Issue	**Correspondence**			**Regulatory History**	
	Date	**Ser. No.**			**Descriptio**
Embryofetal development studies				final analysis of IV embryofetal development study conducted in rabbits	
	05/21/98	022	Letter to FDA	Organon provides toxicology information requested in DPP's 02/11/98 letter	
ECGs	06/04/98		Letter from FDA	1. DPP requests additional ECGs in studies 041002 and 041500 2. DPP provides recommendations for ECG frequency in extension trials and timing of ECGs (at the estimated Tmax)	
	07/01/98	025	Letter to FDA	Organon submits Protocol 041500 Amendment 2 which incorporates the DPP's requests regarding ECGs	
	07/20/98	026	Letter to FDA	Organon submits Protocol 041002 Amendment 3 which incorporates the DPP's requests regarding ECGs	
Carcinogenicity studies	05/24/99	044	Letter to FDA	Organon submits proposal for review– design of carcinogenicity studies in rat and mouse	
	02/24/00	059	Letter to FDA	Organon requests comments on proposed carcinogenicity studies	
	04/10/00		Fax from FDA	DPP provides minutes of Exe-CAC -Exe-CAC could not concur with the doses selected by the sponsor; requested additional information	
	09/19/00	063	Letter to FDA	Organon provides information requested in DPP's 04/10/00 fax	
	04/02/01	070	Letter to FDA	Organon requests comments on changes to the mouse carcinogenicity study	
	04/10/02	083	Letter to FDA	Organon requests approval to partially terminate the mouse oncogenicity study	
	04/26/02		E-mail from FDA	FDA concurs with intent to stop mid- and high-dose animals in mouse oncogenicity study and recommend that if the number of male survivors in either group reaches 15, all male groups should be terminated	
	06/21/02	086	Letter to FDA	Organon requests approval to partially terminate the rat oncogenicity study	
	07/03/02		E-mail from FDA	DPP recommends that the sponsor continue to dose all groups in the rat oncogenicity study until scheduled sacrifice	

Topic/Issue		**Correspondence**	**Regulatory History**

	Date	Serial No.		Descriptio
Protocol 041002 unblinded Interim Analysis	06/22/99	047	Letter to FDA	Organon submits proposal for review – addition of unblinded interim analysis to Protocol 041002
	09/14/99		Letter from FDA	FDA comments on proposal for review – addition of unblinded interim analysis to Protocol 041002
	10/15/99	052	Letter to FDA	Organon indicates that it has decided not to conduct proposed interim analysis to Protocol 041002 following review of the DPP's comments
Subject Narratives	09/21/01	075	Letter to FDA	Organon requests comment on proposed criteria for writing subject narratives
	11/06/01	078	Letter to FDA	Organon acknowledges message from Mr. Steve Hardeman that proposed criteria for writing subject narratives are acceptable
EOPII Meeting - November 20, 2002	09/25/02	091	Letter to FDA	Type B (EOPII) Meeting Request
	10/21/02	093	Letter to FDA	Type B (EOPII) Meeting Information Package
	12/05/02	097	Letter to FDA	Sponsor's Minutes – Type B (EOPII) Meeting
	04/09/03	101	Letter to FDA	Organon requests DPP's Minutes – Type B (EOPII) Meeting
	05/06/03		Letter from FDA	DPP Minutes – Type B (EOPII) Meeting
Preclinical questions from November 20, 2002 EOPII Meeting	07/01/03	104	Letter to FDA	Organon requests response to preclinical questions addressed in EOPII meeting information package
	10/07/03		E-mail from FDA	DPP requests information for the review of preclinical questions addressed in EOPII meeting information package
	02/12/04	115	Letter to FDA	Organon provides information requested in 10/07/03 e-mail
	09/16/04	151	Letter to FDA	Organon requests response regarding preclinical questions addressed in EOPII meeting information package
	02/25/05		E-mail from FDA	DPP requests additional information for the review of preclinical questions addressed in EOPII meeting information package
	03/25/05	178	Letter to FDA	Organon provides information requested in 02/25/05 e-mail
	06/25/07		E-mail from FDA	DPP concurs that preclinical studies performed will be sufficient for filing with regard to assessment of general and reproductive/developmental toxicity of Org 5222 upon

Topic/Issue	Correspondence			Regulatory History
	Date	Serial No.		Descriptio
				sublingual administration
CMC questions from November 20, 2002 EOPII Meeting	07/01/03	104	Letter to FDA	Organon requests response to CMC questions addressed in EOPII meeting information package
	12/16/03	111	Letter to FDA	Type B Meeting Request – Teleconference to discuss CMC questions addressed in EOPII meeting information package
	01/15/04		E-mail from FDA	DPP recommends collecting tablet dissolution and disintegration data in stability studies and to present these n NDA in support of disintegration as a discriminating test
	01/16/04		Telephone contact	DPP responds on acceptability of proposed bracketing matrix

(b)

Protocol 041006 (schizophrenia relapse prevention)	08/19/03	106	Letter to FDA	Organon requests comments on Protocol 041006 – schizophrenia relapse prevention trial
	10/30/03		E-mail from FDA	DPP comments on Protocol 041006 – Relapse Prevention Trial
PK/PD modeling and sparse sampling plan*	10/22/03	108	Letter to FDA	Organon requests feedback regarding PK/PD modeling and sparse sampling plan proposals
	01/15/04		E-mail from FDA	DPP comments on PK/PD modeling and sparse sampling plan proposals
	06/03/04	138	Letter to FDA	Organon responds to comments provided in 01/15/04 e-mail
	09/16/04	151	Letter to FDA	Organon requests response regarding PK/PD modeling and sparse sampling plan proposals
	12/01/04		E-mail from FDA	DPP recommends a simulation to help optimize the PK sampling scheme
	07/25/05	197	Letter to FDA	Organon responds to recommendation provided in 12/01/04 e-mail – the proposed simulation is no longer necessary
Protocols 041008, 041503, 041504	03/02/04		Letter from FDA	DPP comments on Protocols 041008, 041503, 041504
	07/27/04	144	Letter to FDA	Organon notifies DPP of cancellation of Studies 041005, 041008, 041010, 041503, 041504, 041506 (prior to administration of study medication to any patients)
EOPII Meeting – April 27, 2004	03/02/04	120	Letter to FDA	Type B (EOPII) Meeting Request
	03/18/04		Letter from FDA	Type B (EOPII) Meeting Confirmation
	03/29/04	125	Letter to FDA	Type B (EOPII) Meeting Information Package

Topic/Issue	**Correspondence**			**Regulatory History**	
	Date	**Serial No.**			**Descriptio**
	04/23/04	130	Letter to FDA	Additional information for Type B (EOPII) Meeting	
	05/14/04	135	Letter to FDA	Sponsors' Minutes – Type B (EOPII) Meeting	
EOPII CMC Meeting – March 31, 2005*	01/31/05	166	Letter to FDA	Type B (EOPII CMC) Meeting Request	
	03/02/05	172	Letter to FDA	Type B (EOPII CMC) Meeting Information Package	
	05/04/05	182	Letter to FDA	Sponsors' Minutes – Type B (EOPII CMC) Meeting	
	10/12/05		E-mail from FDA	DPP Minutes – Type B (EOPII CMC) Meeting	
Drug Substance Regulatory Starting Material (RSM)*				See also EOPII CMC Meeting – March 31, 2005 and Pre-NDA CMC information package	
	12/02/05	222	Letter to FDA	Organon submits additional information on proposed RSM	
	02/27/06		Telephone contact	FDA acknowledges additional RSM information as supportive, pending NDA review	
Chemistry Manufacturing and Controls changes*	09/30/96	000	Letter to FDA	Includes 0.1, 0.2, 0.3, 0.4, 0.6, and 0.8 mg tablet strengths	
	09/24/00	064	Letter to FDA	Updates use of milled drug substance	
	04/04/01	071	Letter to FDA	Adds 2.5 mg, 5 mg, and 15 mg tablet strengths	
	10/24/03	109	Letter to FDA	Adds 10 mg tablet strength	
	02/17/04	117	Letter to FDA	Updates drug substance specifications/analytical methods	
	06/25/04	139	Letter to FDA	Adds drug substance synthesis route	
	09/16/05	209	Letter to FDA	Adds 1 mg and 2 mg tablet strengths	
	12/02/05	222	Letter to FDA	Adds drug substance synthesis route	
	12/14/05	223	Letter to FDA	Modifies tablet moisture content determination method	
	09/11/07	333	Letter to FDA	Update of comparator blinding/testing sites	

Protocol A7501001 (QTc study) & Type C (QTc) Meeting – July 22, 2005*	05/03/04	133	Letter to FDA	Organon requests comments on Protocol A7501001 (QTc Study)
	03/17/05	176	Letter to FDA	Type A (QTc) Meeting Request – discussion of QT study results and labeling implications
	03/29/05		Letter from FDA	Type C (QTc) Meeting Confirmation
	05/23/05	187	Letter to FDA	Type C (QTc) Meeting Information Package
	06/15/05		E-mail from FDA	Confirmation of new meeting date for Type C (QTc) Meeting
	07/18/05		E-mail from FDA	DPP provides Pre-Meeting Questions
	07/20/05	196	Letter to FDA	Organon responds to Pre-Meeting Questions provided in 07/18/05 e-mail
	07/28/05		E-mail from FDA	DPP Minutes - Type C (QTc) Meeting

Topic/Issue	**Correspondence**			**Regulatory History**	
	Date	**Serial No.**			**Descriptio**
	09/06/05	204	Letter to FDA	Organon comments on DPP's Type C (QTc) Meeting Minutes	
	10/26/05	215	Letter to FDA	Organon proposes modification to Phase 3 monitoring plan based on discussion at Type C (QTc) Meeting	
Original IND 70,329	08/03/04	000	Letter to FDA		
	08/13/04		Letter from FDA	IND acknowledgement letter	
	08/31/04		E-mail from FDA	DPP notifies Organon that IND may proceed	
Protocol A7501013 (negative symptoms of schizophrenia)	08/06/04	145	Letter to FDA	Request for Special Protocol Assessment – Phase III Protocol A7501013	
	10/27/04	154	Letter to FDA	Organon notes that Special Protocol Assessment is overdue	
	02/15/05		Letter from FDA	Special Protocol Assessment – Protocol A7501013 (letter dated 11/02/04)	
Protocol A7501012 (schizophrenia relapse prevention)	08/27/04	149	Letter to FDA	Request for Special Protocol Assessment – Phase III Protocol A7501012 (schizophrenia relapse prevention)	
	10/26/04		Letter from FDA	Special Protocol Assessment – Protocol A7501012	
	11/12/04	158	Letter to FDA	Type A Meeting Request – Teleconference to discuss A7501012 Special Protocol Assessment	
	12/02/04		E-mail from FDA	DPP indicates that Type A Meeting is unnecessary, responses to sponsor questions will be provided in a letter	
	12/07/04		E-mail from FDA	DPP responds to Type A Meeting Request	
	12/20/05	224	Letter to FDA	Organon requests modification of Special Protocol Assessment – Protocol A7501012	
	05/16/06		E-mail from FDA	DPP statistical comments on Protocol A7501012 Interim Analysis	
	07/05/06	261	Letter to FDA	Organon responds to comments provided in 05/16/06 e-mail	
	11/21/06		E-mail from FDA	DPP provides additional statistical comments on Protocol A7501012 Interim Analysis	
	04/20/07	313	Letter to FDA	Organon notifies DPP that it has decided not to perform the interim analysis planned for Protocol A7501012	

Harmonization of IND Annual Reporting period	12/27/04		E-mail to FDA	Organon proposes to harmonize the annual reporting period for INDs 51,641 and 70,329

Topic/Issue	Correspondence			Regulatory History	
	Date	Serial No.			Descriptio
	12/27/04		E-mail from FDA	DPP agrees to proposal for harmonization of annual reporting period	
	01/03/05	IND 70,329 SN 005	Letter to FDA	Organon documents agreement with DPP for harmonization of annual reporting period	
Drug-drug interaction studies*	07/25/05	197	Letter to FDA	Organon updated clinical development plan for the study of drug-drug interactions	
	12/21/05		E-mail from FDA	DPP responds to drug-drug interaction study plan – fluvoxamine study requested	
Duration of pediatric PK trial*	08/18/05	200	Letter to FDA	Organon proposes to reduce the duration of treatment in pediatric PK, safety, and tolerability study from 3-weeks to 10 days	
	09/07/05		E-mail from FDA	DPP agrees with the reduction of the study duration from 3-weeks to 10 days	
DSMC*	08/23/05	202	Letter to FDA	Organon requests comment on DSMC proposal	
	08/31/05		E-mail from FDA	DPP confirms that the proposal, as currently written, is acceptable	
N+-glucuronide metabolite*	12/22/05	225	Letter to FDA	Organon proposes that addition toxicology studies for further testing of newly identified major metabolite (N-glucuronide) will not provide additional useful information regarding the safety of asenapine in humans	
	05/03/06		E-mail from FDA	DPP agrees that further testing of N-glucuronide would not provide additional useful information regarding the safety of asenapine in humans	
Trademark*	01/12/06	226	Letter to FDA	Organon submits proposed Trademark for review	
Pre-NDA Meeting – July 18, 2006*	04/21/06	240	Letter to FDA	Type B (Pre-NDA) Meeting Request	
	06/09/06	254	Letter to FDA	Type B (Pre-NDA) Meeting Information Package	
	07/12/06		E-mail from FDA	DPP's preliminary responses to Pre-NDA Meeting Questions	
	07/21/06	266	Letter to FDA	Sponsors' Minutes – Type B (Pre-NDA) Meeting	
	07/26/06		E-mail from FDA	DPP's Minutes – Type B (Pre-NDA) Meeting	
IND safety reporting procedure*	05/23/06		E-mail to FDA	Organon requests clarification whether IND safety reports should be submitted to both INDs (via cross-reference)	

Topic/Issue	Correspondence			Regulatory History	
	Date	Serial No.			Descriptio
	06/08/06		E-mail from FDA	DPP confirms IND Safety Reports should be submitted to both INDs (via cross-reference)	
Degradation products (Org 43156 and Org	07/28/06	268	Letter to FDA	Organon submits proposal regarding toxicological qualification of two asenapine degradants	

43474)*	01/30/07	302	Letter to FDA	Organon provides toxicological qualification results and requests DPP concurrence that the asenapine degradants have been qualified for genotoxicity
	02/13/07		E-mail from FDA	DPP responds that strategy provided in Serial No. 268 is reasonable
	03/14/07		E-mail from FDA	DPP concurs that the asenapine degradants have been qualified for genotoxicity
Pre-NDA Meeting – February 22, 2007*	12/21/06	294	Letter to FDA	Type B (Pre-NDA) Meeting Request
	01/22/07	300	Letter to FDA	Type B (Pre-NDA) Meeting Information Package
	02/20/07		E-mail from FDA	DPP's preliminary responses to Pre-NDA Meeting Questions
	02/28/07	307	Letter to FDA	Sponsor's Minutes – Type B (Pre-NDA) Meeting
	03/06/07		Letter from FDA	DPP's Minutes – Type B (Pre-NDA) Meeting
	03/13/07	310	Letter to FDA	Organon provides comments on DPP's Minutes – Type B (Pre-NDA) Meeting
	03/21/07		E-mail from FDA	DPP states that Sponsor comments will be on permanent record as additions to the meeting minutes, correspondence related to the meeting minutes
Patient safety profiles*	04/23/07	314	Letter to FDA	Organon requests comments on sample time-by-variable display of patient safety information
	06/11/07	322	Letter to FDA	Organon submits revised sample time-by-variable display of patient safety information for comment and proposes patients for whom these displays would be provided in the NDA
	06/18/07		E-mail from FDA	DPP responds that time-by-variable display and proposal regarding types of patients are acceptable
Data components of NDA*	05/02/07	316	Letter to FDA	Organon requests feedback from statistical reviewers on data components of the NDA
	05/08/07		E-mail from FDA	Statistical reviewer(s) find proposals for data components

Topic/Issue	**Correspondence**		**Regulatory History**	
	Date	**Serial No.**		**Descriptio**
				of the NDA acceptable
	07/18/07	325	Letter to FDA	Organon requests feedback from statistical reviewers (splitting of datasets greater than 100 mb)
	07/26/07		E-mail to FDA	Organon confirms that it will provide safety data sets in the NDA as SAS export files broken down by Cohort as requested and discussed during 07/26/07 telephone call with Dr. Robert Levin
Pre-NDA CMC information package*	08/08/07	330	Letter to FDA	Organon updates status of EOPII CMC Meeting – March 31, 2005 issues

APPENDIX 2. TABLE OF CLINICAL STUDIES

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Statu Type of Report
BIOAVAILABILITY (BA) STUDY REPORTS							
BA	25533 Netherlands (1 center)	An absolute bioavailability study with sublingually and intravenously administered asenapine in healthy male subjects	placebo Route: SL tablet and IV asenapine Route: SL tablet Dose Regimen: 5 mg asenapine Route: IV Dose Regimen: 10 µg solution asenapine with 200 nCi ^{14}C-radioactivity.	Randomized: 8 Treated: 8 Completed: 8 healthy subjects	Sex: 8M/0F Mean Age (min/max): 27.5 (18-51) years Race: W/B/A/O: 8/0/0/0	single dose	Started: November 2005 Completed: December 2005 full
BA	041036 Netherlands (1 center)	A single dose two-way crossover study to assess the absolute bioavailability of sublingually administered asenapine in healthy male subjects	asenapine: Route: IV Dose Regimen: 0.5 mg	Randomized: 3 Treated: 3 Completed: 3 healthy subjects	Sex: 3M/0F Mean Age (min/max): 24.3 (20-31) years Race: W/B/A/O: 2/1/0/0	single dose	Started: October 20 Completed: November 2006 full
BA	R&DRR INT00035825	PK evaluation of data from trials 041036 and 25506 to estimate absolute bioavailability of asenapine	analyte = asenapine	NA	NA	NA	Completed full

M = Male; F = Female; W = White; B = Black; A = Asian; O = Other; BID = Twice daily; QD – Daily SL = sublingual formulation; NA = Not applicable; IV = intravenous; BA = Bioavailability trial; BE = Bioequivalence Trial; BAM = Bioanalytical and Analytical Methods Report; E = Efficacy trial; PD = Pharmacodynamic trial; PK Pharmacokinetic trial; S = Safety trial

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial St Type Repo
BA	25545 Belgium (1 center)	An open label, randomized, two-way cross-over, bioequivalence trial in healthy, smoking volunteers to assess the effect of smoking during sublingual asenapine dosing on the absorption of asenapine	placebo Route: SL tablet asenapine Route: SL tablet Dose Regimen: 5 mg	Randomized: 24 Treated: 24 Completed: 24 healthy subjects	Sex: 24M/0F Mean Age (min/max): 32.5 (21-45) years Race: W/B/A/O: 24/0/0/0	Single dose x 2 (on Day 1 and Day 8)	Started: January 2 Complete March 20 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial S Typ Rep
COMPARATIVE BA AND BIOEQUIVALENCE (BE) STUDY REPORTS							
BA	041009 United States (1 center)	A single center, 2-way crossover relative bioavailability and safety study with differing formulated tablets of sublingually administered Org 5222 in subjects with schizophrenia or schizoaffective disorder	placebo Route: SL tablet asenapine Route: SL tablet Dose Regimen: **Block 1:** **Sequence 1** 2.4 mg Old Formulation tablet BID followed by 2.5 mg New Formulation tablet BID **Sequence 2** 2.5 mg New Formulation tablet BID followed by 2.4 mg Old Formulation tablet BID	**Block 1** Randomized: 6 Treated: 6 Completed: 6 **Block 2** Randomized: 6 Treated: 6 Completed: 6 schizophrenic patients	**Block 1** Sex: 6M/0F Mean Age (min/max): 38.1 (22-47) years Race: W/B/A/O: 2/4/0/0 **Block 2** Sex: 6M/0F Mean Age (min/max): 39.6 (32-48 years Race: W/B/A/O: 2/4/0/0	**Block 1**: 7 days **Block 2:** 9 days	Started: October Comple July 200 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Stat Type o Repor
	041009 (cont'd)		**Block 2:** **Sequence 1** 5 mg New Formulation tablet, (b) (4) followed by 5 mg New Formulation tablet, (b) (4) BID **Sequence 2** 5 mg New Formulation tablet, (b) (4) followed by 5 mg New Formulation tablet, (b) (4) BID					
BA, BE	25512 United Kingdom (1 center)	A Phase I, 3-way cross-over bioequivalence study with sublingually, supralingually and buccally administered 200 µg Org 5222 in healthy male volunteers	asenapine Route: SL tablet administered sublingually, supralingually and bucally Dose Regimen: 200µg	Randomized: 24 Treated: 24 Completed: 23 healthy subjects	Sex: 24M/0F Mean Age (min/max): 26.5 (19-35) years Race: W/B/A/O: 24/0/0/0	single dose x 3 (7-day washout between doses)	Started: March 199 Completed April 1996 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	T
BA	041014 United States (1 center)	A single-center, open-label, 2-way crossover relative bioavailability and safety trial with two differing strength tablets (3 x 5mg vs. 1 x 15 mg) of sublingually administered Org 5222 in subjects with schizophrenia or schizoaffective disorder	placebo Route: SL tablet asenapine Route: SL tablet Dose Regimen: 5 mg BID titrated upward to 15 mg BID - Sequence 1 or Sequence 2	asenapine **Sequence 1** Randomized: 4 Treated: 4 Completed: 4 asenapine **Sequence 2** Randomized: 4 Treated: 4 Completed: 4 schizophrenic patients	asenapine **Sequence 1** Sex: 3M/1F Mean Age (min/max): 41.5 (25-51) years Race: W/B/A/O: 2/1/0/1 asenapine **Sequence 2** Sex: 3M/1F Mean Age (min/max): 39.5 (34-48) years Race: W/B/A/O: 3/0/0/1	7 days	Sta Au Co De 20 full
BE	A7501015 United States (1 center)	A bioequivalence study of sublingual asenapine tablets (5 mg) in healthy volunteers	placebo Route: (b) (4) SL tablet asenapine Route: SL tablet Dose Regimen: (b) (4) 5 mg	Randomized: 38 Treated: 38 Completed: 32 healthy subjects	Sex: 27M/11F Mean Age (min/max): 25.3 (18-43) years Race: W/B/A/O: 26/8/3/1	single dose x 3 (7-day washout between doses)	Sta Ma Co Ma full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Tri
BE	A7501016 United States (1 center)	A Phase 1, open label, single-dose, bioequivalence study (b) (4) asenapine tablets (5 mg) in healthy volunteers	placebo Route: SL tablet asenapine cross-over study Route: SL tablet Dose Regimen: **Treatment A** (b) ablet 5 mg **Treatment B** (b) (4) tablet 5 mg	Randomized: 36 Treated: 36 Completed: 33 healthy subjects	Sex: 22M/14F Mean Age (min/max): 24.1 (18-50) years Race: W/B/A/O: 31/4/0/1	Single dose x 2 (7-day washout between doses)	Star May Con July full
BA, BE	041030 Belgium (1 center)	A single dose, open label, randomized, three period, three-way cross-over bioequivalence study with sublingually, supralingually and bucally administered asenapine in healthy male subjects	placebo Route: SL tablet administered Sublingually, Supralingually or Buccally asenapine Route: SL tablet **Treatment A** Sublingual dose **Treatment B** Supralingual dose **Treatment C** Buccal dose Dose Regimen: 5 mg	**Treatment A** Randomized: 12 Treated: 12 Completed: 11 **Treatment B** Randomized: 12 Treated: 12 Completed: 10 **Treatment C** Randomized: 12 Treated: 12 Completed: 11 healthy subjects	**Treatment A** Sex: 12M/0F Mean Age (min/max): 37.6 (18-53) years Race: W/B/A/O: 12/0/0/0 **Treatment B** Sex: 12M/0F Mean Age (min/max): 37.6 (18-53) years Race: W/B/A/O: 12/0/0/0 **Treatment C** Sex: 12M/0F Mean Age (min/max): 37.6 (18-53) years Race: W/B/A/O: 12/0/0/0	Single dose x 3 (7-day washout between doses)	Star Aug Con Dec 200 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Tri
REPORTS OF BIOANALYTICAL AND ANALYTICAL METHODS FOR HUMAN STUDIES							
BAM	SDGRR 3569	Validation of the gas chromatographic mass spectrometric assay for the determination of Org 5222 in human plasma	Org 5222	NA	NA	NA	Con full
BAM	SDGRR 3570	Validation of the gas chromatographic assay for the determination of Org 30526 in human plasma	Org 30526	NA	NA	NA	Con full
BAM	R&DRR NL0012937	Method transfer validation of the GC-MS assay for the determination of Org 5222 in human plasma	Org 5222	NA	NA	NA	Con full
BAM	R&DRR NL0039449	Re-validation of the GC-MS assay for the determination of Org 5222 in human plasma	Org 5222	NA	NA	NA	Con full
BAM	R&DRR NL0054225	Validation of the LC-MS-MS assay for the determination of asenapine (Org 5222), Org 30526 and Org 31437 in human plasma	Org 5222 Org 30526 Org 31437	NA	NA	NA	Con full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Status Type of Report
BAM	R&DRR NL0061697	Amendment I to R&D RR NL0054255	Org 5222 Org 30526 Org 31437	NA	NA	NA	Completed full
BAM	R&DRR NL0058575	Re-validation of the LC-MS-MS assay for the determination of asenapine (Org 5222), Org 30526 and Org 31437 in human plasma	Org 5222 Org 30526 Org 31437	NA	NA	NA	Completed full
BAM	R&DRR NL0065058	Amendment I to R&DRR NL0058575	Org 5222 Org 30526 Org 31437	NA	NA	NA	Completed full
BAM	R&DRR INT00013367	Amendment II to R&DRR NL0058575	Org 5222 Org 30526 Org 31437	NA	NA	NA	Completed full
BAM	R&DRR NL0046846	Cross-validation of the LC-MS-MS assay for the determination of Org 5222 and Org 30526 in human plasma	Org 5222 Org 30526	NA	NA	NA	Completed full
BAM	R&DRR INT00003244	Validation of a method for the determination of asenapine-glucuronide (Org 216761-0) in human Li-heparin samples by LC-MS/MS	Org 216761-0	NA	NA	NA	Completed full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Stat Type o Repor
BAM	R&DRR INT00003248	Validation of a method for the determination of asenapine-glucuronide (Org 216761-0) in human urine samples by LC-MS/MS	Org 216761-0	NA	NA	NA	Completed full
BAM	R&DRR INT00006666	Validation of a Method for the Determination of Org 5222 and Org 30526 in Human Urine Samples by LC-MS/MS	Org 5222 Org 30526	NA	NA	NA	Completed full
BAM	R&DRR NL00005948	Validation of the LC-MS-MS assay for the determination of asenapine, Org 30526 and Org 214025 in human plasma	Org 5222 Org 30526 Org 214025	NA	NA	NA	Completed full
BAM	R&D RR INT00029604	Amendment 1 to NL00005948	Org 5222 Org 30526 Org 214025	NA	NA	NA	Completed full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Stat Type o Repor
REPORTS OF STUDIES PERTINENT TO PHARMACOKINETICS USING HUMAN BIOMATERIALS							
PLASMA PROTEIN BINDING STUDY REPORTS							
PK	SDG RR 2972	In vitro binding of [3H]-Org 5222 to male rat, dog and human plasma proteins and in vivo plasma protein binding after a single oral dose of [3H]-Org 5222 to male rats	Org 5222	NA	NA	NA	Completed full
PK	DM2005-005222-007	Plasma protein binding of asenapine (Org 5222) and N-desmethyl asenapine (Org 30526) in human, rat, dog, monkey, rabbit and mouse plasma, human alpha1-acid glycoprotein and human serum albumin	Org 5222 Org 30526	NA	NA	NA	Completed full
PK	DM2005-005222-015	Plasma protein binding of 11-hydroxyasenapinesulfate in human, rat and rabbit plasma	Org 214025 (asenapine 11-O-sulfate)	NA	NA	NA	Completed full
PK	R&DRR NL0029630	An in vitro binding study with Org 5222 by mouse, rat, rabbit, dog and human erythrocytes	Org 5222	NA	NA	NA	Completed full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Sta Type Repo
REPORTS OF HEPATIC METABOLISM AND DRUG INTERACTIONS STUDIES							
PK	SDGRR 2874	In vitro metabolism of Org 5222 by rat, dog and human hepatic microsomes	Org 5222	NA	NA	NA	Complete full
PK	SDGRR 5067	In vitro metabolism of Org 5222 by rat and human hepatocytes	Org 5222	NA	NA	NA	Complete full
PK	R&DRR INT00003054	An in vitro metabolism study with Org 5222 by male mouse, rat, rabbit, dog and human liver microsomes	Org 5222	NA	NA	NA	Complete full
PK	R&DRR NL0060905	An in vitro metabolism study with Org 5222 by male mouse, rat, dog and human and female rabbit hepatocytes	Org 5222	NA	NA	NA	Complete full
PK	DM2006-005222-013	Determination of the Enzyme Kinetics and UGT Involved in the Metabolism of asenapine to the N-Glucuronide Conjugate of asenapine	Org 5222	NA	NA	NA	Complete full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Status Type of Report
PK	R&DRR NL0010293	Characterization of human cytochrome P450 enzymes involved in the in vitro metabolism of Org 5222	substrate = asenapine inhibitor = fluvoxamine, ketoconazole	NA	NA	NA	Completed full
PK	R&DRR NL0060848	A second characterization of the human cytochrome P450 enzymes CYP1A2, CYP2B6, CYP2C19, CYP2D6 and CYP3A4 involved in the in vitro metabolism of asenapine (Org 5222)	substrate = asenapine inhibitor = furafylline, orphenadrine, MPEP: 1-(1-methyl-1-phenylethyl)piperidine, tranylcypromine, benzylnirvanol, quinidine, ketoconazole	NA	NA	NA	Completed full
PK	R&DRR NL0017588	The inhibition of the human cytochrome P450 enzymes CYP1A2 and CYP2D6 by Org 5222 (in vitro)	substrate = CEC: 7-ethoxy-3-cyanocoumarin, AMMC: 3-[2-(N,N-diethyl-N-methylamino)ethyl]-7-methoxy-4-methylcoumarin inhibitor = asenapine, furafylline	NA	NA	NA	Completed full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Statu Type of Report
PK	R&DRR NL0048836	The assessment of the human cytochrome P450 enzyme CYP2D6 with Org 5222 and its metabolites Org 30526 and Org 31438 in vitro"	substrate = AMMC: 3-[2-(N,N-diethyl-N-methylamino)ethyl]-7-methoxy-4-methylcoumarin inhibitor = asenapine, N-desmethyl, N-oxide, quinidine	NA	NA	NA	Completed full
PK	R&DRR NL0050059	The assessment of inhibition of the human cytochrome p450 enzymes with asenapine (Org 5222) and its metabolites Org 30526 and Org 31437 in vitro	coumarin, DBF: dibenzylfluorescein, MFC: 7-methoxy-4-trifluoromethylcoumarin, BzRes: benzyloxyresorufin, BQ: 7-benzyloxyquinoline inhibitor = asenapine, N-desmethyl, N-oxide, furafylline, tranylcypromine, quercetin, sulfaphenazole, ketoconazole	NA	NA	NA	Completed full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Statu Type of Report
PK	R&DRR NL0013163	The inhibition of the human cytochrome p450 enzymes CYP2C19 and CYP3A4 by Org 5222 (in vitro)	substrate - mephenytoin, testosterone inhibitor - asenapine, tranylcypromine, ketoconazole	NA	NA	NA	Completed full
PK	R&DRR NL0050307	The assessment of inhibition of the human cytochrome P450 enzyme CYP2D6 with Org 10968 and Org 10969 (both enantiomers of asenapine (Org 5222)) in vitro	substrate - AMMC: 3-[2-(N,N-diethyl-N-methylamino)ethyl]-7-methoxy-4-methylcoumarin inhibitor - (R,R)-asenapine, (S,S)-asenapine, quinidine	NA	NA	NA	Completed full
PK	DM2005-00522-009	Inhibition of P450 enzymes	substrate - phenacetin, bupropion, amodiaquine, diclofenac, S-mephenytoin, dextromethorphan, felodipine, midazolam, testosterone inhibitor - asenapine	NA	NA	NA	Completed full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Statu Type of Report
PK	RR 764-04914	Induction potential of asenapine (Org 5222) on Cytochrome P450 enzymes 1A2 and 3A4 in human hepatocytes	substrate: O-deethylase, testosterone 6beta-hydroxylase inducer: asenapine	NA	NA	NA	Completed full
REPORTS OF STUDIES USING OTHER HUMAN BIOMATERIALS							
PK	DM2005-005222-008	In Vitro Transport Study of asenapine (ORG-5222) and N-Desmethyl asenapine (ORG-30526) in MDCK and MDR1 Cells	Org 5222 Org 30526	NA	NA	NA	Completed full
REPORTS OF HUMAN PHARMACOKINETIC (PK) STUDIES							
HEALTHY SUBJECT PHARMACOKINETIC (PK) AND INITIAL TOLERABILITY STUDY REPORTS							
PK, S	25509 United Kingdom (1 center)	Phase I, double-blind, placebo crossover, single rising dose study with Org 5222 (Org SL94) in healthy male volunteers to assess its tolerance and safety	placebo Route: SL tablet asenapine Route: SL tablet Dose Regimen: 10, 20, 35, 50, 75 100, 150, 200, 300 µg	asenapine groups 10 µg 4 20 µg 4 35 µg 8 50 µg 8 75 µg 8 100 µg 8 150 µg 8 200 µg 8 300 µg 8 healthy subjects	Sex: 64M/0F Age: 19-31 years Race: Not available	single dose	Started: November 1994 Completed: April 1995 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Status Type of Report
PK	25511 United Kingdom (1 center)	A Phase I, double-blind, placebo-controlled, parallel groups, multiple, sublingual dose study with Org 5222 in healthy male volunteers to assess its tolerability as well as its pharmacodynamic and pharmacokinetic characteristics	placebo Route: SL tablet asenapine Route: SL tablet Dose Regimen: 150 µg BID	placebo Randomized: 6 Treated: 6 Completed: 6 asenapine Randomized: 18 Treated: 18 Completed: 17 healthy subjects	placebo Sex: 6M/0F Mean Age (min/max): 26.5 (20-31) years Race: W/B/A/O: 6/0/0/0 asenapine Sex: 18M/0F Mean Age (min/max): 24.9 (19-33) years Race: W/B/A/O: 18/0/0/0	6.5 days or 13.5 days	Started: September 1995 Completed: February 199 full
PK	25514 United Kingdom (1 center)	A Phase I, double blind, placebo-controlled, parallel groups, multiple, sublingual titrating dose study of 200 to 300 µg Org 5222 in healthy male volunteers to assess its tolerability as well as its pharmacodynamic and pharmacokinetic characteristics	placebo Route: SL tablet asenapine Route: SL tablet Dose Regimen: 200 µg BID for 2 days, then 300 µg BID for 4.5 days	placebo Randomized: 4 Treated: 4 Completed: 4 asenapine Randomized: 12 Treated: 12 Completed: 12 healthy subjects	placebo Sex: 4M/0F Mean Age (min/max): 24.5 (22-27) years Race: W/B/A/O: 4/0/0/0 asenapine Sex: 12M/0F Mean Age (min/max): 27.5 (23-35) years Race: W/B/A/O: 12/0/0/0	6.5 days	Started: July 1996 Completed: August 1996 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Stat Type o Report
PK, S	25542 Netherlands (1 center)	A multiple dose, double-blinded, randomized, placebo- controlled, parallel group, safety and tolerability study with asenapine in healthy male volunteers	placebo Route: SL tablet asenapine Route: SL tablet Dose Regimen: **Group 1** 0.3 mg, 0.6 mg, 1 mg and 3 mg BID **Group 2** 0.3 mg, 1 mg, 3 mg, and 5 mg BID **Group 3** 1 mg, 3 mg, 5 mg and 10 mg BID **Group 4** 1 mg, 3 mg, 5 mg, 10 mg and 15 mg BID **Group 5** 2 mg and 5 mg QD	asenapine **Group 1** Randomized: 8 Treated: 8 Completed: 7 **Group 2** Randomized: 8 Treated: 8 Completed: 8 **Group 3** Randomized: 8 Treated: 8 Completed: 7 **Group 4** Randomized: 8 Treated: 8 Completed: 0 **Group 5** Randomized: 8 Treated: 8 Completed: 8 healthy subjects	asenapine Sex: 40M/0F Mean Age (min/max): 23.6 (18-43) years Race: W/B/A/O: 38/1/1/0	11 days and single dose x 2 (on day 1 and day 8)	Started: June 2004 Completed August 200 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Stat Type o Report
PK	041028 Netherlands (1 center)	Single dose, open label trial to investigate the pharmacokinetics of the enantiomers of asenapine healthy male subjects	placebo Route: SL tablet asenapine Route: SL tablet Dose Regimen: 5 mg – [2.5 mg (R, R)- asenapine and 2.5 mg13C6 labeled (S, S)-asenapine]	Randomized: 8 Treated: 8 Completed: 8 healthy subjects	Sex: 8M/0F Mean Age (min/max): 28 (19-52) years Race: W/B/A/O: 7/0/1/0	single dose	Started: November 2005 Completed December 2005 full
PK	25532 Netherlands (1 center)	Open, non-randomized, single center trial to determine the excretion balance, metabolic profile and pharmacokinetics of asenapine after a sub-lingual dose of [^{14}C]-labeled asenapine	placebo Route: SL tablet asenapine Route: SL Dose Regimen: multiple rising doses (0.3 - 10 mg) BID and on day 10 a single dose of10 mg asenapine + [^{14}C]	Randomized: 6 Treated: 6 Completed: 4 healthy subjects	Sex: 6M/0F Mean Age (min/max): 32.3 (21-54) years Race: W/B/A/O: 5/0/1/0	10 days	Started: July 2004 Completed September 2004 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Stat Type o Report
PK	25540 Belgium (1 center)	An open label, randomized, single dose, explorative study in healthy volunteers to investigate the pharmacokinetics of sublingual and oral administered asenapine with and without charcoal to prevent gastro-intestinal absorption	placebo Route: SL tablet administered either by the SL or oral route asenapine Route: SL tablet administered either by SL or oral route Dose Regimen: 5 mg (with or without 50 g active charcoal)	Randomized: 16 Treated: 16 Completed: 16 healthy subjects	Sex: 16M/0F Mean Age (min/max): 33.4 (25-42) years Race: W/B/A/O: 16/0/0/0	single dose x 2 (on day 1 and on day 8)	Started: December 2004 Completed January 20 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Stat Type o Repor
PATIENT PK AND INITIAL TOLERABILITY STUDY REPORTS							
PK, S	041001 United States (1 center)	A double-blind, placebo-controlled, titration study with sublingual Org 5222 to establish the maximum tolerated dose in subjects with schizophrenia and schizoaffective disorder	placebo Route: SL tablet asenapine Route: SL tablet Dose Regimen: Escalating BID doses (starting with 200 µg BID and increased to 300 µg, 400 µg, 600 µg and 800 µg BID) with dose up-titration every 3 days **Block 1,** every other day **Block 2,** or every day **Block 3**	placebo **Block 1** Randomized: 2 Treated: 2 Completed: 1 **Block 2** Randomized: 2 Treated: 2 Completed: 2 **Block 3** Randomized: 2 Treated: 2 Completed: 2	placebo **Block 1** Sex: 2M/0F Mean Age (min/max): 32 (29-34) years Race: W/B/A/O: 1/0/0/1 **Block 2** Sex: 2M/0F Mean Age (min/max): 46 (45-46) years Race: W/B/A/O: 2/0/0/0 **Block 3** Sex: 2M/0F Mean Age (min/max): 37 (20-54) years Race: W/B/A/O: 2/0/0/0	**Block 1** 17 days **Block 2 and 3** 14 days	Started: March 199 Completed August 19 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Status Type of Report
	041001 (continued)			asenapine **Block 1** Randomized: 8 Treated: 8 Completed:8 **Block 2** Randomized: 8 Treated: 8 Completed:4 **Block 3** Randomized: 8 Treated: 8 Completed:8 schizophrenic patients	asenapine **Block 1** Sex: 7M/1F Mean Age (min/max): 37 (27-47) years Race: W/B/A/O: 6/0/0/2 **Block 2** Sex: 7M/1F Mean Age (min/max): 37 (27-54) years Race: W/B/A/O: 6/1/0/1 **Block 3** Sex: 7M/1F Mean Age (min/max): 42 (35-46) years Race: W/B/A/O: 6/0/0/2		

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Stat Type o Repor
PK, S, PD	041007 United States (1 center)	A single-center, randomized, double-blind, placebo-controlled, titration trial with sublingual Org 5222 to establish the maximum tolerated dose up to 4800 µg twice daily in subjects with schizophrenia or schizoaffective disorder. A positron emission tomography (PET) substudy in selected subjects on Org 5222, healthy volunteers, and subjects on marketed antipsychotics	placebo Route: SL tablet asenapine Route: SL tablet Dose Regimen: Escalating BID doses (starting with 200 µg, 300 µg, 400 µg, or 600 µg, BID and increasing to 2400 µg, or 4800 µg, BID) with dose uptitration every day	placebo **Block 1** Randomized: 2 Treated: 2 Completed: 0 **Block 2** Randomized: 2 Treated: 2 Completed: 1 **Block 3** Randomized: 2 Treated: 2 Completed: 2 asenapine **Block 1** Randomized: 6 Treated: 6 Completed: 4 **Block 2** Randomized: 6 Treated: 6 Completed: 6 **Block 3** Randomized: 8 Treated: 8 Completed: 6 schizophrenic patients and healthy subjects	placebo **Block 1** Sex: 2M/0F Mean Age (min/max): 41.5 (36-47) years Race: W/B/A/O: 1/0/0/1 **Block 2** Sex: 1M/1F Mean Age (min/max): 41.5 (31-52) years Race: W/B/A/O: 2/0/0/0 **Block 3** Sex: 2M/0F Mean Age (min/max): 29.5 (22-37) years Race: W/B/A/O: 2/0/0/0 asenapine **Block 1** Sex: 5M/1F Mean Age (min/max): 34.8 (21-38) years Race: W/B/A/O: 4/1/0/1	**Block 1** 18 days **Block 2** 11 days **Block 3** 16 days	Started: February 1 Completed January 20 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Statu Type of Report
	041007 (cont'd)				**Block 2** Sex: 5M/1F Mean Age (min/max): 36.1 (29-45) years Race: W/ B/A/O: 3/1/1/1 **Block 3** Sex: 6M/2F Mean Age (min/max): 38.5 (22-51) years Race: W/B/A/O: 6/2/0/0		

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Stat Type o Repor
PK, S	041012 United States (1 center)	A single-center randomized, double-blind, placebo-controlled, titration study to evaluate the tolerability of sublingual Org 5222 up to 20 mg twice daily in subjects with schizophrenia or schizoaffective disorder	placebo Route: SL tablet asenapine Route: SLtablet Dose Regimen: **Block 1:** 2, 3, 5, 8, 10, 15 mg BID on day 1, 2, 3, 4, 5, 6-10 resp. **Block 2:** 3, 5, 8, 10, 15 mg BID on day 1, 2, 3, 4, 5-9 resp. **Block 3:** 5, 10, 15, 20 mg BID on day 1, 2, 3, 4-8 resp.	placebo **Block 1:** Randomized: 2 Treated: 2 Completed: 2 **Block 2:** Randomized: 2 Treated: 2 Completed: 2 **Block 3:** Randomized: 2 Treated: 2 Completed: 1 asenapine **Block 1:** Randomized: 6 Treated: 6 Completed: 6 **Block 2:** Randomized: 6 Treated: 6 Completed: 6	placebo **Block 1:** Sex: 2M/0F Mean Age (min/max): 46.5 (43-50) years Race: W/B/A/O: 0/2/0/0 **Block 2:** Sex: 2M/0F Mean Age (min/max): 41 (34-48) years Race: W/B/A/O: 1/1/0/0 **Block 3:** Sex: 2M/0F Mean Age (min/max): 48 (47-49) years Race: W/B/A/O: 0/2/0/0	**Block 1** 10 days **Block 2** 9 days **Block 3** 8 days	Started: March 200 Completed September 2002 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Status Type of Report
	041012 (con't)			**Block 3:** Randomized: 6 Treated: 6 Completed: 5 schizophrenic patients	asenapine **Block 1:** Sex: 6M/0F Mean Age (min/max): 47.8 (44-54) years Race: W/B/A/O: 1/5/0/0 **Block 2:** Sex: 6M/0F Mean Age (min/max): 43.2 (35-49) years Race: W/B/A/O: 1/5/0/0 **Block 3:** Sex: 5M/1F Mean Age (min/max): 41.5 (20-55) years Race: W/B/A/O: 1/5/0/0		

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Statu Type of Report
INTRINSIC FACTOR PK STUDY REPORTS							
PK	25546 United Kingdom (1 center)	A placebo controlled, double blind, randomized, parallel groups, single and multiple dose study with asenapine in healthy Japanese and Caucasian subjects, to evaluate safety and pharmacokinetic parameters in a Japanese population in comparison to a Caucasian population	placebo Route: SL tablet asenapine **Group 1** Route: SL tablet Dose Regimen: 1 mg, 3 mg **Group 2** Route: SL tablet Dose Regimen: 3 mg, 5 mg **Group 3** Route: SL tablet Dose Regimen: 5 mg, 10 mg	Randomized: 49 Treated: 49 Completed: 45 healthy subjects	**Group 1** Sex: 16M/0F Mean Age (min/max): 22.9 (23-27) years Race: W/B/A/O: 8/0/8/0 **Group 2** Sex: 16M/0F Mean Age (min/max): 24.2 (24-29) years Race: W/B/A/O: 8/0/8/0 **Group 3** Sex: 17M/0F Mean Age (min/max): 26.1 (26-36) years Race: W/B/A/O: 9/0/8/0	**Group 1** 8 days **Group 2** 9 days **Group 3** 10 days	Started: November 2004 Completed: March 2005 full
PK	25522 Ukraine (1 center)	Open label, single dose, study with Org 5222 to assess the effect of hepatic impairment on the pharmacokinetics of Org 5222 and its metabolite demethyl-Org 5222	asenapine Route: SL tablet Dose Regimen: 0.3 mg	Randomized: 32 Treated: 32 Completed: 32 hepatically impaired subjects	Sex: 16M/16F Mean Age (min/max): 48 (33-60) years Race: Not available	single dose	Started: September 2003 Completed: December 2003 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Status Type of Report
PK, S	A7501018 United States (2 centers)	A Phase 1, open label, parallel group, single-dose study to evaluate the pharmacokinetics, safety, and tolerability of asenapine in subjects with various degrees of hepatic function	placebo Route: SL tablet asenapine Route: SL tablet Dose Regimen: 5 mg	Randomized: 30 Treated: 30 Completed: 30 hepatically impaired subjects	Sex: 20M/10F Mean Age (min/max): 55.7 (46-72) years Race: W/B/A/O: 29/1/0/0	single dose	Started: June 2005 Completed: December 2005 full
PK	25521 Poland (1 center)	Open label, single dose, study with Org 5222 to assess the effect of renal impairment on the pharmacokinetics of Org 5222 and its metabolite demethyl-Org 5222	asenapine Route: SL tablet Dose Regimen: 0.3 mg	Randomized: 32 Treated: 32 Completed: 32 renally impaired subjects	Sex: 16M/16F Mean Age (min/max): 46.9 (26-65) years Race: Not available	single dose	Started: September 2003 Completed: November 2003 full
PK, S	A7501017 United States (1 center)	A Phase 1, open label, parallel group, single-dose study to evaluate the pharmacokinetics, safety, and tolerability of asenapine in subjects with various degrees of renal function	placebo Route: SL tablet asenapine Route: SL tablet Dose Regimen: 5 mg	Randomized: 33 Treated: 33 Completed: 33 renally impaired subjects	Sex: 15M/18F Mean Age (min/max): 63.7 (36-78) years Race: W/B/A/O: 26/7/0/0	single dose	Started: May 2005 Completed: August 2005 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Statu Type of Report
PK, S	A7501022 United States (2 centers)	A placebo-controlled, double-blind, randomized, parallel group, multiple-dose study with asenapine in adolescent subjects with a psychotic disorder to evaluate safety, tolerability, and pharmacokinetic parameters	placebo Route: SL tablet asenapine Route: SL tablet Dose Regimen: 1 mg – 10 days or 3 mg – 10 days or 5 mg – 10 days or 5 mg – 1 day 10 mg – 10 days	Randomized: 40 Treated: 40 Completed: 38 adolescent patients with psychotic disorder	Sex: 23M/17F Mean Age (min/max): 14.8 (12-17) years Race: W/B/A/O: 13/27/0/0	10 or 11 days	Started: October 20 Completed: March 2006 full
EXTRINSIC FACTOR PK STUDY REPORTS							
PK	25525 Netherlands (1 center)	An open-label, randomized, two parallel group, multiple dose, interaction trial between asenapine, paroxetine and dextromethorphan in healthy male volunteers	**Sequence A** Dextromethorphan 30 mg SD (oral tablet) at screening and Day 12, Paroxetine 20 mg SD (oral tablet) on Days 1 and 14, Placebo (SL tablet) SD on Day 3, asenapine (SL tablet) 1 mg BID on Day 4, 3 mg BID on Day 5, 5 mg BID on Days 6-16 **Sequence B** Dextromethorphan 30 mg SD (oral	**Sequence A** Randomized: 17 Treated: 17 Completed: 13 **Sequence B** Randomized: 30 Treated: 30 Completed: 26 healthy subjects	**Sequence A** Sex: 17M/0F Mean Age (min/max): 36 (24-55) years Race: Not available **Sequence B** Sex: 30M/0F Mean Age (min/max): 33 (18-51) years Race: Not available	**Sequence A** 16 days **Sequence B** 15 days	Started: August 200 Completed: December 2005 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Stat Type o Report
	25525 (con't)		tablet) at screening and Day 11, Placebo (SL tablet) SD on Days 1 and 12, asenapine 5 mg (SL tablet) SD on Days 2 and 13, Paroxetine 20 mg SD (oral tablet) on Days 7-15				
PK	25526 Netherlands (1 center)	An open-label, randomized, three-period crossover study to assess the pharmacokinetic interaction between imipramine and asenapine in healthy male subjects	placebo Route: SL tablet asenapine Route: SL tablet Dose Regimen: 5 mg Imipramine Route: oral tablet Dose Regimen: 75 mg	Randomized: 25 Treated: 25 Completed: 24 healthy subjects	Sex: 25M/0F Mean Age (min/max): 35 (18-54) years Race: Not available	single dose	Started: August 20 Completed December 2005 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Stat Type o Repor
PK	25527 Netherlands (1 center)	An open-label, randomized, two-way crossover interaction study to investigate the effect of steady state valproate on the single dose pharmacokinetics of 5 mg asenapine in healthy male subjects	**Treatment A** asenapine Route: SL tablet Dose Regimen: 5 mg **Treatment B** Valproate Route: oral tablet Dose Regimen: 500 mg BID days 1-9 and 5 mg asenapine SL on day 7	**Treatment AB** Randomized: 14 Treated: 14 Completed: 12 **Treatment BA** Randomized: 14 Treated: 14 Completed: 12 healthy subjects	Sex: 28M/0F Mean Age (min/max): 31 (19-53) years Race: Not available	asenapine single dose, valproate 9 days	Started: July 2005 Completed November 2005 full
PK	25528 Germany (1 center)	An open-label, interaction study to investigate the effect of steady state carbamazepine on the single dose pharmacokinetics of 5 mg asenapine in healthy male subjects	placebo Route: SL tablet days -1 and 19 asenapine Route: SL tablet Dose Regimen: 5 mg QD day 1 and day 20 Carbamazepine Route: oral tablet Dose Regimen: 200 mg BID days 4 – 7 and 400 mg BID days 8 - 22	Randomized: 29 Treated: 29 Completed: 24 healthy subjects	Sex: 29M/0F Mean Age (min/max): 31.3 (18-45) years Race: W/B/A/O: 29/0/0/0	asenapine single dose x 2 Carbam-azepine 19 days	Started: May 2005 Completed September 2005 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Status Type of Report
PK	25529 Germany (1 center)	An open-label, randomized, two-way cross-over study to investigate the effect of steady state cimetidine on the single dose pharmacokinetics of 5 mg asenapine in healthy male subjects	placebo Route: SL tablet asenapine Route: SL tablet Dose Regimen: 5 mg Cimetidine Route: oral tablet Dose Regimen: 800 mg BID	Randomized: 29 Treated: 29 Completed: 24 healthy subjects	Sex: 29M/0F Mean Age (min/max): 32.8 (18-43) years Race: W/B/A/O: 29/0/0/0	asenapine single dose Cimetidine 7 days	Started: May 2005 / Completed: August 2005 full
PK	041033 Netherlands (1 center)	An open-label, randomized, two-period crossover study to assess the pharmacokinetic interaction between fluvoxamine and asenapine in healthy male subjects	placebo Route: SL tablet asenapine Route: SL tablet Dose Regimen: 5 mg Fluvoxamine Route: oral tablet Dose Regimen: 25 mg BID Caffeine tablet 100 mg	Randomized: 26 Treated: 26 Completed: 25 healthy subjects	Sex: 26M/0F Mean Age (min/max): 33.6 (21-53) years Race: W/B/A/O: 21/1/3/1	asenapine and caffeine - single dose fluvoxamine - 7 days	Started: March 2006 Completed: May 2006 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Stat Type o Repor
POPULATION PK STUDY REPORTS							
PK	INT00036661	asenapine Population Pharmacokinetics in Healthy Volunteers and Patients with Schizophrenia Based on Data from Phase 1 and Phase 2 Trials	asenapine	healthy subjects and schizophrenic patients	NA	NA	Completed full
PK	INT00036719	Population Pharmacokinetic Analysis Using Phase 2/3 asenapine Concentration Data from Patients with Schizophrenia or Bipolar Disorder	asenapine	schizophrenic patients and bipolar patients	NA	NA	Completed full
REPORTS OF HUMAN PHARMACODYNAMIC (PD) STUDIES							
HEALTHY SUBJECT PD AND PK/PD STUDY REPORTS							
PK, PD	25510 Sweden (1 center)	PET study on central D_2 dopamine and 5-HT_2 serotonin receptor binding after sublingual administration of 100 µg Org 5222 to healthy male volunteers	placebo Route: SL tablet asenapine Route: SL tablet Dose Regimen: 100µg	Randomized: 3 Treated: 3 Completed: 3 healthy subjects	Sex: 3M/0F Age:23, 28 & 29 years Race: Not available	single dose	Started: January 19 Completed April 1996 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Stat Type o Report
PK, PD	25503 Sweden (1 center)	Positron emission tomography (PET) determination of central D_1-dopamine receptor occupancy after oral administration of Org 5222 to two healthy male volunteers	asenapine Route: oral tablet Dose Regimen: 10 mg	Randomized: 2 Treated: 2 Completed: 2 healthy subjects	Sex: 2M/0F Age: 22 & 26 years Race: Not available	single dose	Started: February 1 Completed February 1 full
PATIENT PD AND PK/PD STUDY REPORT							
PK, PD	INT00032958	Org5222 for the Management of Schizophrenia Dose-Finding Strategy (D2 report)	asenapine	NA	NA	NA	Completed full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Statu Type of Report
REPORTS OF EFFICACY AND SAFETY STUDIES INDICATION = "SCHIZOPHRENIA"							
STUDY REPORTS OF CONTROLLED CLINICAL STUDIES PERTINENT TO THE CLAIMED INDICATION							
E, S	041013 United States (22 centers)	A double-blind, three-armed, fixed-dose, placebo- controlled, dose-finding study with sublingual Org 5222 in subjects with acute phase schizophrenia	placebo Route: SL tablet asenapine Route: SL tablet Dose Regimen: 1600 mcg BID asenapine Route: SL tablet Dose Regimen: 2400 mcg BID	placebo Randomized: 64 Treated: 64 Completed: 18 asenapine 1600 mcg Randomized: 58 Treated: 57 Completed: 20 asenapine 2400 mcg Randomized: 61 Treated: 61 Completed: 17 schizophrenic patients	placebo Sex: 51M/13F Mean Age (min/max): 38.9 (19-59) years Race: W/B/A/O: 34/25/1/4 asenapine 1600 mcg Sex: 40M/17F Mean Age (min/max): 40.8 (19-59) years Race: W/B/A/O: 36/14/1/6 asenapine 2400 mcg Sex: 46M/15F Mean Age (min/max): 39.2 (19-62) years Race: W/B/A/O: 21/34/2/4	42 days	Started: February 20 Completed: June 2001 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Status Type of Report
E, S	041002 United States (20 centers)	A double-blind, five armed, fixed-dose, active- and placebo-controlled dose-finding study with sublingual Org 5222 in subjects with acute phase schizophrenia	placebo Route: SL tablet or capsule asenapine Route: SL tablet Dose Regimen: 200 mcg BID asenapine Route: SL tablet Dose Regimen: 400 mcg BID asenapine Route: SL tablet Dose Regimen: 800 mg BID risperidone Route: capsules Dose Regimen: 3 mg BID	placebo Randomized: 61 Treated: 61 Completed: 17 asenapine 200 mcg Randomized: 60 Treated: 60 Completed: 11 asenapine 400 mcg Randomized: 59 Treated: 59 Completed: 17 asenapine 800 mcg Randomized: 61 Treated: 61 Completed: 22 risperidone Randomized: 61 Treated: 61 Completed: 23 schizophrenic patients	placebo Sex: 49M/12F Mean Age (min/max): 41.0 (20-63) years Race: W/B/A/O: 32/23/0/6 asenapine 200mcg Sex: 55M/5F Mean Age (min/max): 39.8 (17-63) years Race: W/B/A/O: 33/22/0/5 asenapine 400mcg Sex: 47M/12F Mean Age (min/max): 40.9 (18-62) years Race: W/B/A/O: 31/22/0/6 asenapine 800mcg Sex: 51M/10F Mean Age (min/max): 38.1 (18-55) years Race: W/B/A/O: 34/21/2/4	42 days	Started: May 1998 Completed: May 2000 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Stat Type o Repor
	041002 (con't)				risperidone Sex: 49M/12F Mean Age (min/max): 40.1 (19-67) years Race: W/B/A/O: 29/23/2/7		
E, S	041004 United States (21 centers)	An assessment of the efficacy and safety of a sublingual dose of Org 5222 in subjects with schizophrenia (in an acutely exacerbated state) compared to risperidone and placebo in a randomized double blind, fixed-dose 6-week trial	placebo Route: SL tablet or capsules asenapine Route: SL tablet Dose Regimen: 5 mg BID risperidone Route: capsules Dose Regimen: 3 mg BID	placebo Randomized: 62 Treated: 62 Completed: 21 asenapine 5 mg Randomized: 60 Treated: 59 Completed:27 risperidone 3 mg Randomized: 60 Treated: 59 Completed:25 schizophrenic patients	placebo Sex: 49M/13F Mean Age (min/max): 42.1 (22-68) years Race: W/B/A/O: 20/32/0/10 asenapine 5 mg Sex: 46M/13F Mean Age (min/max): 38.2 (21-70) years Race: W/B/A/O: 25/28/0/6 risperidone 3 mg Sex: 36M/23F Mean Age (min/max): 42.7 (22-61) years Race: W/B/A/O: 25/26/2/6	42 days	Started: August 200 Completed May 2002 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Stat Type o Report
E, S	041023 Canada (1 center), Russia (12 centers), India (8 centers), Romania (7 centers), United States (18 centers)	A multicenter, randomized, double-blind, fixed dose, 6-week trial of the efficacy and safety of asenapine compared with placebo using haloperidol positive control in subjects with an acute exacerbation of schizophrenia	placebo Route: SL tablet or capsule asenapine 5 mg Route: SL tablet Dose Regimen: 5 mg BID asenapine 10 mg Route: SL tablet Dose Regimen: 10 mg BID haloperidol Route: oral capsule Dose Regimen: 4 mg BID	placebo Randomized: 123 Treated: 123 Completed: 70 asenapine 5 mg Randomized: 114 Treated: 111 Completed: 70 asenapine 10 mg Randomized: 106 Treated: 106 Completed: 71 haloperidol Randomized: 115 Treated: 115 Completed: 68 schizophrenic patients	placebo Sex: 64M/59F Mean Age (min/max): 40.1 (18-70) years Race: W/B/A/O: 76/31/11/5 asenapine 5 mg Sex: 75M/36F Mean Age (min/max): 38.0 (18-69) years Race: W/B/A/O: 71/22/11/7 asenapine 10 mg Sex: 67M/39F Mean Age (min/max): 37.1 (19-68) years Race: W/B/A/O: 67/29/10/0 haloperidol Sex: 63M/52F Mean Age (min/max): 39.0 (18-67) years Race: W/B/A/O: 68/35/12/0	42 days	Started: June 2005 Completed September 2006 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Stat Type o Repor
E, S	041021 Russia (5 centers) United Kingdom (9 centers) United States (31 centers)	A multicenter, randomized, double-blind, fixed-dose, 6-week trial of the efficacy and safety of asenapine compared with placebo using olanzapine positive control in subjects with an acute exacerbation of schizophrenia	placebo Route: SL tablet or oral tablet asenapine Route: SL tablet Dose Regimen: 5 mg BID asenapine Route: SL tablet Dose Regimen: 10 mg BID olanzapine Route: oral tablet Dose Regimen: 15 mg QD	placebo Randomized: 106 Treated: 100 Completed: 50 asenapine 5 mg Randomized: 106 Treated: 104 Completed: 60 asenapine 10 mg Randomized: 102 Treated: 102 Completed: 51 olanzapine Randomized: 103 Treated: 102 Completed: 58 schizophrenic patients	placebo Sex: 58M/42F Mean Age (min/max): 39.5 (18-62) years Race: W/B/A/O: 46/45/0/9 asenapine 5 mg Sex: 77M/27F Mean Age (min/max): 40.4 (18-70) years Race: W/B/A/O: 50/47/3/4 asenapine 10 mg Sex: 72M/30F Mean Age (min/max): 41.2 (18-60) years Race: W/B/A/O: 49/44/2/7 olanzapine Sex: 80M/22F Mean Age (min/max): 39.7 (19-61) years Race: W/B/A/O: 44/47/2/9	42 days	Started: May 2005 Completed May 2006 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Statu Type of Report
E, S	041022 Russian Federation (3 centers) Ukraine (5 centers) United States (23 centers)	A multicenter, randomized, double-blind, flexible-dose, 6- week trial of the efficacy and safety of asenapine compared with placebo using olanzapine positive control in subjects with an acute exacerbation of schizophrenia	placebo Route: SL tablet or oral tablet asenapine Route: SL tablet Dose Regimen: 5 – 10 mg BID olanzapine Route: oral tablet Dose Regimen: 10 mg – 20 mg QD	placebo Randomized: 93 Treated: 93 Completed: 48 asenapine Randomized: 91 Treated: 90 Completed: 42 olanzapine Randomized: 93 Treated: 92 Completed: 43 schizophrenic patients	placebo Sex: 74M/19F Mean Age (min/max): 41.9 (20-61) years Race: W/B/A/O: 42/43/0/8 asenapine Sex: 67M/23F Mean Age (min/max): 44.0 (23-67) years Race: W/B/A/O: 45/38/2/5 olanzapine Sex: 72M/20F Mean Age (min/max): 41.6 (20-63) years Race: W/B/A/O: 41/43/2/6	6 weeks	Started: February 20 Completed: February 20 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Stat Type o Report
E, S	041505 United States (19 centers)	Long-term maintenance of subjects with schizophrenia with Org 5222 Extension of Protocol 041013 (A double-blind, three-armed, fixed-dose, placebo-controlled, dose-finding study with sublingual Org 5222 in subjects with acute phase schizophrenia)	placebo Route: SL tablet asenapine Route: SL tablet Dose Regimen: 1600 mcg BID asenapine Route: SL tablet Dose Regimen: 2400 mcg BID	placebo Randomized: 8 Treated: 8 Completed: 0 asenapine 1600 mcg Randomized: 11 Treated: 10 Completed: 0 asenapine 2400 mcg Randomized: 10 Treated: 10 Completed: 0 schizophrenic patients	placebo Sex: 6M/2F Mean Age (min/max): 31.1 (23-40) years Race: W/B/A/O: 5/2/0/1 asenapine 1600 mcg Sex: 5M/5F Mean Age (min/max): 39.2 (20-53) years Race: W/B/A/O: 5/3/1/1 asenapine 2400 mcg Sex: 7M/3F Mean Age (min/max): 43.7 (32-56) years Race: W/B/A/O: 5/5/0/0	placebo 167 days asenapine 1600 mcg 419 days asenapine 2400 mcg 510 days	Started: June 2000 Completed January 20 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Stat Type o Repor
E, S	041500 United States (20 centers)	Org 5222 long-term extension to Protocol 041002. (A double-blind, five armed, fixed-dose, active- and placebo-controlled dose-finding study with sublingual Org 5222 in subjects with acute phase schizophrenia)	placebo Route: SL tablet or capsule asenapine Route: SL tablet Dose Regimen: 200 mcg BID asenapine Route: SL tablet Dose Regimen: 400 mcg BID asenapine Route: SL tablet Dose Regimen: 800 mg BID risperidone Route: capsules Dose Regimen: 3 mg BID	placebo Randomized: 9 Treated: 8 Completed: 0 asenapine 200 mcg Randomized: 9 Treated: 8 Completed: 0 asenapine 400 mcg Randomized: 6 Treated: 6 Completed: 0 asenapine 800 mcg Randomized: 14 Treated: 14 Completed: 1 risperidone Randomized: 13 Treated: 13 Completed: 0 schizophrenic patients	placebo Sex: 6M/2F Mean Age (min/max): 43.5 (31-62) years Race: W/B/A/O: 32/23/0/6 asenapine 200mcg Sex: 7M/1F Mean Age (min/max): 46.6 (35-63) years Race: W/B/A/O: 7/1/0/0 asenapine 400mcg Sex: 4M/2F Mean Age (min/max): 32.3 (18-43) years Race: W/B/A/O: 2/2/0/2	placebo 207 days asenapine 200 mcg 436 days asenapine 400 mcg 119 days asenapine 800 mcg 322 days Risperid-one 575 days	Started: June 1998 Completed November 2000 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Stat Type o Repor
	041500 (con't)				asenapine 800mcg Sex: 11M/3F Mean Age (min/max): 37 (20-51) years Race: W/B/A/O: 7/5/1/1 risperidone Sex: 9M/4F Mean Age (min/max): 33.8 (19-51) years Race: W/B/A/O: 7/3/0/3		
E, S	041502 United States (27centers)	Org 5222 long-term extension to Protocol 041004. (An assessment of the efficacy and safety of a sublingual dose of Org 5222 in subjects with schizophrenia (in an acutely exacerbated state) compared to risperidone and placebo in a randomized double blind, fixed-dose trial)	placebo Route: SL tablet or capsule asenapine Route: SL tablet Dose Regimen: 5 mg BID risperidone Route: capsule Dose Regimen: 3 mg p.o. BID	placebo Randomized: 7 Treated: 7 Completed: 0 asenapine Randomized: 15 Treated: 15 Completed: 0 risperidone Randomized: 17 Treated: 17 Completed: 1 schizophrenic patients	placebo Sex: 6M/1F Mean Age (min/max): 39.7 (23-66) years Race: W/B/A/O: 0/6/0/1 asenapine Sex: 11M/4F Mean Age (min/max): 38.2 (22-51) years Race: W/B/A/O: 8/6/0/1 risperidone Sex: 10M/7F Mean Age (min/max): 43.9 (23-61) years Race: W/B/A/O: 7/6/0/4	placebo 225 days asenapine 365 days risperidone 477 days	Started: October 20 Completed May 2003 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Statu Type of Report
E, S	25517 Australia (9 centers), Belgium (10 centers), Czech Republic (14 centers), France (10 centers), Germany (11 centers), Netherlands (2 centers), Poland (15 centers), Russian Federation (15 centers), South Africa (11 centers), Spain (5 centers), United Kingdom (2 centers)	A Phase III, double-blind, randomized, active-controlled two-armed, multicenter, efficacy and safety assessment (ACTAMESA) of Org 5222 and olanzapine in the treatment of patients with schizophrenia or schizoaffective disorder	placebo: Route: SL tablet or film coated tablet asenapine Route: SL tablet Dose Regimen: 5 mg - 10 mg BID olanzapine Route: film-coated tablet Dose Regimen: 10 mg - 20 mg QD	asenapine Randomized: 913 Treated: 908 Completed: 350 olanzapine Randomized: 312 Treated: 311 Completed: 178 schizophrenic patients	asenapine Sex: 475M/433F Mean Age (min/max): 36.8 (16-71) years Race: W/B/A/O: 840/50/10/8 olanzapine Sex: 182M/129F Mean Age (min/max): 36.2 (18-81) years Race: W/B/A/O: 289/19/1/2	52 weeks	Started: September 2003 Completed: February 20 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Statu Type of Report
REPORTS OF EFFICACY AND SAFETY STUDIES INDICATION = "BIPOLAR MANIA"							
STUDY REPORTS OF CONTROLLED CLINICAL STUDIES PERTINENT TO THE CLAIMED INDICATION							
E, S	A7501004 Bulgaria (2 centers), India (6 centers), Korea (2 centers), Malaysia (2 centers), Philippines (3 centers), Romania (2 centers), Russia (4 centers), Ukraine (centers), United States (32 centers)	A Phase III, randomized, placebo-controlled, double-blind trial evaluating the safety and efficacy of sublingual asenapine vs. olanzapine and placebo in patients with an acute manic episode	placebo Route: SL tablet or oral tablet asenapine Route: SL tablet Dose Regimen: 5 mg – 10 mg BID olanzapine Route: oral tablet Dose Regimen: 5 - 20 mg QD	placebo Randomized: 98 Treated: 98 Completed: 57 asenapine Randomized: 185 Treated: 185 Completed: 124 olanzapine Randomized: 205 Treated: 205 Completed:161 bipolar patients	placebo Sex: 48M/50F Mean Age (min/max): 38.1 (18-69) years Race: W/B/A/O: 55/16/22/5 asenapine Sex: 92M/93F Mean Age (min/max): 39.1 (18-76) years Race: W/B/A/O: 104/38/40/3 olanzapine Sex: 117M/88F Mean Age (min/max): 38.4 (18-66) years Race: W/B/A/O: 110/41/44/10	21 days	Started: November 2004 Completed: April 2006 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Status Type of Report
E, S	A7501005 Bulgaria (2 centers) India (6 centers) Korea (3 centers) Malaysia (1 center) Philippines (2 centers) Romania (2 centers) Russian Federation (4 centers) Turkey (2 centers) Ukraine (4 centers) United States (31 centers)	A Phase III, randomized, placebo-controlled, double-blind trial evaluating the safety and efficacy of sublingual asenapine vs. olanzapine and placebo in patients with an acute manic episode	placebo Route: SL tablet or oral tablet asenapine Route: SL tablet Dose Regimen: 5 mg – 10 mg BID olanzapine Route: oral tablet Dose Regimen: 5 - 20 mg QD	placebo Randomized: 104 Treated: 104 Completed: 64 asenapine Randomized: 194 Treated: 194 Completed: 122 olanzapine Randomized: 191 Treated: 190 Completed: 152 bipolar patients	placebo Sex: 52M/52F Mean Age (min/max): 41.5 (18-66) years Race: W/B/A/O: 59/19/19/7 asenapine Sex: 114M/80F Mean Age (min/max): 40.0 (18-68) years Race: W/B/A/O: 122/31/35/6 olanzapine Sex: 114M/76F Mean Age (min/max): 40.0 (19-67) years Race: W/B/A/O: 114/31/34/11	21 days	Started: December 2004 Completed: April 2006 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Status Type of Report
E, S	A7501006 Bulgaria (4 centers), India (12 centers), Korea (5 centers,) Malaysia (4 centers), Philippines (6 centers), Romania (4 centers), Russia (7 centers), Turkey (2 centers), Ukraine (11 centers), United States (68 centers)	A double-blind, 9-week extension study evaluating the safety and maintenance of effect of asenapine vs. olanzapine in the treatment of subjects with acute mania	placebo Route: SL tablet or oral tablet asenapine Route: SL tablet Dose Regimen: 5 - 10 mg BID olanzapine Route: oral tablet Dose Regimen: 5 – 20 mg QD	placebo Randomized: 94 Treated: 94 Completed: 50 asenapine Randomized: 181 Treated: 181 Completed: 121 olanzapine Randomized: 229 Treated: 229 Completed: 146 bipolar patients	placebo Sex: 45M/49F Mean Age (min/max): 40.0 (19-69) years Race: W/B/A/O: 59/19/10/6 asenapine Sex: 97M/84F Mean Age (min/max): 39.1 (18-73) years Race: W/B/A/O: 108/20/49/4 olanzapine Sex: 135M/94F Mean Age (min/max): 39.6 (18-67) years Race: W/B/A/O: 131/27/62/9	9 weeks	Started: January 200 Completed: June 2006 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Status Type of Report
STUDY REPORTS OF UNCONTROLLED CLINICAL STUDIES							
E, S	041590 United States (5 centers)	A multi-center, open-label, humanitarian study with sublingual Org 5222 (Extension of Protocols 041500 and 041505)	asenapine Route: SL tablet Dose Regimen: 0.8 mg BID asenapine Route: SL tablet Dose Regimen: 1.6 mg BID asenapine Route: SL tablet Dose Regimen: 2.4 mg BID	asenapine 0.8 mg Randomized: 1 Treated: 1 Completed: 0 asenapine 1.6 mg Randomized: 3 Treated: 3 Completed: 0 asenapine 2.4 mg Randomized: 1 Treated: 1 Completed: 0 schizophrenic patients	asenapine 0.8 mg Sex: 0M/1F Age: 28 years Race: Not available asenapine 1.6 mg Sex: 3M/0F Age: 21, 46 & 49 years Race: Not available asenapine 2.4 mg Sex: 0M/1F Age: 46 years Race: Not available	231 to 682 days total length of exposure (includes short-term trial duration)	Started: November 2000 Completed: March 2003 full
REPORTS OF ANALYSES OF DATA FROM MORE THAN ONE STUDY							
E	INT00039918	Exposure response analysis of total PANSS based on Phase 2 and Phase 3 trials for asenapine	asenapine	NA	NA	NA	Completed full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Status Type of Report
E	INT00039919	An Exposure-Response Model Relating asenapine Exposure to the Young-Mania Rating Scale (YMRS) Measurements for Bipolar Disorder	asenapine	NA	NA	NA	Completed full
E	INT00043090	Position Paper for asenapine: LOCF vs. MMRM in the Efficacy Analyses for asenapine Trials	asenapine	NA	NA	NA	Completed full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial S Typ Rep
Other Clinical Study Reports							
S	A7501001 South Africa (1 center), United States (6 centers)	A double-blind, parallel, multicenter study to assess the effect of asenapine, Quetiapine (Seroquel®), and placebo on the QTc interval in patients with schizophrenia	placebo Route: SL tablet or oral tablet asenapine 5/10mg Route: SL tablet Dose Regimen: 5 mg BID 10 days 10 mg BID 6 days asenapine15/20mg Route: SL tablet Dose Regimen: 5 mg BID 1 day 10 mg BID 1 day 15 mg BID 8 days 20 mg BID 6 days Quetiapine Route: tablet Dose Regimen: 25 mg BID 1 day 50 mg BID 1 day 100 mg BID 1 day 150 mg BID 1 day 200 mg BID 1 day 250 mg BID 1 day 300 MG BID 1 day 375 mg BID 9 days	placebo Randomized: 37 Treated: 35 Completed: 31 asenapine 5/10 mg Randomized: 38 Treated: 38 Completed: 27 asenapine 15/20 mg Randomized: 38 Treated: 38 Completed: 29 Quetiapine Randomized: 38 Treated: 37 Completed: 27 schizophrenic patients	placebo Sex: 28M/7F Mean Age (min/max): 44.8 (19-57) years Race: W/B/A/O: 16/13/1/5 asenapine 5/10 mg Sex: 33M/5F Mean Age (min/max): 42.4 (23-57) years Race: W/B/A/O: 12/19/1/6 asenapine 15/20 mg Sex: 26M/12F Mean Age (min/max): 43.6 (28-56) years Race: W/B/A/O: 18/18/0/2 Quetiapine Sex: 27M/10F Mean Age (min/max): 39.6 (26-53) years Race: W/B/A/O: 11/21/1/4	16 days	Started: June 20 Comple Decemb 2004 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial St Type Repo
S	754-0046	Exposure-Response Analysis to Assess the Effect of asenapine, Quetiapine (Seroquel®) or placebo Administration on the QTc Interval in Patients With Schizophrenia (A7501001)	asenapine and quetiapine	NA schizophrenic patients	NA	NA	Complete full
S	INT00036960	Exposure-Response Analysis to Assess the Effect of asenapine Administration on the QTc Interval in Patients with Schizophrenia (Phase 3 ACTAMESA Study)	asenapine	NA schizophrenic patients	NA	NA	Complete full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Stat Type o Repor
	A7501024 United States (6 centers)	A randomized, crossover study evaluating the acceptability of unflavored asenapine and raspberry flavored asenapine in stable subjects with a psychotic disorder	asenapine Route: SL tablet Dose Regimen: 5 mg white raspberry flavored, asenapine Route: SL tablet Dose Regimen: 5 mg red raspberry flavored asenapine Route: SL tablet Dose Regimen: 5 mg white unflavored	Randomized: 173 Treated: 173 Completed: 168 schizophrenic patients	Sex: 110M/63F Mean Age (min/max): 43.2 (19-62) years Race: W/B/A/O: 69/79/1/24	3 days	Started : June 2005 Completed October 20 full
PK	25501 United Kingdom (1 center)	A pharmacokinetic study in 12 young healthy male volunteers, using Org 5222 both after a single oral dose (30 mg) and at steady state (5 days, 15 mg twice daily)	asenapine Route: oral tablet Dose Regimen: 30 mg	Randomized: 6 Treated: 6 Completed: 0 healthy subjects	Sex: 6M/0F Mean Age (min/max): 23.7 (22-26) years Race: W/B/A/O: 6/0/0/0	single dose	Started: June 1992 Completed July 1992 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Stat Type o Report
PK	25506 United Kingdom (1 center)	An open pilot pharmacokinetic study concerning the intravenous administration of Orq 5222 at four different doses each dose administered to two healthy male volunteers followed by a pilot bioavailability study of oral 30 mg Org 5222 in the two healthy volunteers receiving the highest tolerated intravenous dose	asenapine Route: IV Dose Regimen: 0.7 mg	Randomized: 2 Treated: 2 Completed: 2 healthy subjects	Sex: 2M/0F Age: 27 years Race: Not available	single dose	Started: December 1991 Completed December 1991 full
PK	25507 Netherlands (1 center)	An open pilot pharmacokinetic study in two healthy volunteers, using a single oral dose of 30 mg Org 5222	asenapine Route: oral tablet Dose Regimen: 30 mg	Randomized: 2 Treated: 2 Completed: 2 healthy subjects	Sex: 2M/0F Age: 26 & 27 years Race: W/B/A/O: 2/0/0/0	single dose	Started: June 1991 Completed July 1991 full
S	85029 United Kingdom (1 center)	Phase I, double-blind, placebo controlled, single rising oral dose study with Org 5222 in healthy male volunteers to assess tolerance and safety	placebo Route: tablet asenapine Route: oral tablet Dose Regimen: 0.3 mg, 1 mg, 3 mg, 10 mg or 30 mg	Randomized: 18 Treated: 18 Completed: 18 healthy subjects	Sex: 18M/0F Mean Age (min/max): 22.3 (20-28) years Race: W/B/A/O: 16/0/2/0	single dose	Started: December 1985 Completed December 1985 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Stat Type o Report
S	85136 United Kingdom (1 center)	Phase I, double-blind, placebo controlled, sub-chronic study with increasing doses of Org 5222 up to 30 mg daily in healthy male volunteers	placebo Route: tablet asenapine Route: oral tablet Dose Regimen: 3 mg, 10, mg, 20 mg or 30 mg	Randomized: 28 Treated: 28 Completed: 28 healthy subjects	Sex: 28M/0F Mean Age (min/max): 23.25 years Race: W/B/A/O: 28/0/0/0	14 days	Started: February 1 Completed February 1 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Stat Type o Repor
E, S	25504 Finland (3 centers) Norway (5 centers)	A multi-country, multi-centre, double-blind, placebo-controlled, randomized group comparative study to evaluate the effects of 6 weeks of oral treatment with 4 different fixed doses of Org 5222 (0.2 mg bid, 0.5 mg bid, 1.0 mg bid, 2.0 mg bid) administered to (sub)chronic schizophrenic patients	placebo Route: tablet asenapine Route: oral tablet Dose Regimen: 0.4 mg (0.2 mg BID) asenapine Route: oral tablet Dose Regimen: 1.0 mg (0.5 mg BID) asenapine Route: oral tablet Dose Regimen: 2.0 mg (1 mg BID) asenapine Route: oral tablet Dose Regimen: 4.0 mg (2 mg BID)	placebo Randomized: 26 Treated: 26 Completed: 15 asenapine 0.4 mg Randomized: 26 Treated: 26 Completed: 10 asenapine 1.0 mg Randomized: 25 Treated: 25 Completed: 10 asenapine 2.0 mg Randomized: 25 Treated: 25 Completed: 15 asenapine 4.0 mg Randomized: 28 Treated: 28 Completed: 17 schizophrenic patients	placebo Sex: 18M/8F Mean Age (min/max): 39.2 (21-66) years Race: Not available asenapine 0.4 mg Sex: 11M/15F Mean Age (min/max): 41.6 (19-70) years Race: Not available asenapine 1.0 mg Sex: 9M/16F Mean Age (min/max): 41.6 (22-67) years Race: Not available asenapine 2.0 mg Sex: 16M/9F Mean Age (min/max): 43.4 (25-66) years Race: not available asenapine 4.0 mg Sex: 11M/17F Mean Age (min/max): 43.2 (19-68) years Race: Not available	42 days	Started: October 19 Completed February 1 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Status Type of Report
E, S	87039 Belgium (5 centers)	A double-blind, active-controlled, fixed dose, pilot efficacy and safety study with Org 5222 and haloperidol administered orally for a period of six weeks to patients with (sub)chronic schizophrenia	placebo Route: tablet asenapine Route: oral tablet Dose Regimen: 1 mg BID haloperidol Route: oral tablet Dose Regimen: 10 mg BID	asenapine Randomized: 36 Treated: 36 Completed: 22 haloperidol Randomized: 34 Treated: 34 Completed: 31 schizophrenic patients	asenapine Sex: 22M/14F Mean Age (min/max): 36.1 (22 – 58) years Race: Not available haloperidol Sex: 15M/19F Mean Age (min/max): 39.3 (25 – 55) years Race: Not available	42 days	Started: May 1988 Completed: August 1989 full
E, S	25505 Finland (9 centers)	A multicentre, double-blind, randomized, group comparative study to evaluate the effects of six weeks of oral treatment with Org 5222 (0.5-2.0 mg twice daily), haloperidol (2-8 mg twice daily) and placebo, administered to (sub)chronic schizophrenic patients	placebo Route: tablet asenapine Route: oral tablet Dose Regimen: 0.5 – 2.00 mg BID haloperidol Route: tablet Dose Regimen: 2 – 8 mg BID	placebo Randomized: 19 Treated: 19 Completed: 8 asenapine Randomized: 17 Treated: 17 Completed: 10 haloperidol Randomized: 16 Treated: 15 Completed: 11 schizophrenic patients	placebo Sex: 12M/7F Mean Age (min/max): 39.4 (26-70) years Race: Not available asenapine Sex: 7M/10F Mean Age (min/max): 40.5 (22-61) years Race: Not available haloperidol Sex: 9M/6F Mean Age (min/max): 35.1 (26-50) years Race: Not available	42 days	Started: November 1991 Completed: October 1993 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Statu Type of Report
S, PK	CNS-9041 Japan (1 center)	Org 5222 Phase I study in Japanese male volunteers to assess the safety & pharmacokinetics of Org 5222 after single and multiple dosing in healthy male volunteers and to compare the clinical pharmacological effects with those of haloperidol	placebo Route: oral tablet asenapine Route: oral tablet Dose Regimen: single rising dose Step 1 - 0.25 mg, Step 2 - 0.50 mg, Step 3 - 1 mg, Step 4 - 2 mg, Step 5 - 4 mg Multiple dose: 0.5 mg BID – 7 days haloperidol Route: oral tablet Dose Regimen: 3 mg	Randomized: 29 Treated: 29 Completed: 29 healthy subjects	Sex: 29M/0F Age: Not available Race: Not available	single rising dose or 7 days	Started: December 1990 Completed February 19 abbreviated
E, S	CNS-9141 Japan (26 centers)	Multi-center open study to evaluate the efficacy, safety and approximate optimal dosage of Org 5222 in schizophrenic patients.	asenapine Route: oral tablet Dose Regimen: 0.5 mg, 1 mg, 2 mg, 3 mg, or 4 mg, BID:	Randomized: 38 Treated: 38 Completed: 28 schizophrenic patients	Sex: 23M/15F Age: Not available Race: Not available	56 days	Started: December 1991 Completed: October 199 abbreviated

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Status Type of Report
E, S	CNS-9241 Japan (44 centers)	Multi-center open study to evaluate the efficacy, safety and optimal dosage of Org 5222 in schizophrenic patients	asenapine Route: oral tablet Dose Regimen: 0.5 mg, 1 mg, 2 mg, 3 mg, or 4 mg, BID	Randomized: 101 Treated: 101 Completed: 69 schizophrenic patients	Sex: 62M/39F Age: Not available Race: Not available	56 days	Started: June 1993 Completed: August 1994 abbreviated
BA	041026 Netherlands (1 center)	An open label, randomized, two-way cross-over trial to assess the relative bioavailability of asenapine tablets made via direct compression versus freeze dried techniques	asenapine 'direct compressed' tablet Route: SL tablet Dose Regimen: 5 mg asenapine 'freeze dried' tablet Route: SL tablet Dose Regimen: 5 mg	Randomized: 24 Treated: 24 Completed: 24 healthy subjects	Sex: 24M/0F Mean Age (min/max): 22.3 (18-35) years Race: W/B/A/O: 22/1/0/1	single dose on day 1 and 8	Started: June 2005 Completed: August 2005 synopsis

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Statu Type of Report
Ongoing Studies							
E, S	041512 Russia Federation (8 centers), Ukraine (10 centers), United States (56 centers)	A multicenter, double- blind, flexible- dose, long-term extension trial of the safety and maintenance of effect of asenapine using olanzapine positive control in subjects who complete Protocols 041021/ 041022	placebo Route: Oral tablet or SL tablet asenapine Route: SL tablet Dose Regimen: 5 mg BID asenapine Route: SL tablet Dose Regimen: 10 mg BID olanzapine Route: Oral film-coated tablet Dose Regimen: 5mg - 20 mg QD:	662 planned schizophrenic patients	Not available	52 weeks total duration	Started: May 2005 Ongoing interim

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Stat Type o Report
E, S	041513 Canada (1 center), India (8 centers), Romania (6 centers), Russian Federation (13 centers), United States (18 centers)	A multicenter, double- blind, flexible- dose, long-term extension trial of the safety and maintenance of effect of asenapine using a haloperidol positive control in subjects who complete Protocol 041023.	placebo Route: SL tablet or oral capsules asenapine 5 mg Route: SL tablet Dose Regimen: 5 mg BID asenapine 10 mg Route: SL tablet Dose Regimen: 10 mg BID haloperidol Route: oral capsule Dose Regimen: 2 mg – 8 mg BID	404 planned schizophrenic patients	Not available	52 weeks total duration	Started September 2005 Ongoing interim
E, S	25520 Australia (2 centers), Belgium (7centers), Czech Republic (11 centers), France (7 centers), Germany (5 centers), Poland (14 centers), Russian Federation (14 centers), South Africa (11 centers), Spain (3 centers)	Long- term efficacy and safety evaluation of asenapine (10- 20 mg/ day) in subjects with schizophrenia or schizoaffective disorder, in a multicenter trial using olanzapine (10- 20 mg/ day) as a control	placebo: Route: SL tablet or film coated tablet asenapine Route: SL tablet Dose Regimen: 5 mg - 10 mg BID olanzapine Route: film-coated tablet Dose Regimen: 10 mg - 20 mg QD	400 planned schizophrenic patients	Not available	1 year	Started: October 20 Status: terminated September 2006 full

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Stat Type o Report
E, S	25543 Australia (3 centers), Czech Republic (7 centers), Denmark (2 centers), Finland (4 centers), France (3 centers), Germany (6 centers), Hungary (7 centers), Italy (5 centers), Norway (2 centers), Poland (7 centers), Romania (5 centers), Russian Federation (18 centers), 25543 (con't) Scotland (1 center), South Africa (7 centers), Spain (3 centers) Sweden (3 centers) United Kingdom (1 center)	A multicenter, double-blind, flexible-dose, 6- month trial comparing the efficacy and safety of asenapine with olanzapine in stable subjects with predominant, persistent negative symptoms of schizophrenia	placebo: Route: SL tablet or film coated tablet asenapine Route: SL tablet Dose Regimen: 5 mg - 10 mg BID olanzapine Route: film-coated tablet Dose Regimen: 5 mg - 20 mg QD	444 planned schizophrenic patients	Not available	26 weeks	Started: June 2005 Status: Ongoing interim

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Stat Type o Report
E,S	25544 Australia (2 centers), Czech Republic (6 centers), Denmark (2 centers), Finland (3 centers), France (3 centers), Germany (5 centers), Hungary (7 centers), Italy (4 centers), Poland (7 centers), Romania (4 centers), Russian Federation (15 centers), Scotland (1 center), South Africa (6 centers), Spain (3 centers) Sweden (3 centers) United Kingdom (1 center)	A multicenter, double- blind, flexible- dose, 6-month extension trial comparing the safety and efficacy of asenapine with olanzapine in subjects who completed Protocol 25543	placebo: Route: SL tablet or film coated tablet asenapine Route: SL tablet Dose Regimen: 5 mg - 10 mg BID olanzapine Route: film-coated tablet Dose Regimen: 5 mg - 20 mg QD	300 planned schizophrenic patients	Not available	52 weeks total duration	Start: November 2005 Status: Ongoing interim

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Status Type of Report
E, S	A7501007 Bulgaria (4 centers), India (10 centers), Korea (2 centers), Malaysia (3 centers), Philippines (4 centers), Romania (2 centers), Russian Federation (7 centers), Turkey (2 centers), Ukraine (10 centers), United States (63 centers)	A double-blind, 40-week continuation study evaluating the safety of asenapine and olanzapine in the treatment of subjects with acute mania	placebo Route: SL or film coated tablet asenapine Route: SL tablet Dose Regimen: 5 - 10 mg BID olanzapine Route: film coated tablet Dose Regime: 5 – 20 mg QD:	240 planned bipolar patients	Not available	40 weeks	Started: July 2005 Status: Ongoing interim
E, S	A7501008 Australia (2 centers), Czech Republic (5 centers), India (6 centers), Korea (3 centers), Russian Federation (12 centers), Taiwan (3 centers), Thailand (2 centers), United States (41 centers)	A Phase 3, randomized, placebo-controlled, double-blinded trial evaluating the safety and efficacy of asenapine in subjects continuing lithium or Valproic acid/divalproex sodium for the treatment of an acute manic or mixed episode	placebo: Route: SL tablet asenapine Route: SL tablet Dose Regimen: 5 - 10 mg BID Plus open-label treatment with lithium or VPA	320 planned bipolar patients	Not available	12 weeks	Started: May 2005 Status: Ongoing interim

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Status Type of Report
E, S	A7501009 Australia (1 center), India (3 centers), Korea (3 centers), Russian Federation (5 centers), Thailand (2 centers), United States (39 centers)	A Phase 3, placebo-Controlled, Double-Blinded, Continuation Trial Evaluating the Safety and Efficacy of asenapine in Subjects Completing Trial A7501008 and Continuing Lithium or Valproic Acid/Divalproex Sodium for the Treatment of an Acute Manic or Mixed Episode	placebo Route: SL tablet asenapine: Route: SL tablet Dose Regimen: 5 or 10 mg BID Plus open-label treatment with lithium or VPA	160 planned bipolar patients	Not available	52 weeks total duration	Started: August 2005 Status: Ongoing interim
E, S	A7501012 Croatia (3 centers), India (7 centers), Latvia (3 centers), Russian Federation (16 centers), Tamil Nadu (1 center), Ukraine (8 centers), United States (21 centers)	A randomized, placebo-controlled, double-blind trial of asenapine in the prevention of relapse after long-term treatment of schizophrenia	placebo Route: SL tablet asenapine Route: SL tablet Dose Regimen: 5 – 10 mg BID	600 planned schizophrenic patients	Not available	Open-label treatment: 26 weeks Double-blind treatment: 26 weeks	Started: April 2005 Status: Ongoing interim

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Stat Type o Repor
E, S	A7501013 Brazil (5 centers), Canada (6 centers), Chile (7 centers), Mexico (2 centers), United States (77 centers)	A multicenter, double-blind, flexible-dose, 6-month trial comparing the efficacy and safety of asnapine with Oanzapine in stable subjects with predominant, persistent negative symptoms of schizophrenia	placebo Route: SL tablet or film-coated tablet asenapine Route: SL tablet Dose Regimen: 5 – 10 mg BID Oanzapine Route: film-coated tablet Dose Regimen: 5 – 20 mg QD	444 planned schizophrenic patients	Not available	26 weeks	Started: December 2004 Status: Ongoing interim
E, S	A7501014 Canada (4 centers), Chile (4 centers), Mexico (1 center), United States (69 centers)	A multicenter, double-blind, flexible-dose, 6-month extension trial comparing the safety and efficacy of asenapine with Oanzapine in subjects who completed protocol A7501013	placebo Route: SL or film-coated tablet asenapine Route: SL tablet Dose Regimen: 5 – 10 mg BID Oanzapine Route: film-coated tablet Dose Regimen: 5 – 20 mg QD	300 Planned schizophrenic patients	Not available	52 weeks total duration	Started: July 2005 Status: Ongoing interim

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Stat Type o Repor
S, PK	A7501021 United States (39 centers)	A Randomized, Parallel Group, Multiple Dose, 6-Week Study to Evaluate Safety, Tolerability and Pharmacokinetics of asenapine in Elderly Subjects with Psychosis	asenapine Route: SL tablet Dose Regimen: 5 -10 mg BID	120 planned Elderly patients with psychosis disorder	Not available	6 weeks	Started: February 2 Status: Ongoing interim

APPENDIX 3 22-117 Asenapine Literature

[RLL Synopsis of articles that the sponsor has provided]

Backman 2006
Rofecoxib is a potent inhibitor of CYP1A2. CYP1A2 substrates include: clozapine, olanzapine, tacrine, zolmitriptan, and melatonin.

Benzer 2005
Neuroleptic malignant syndrome review. NMS is characterized by fever, muscular rigidity, altered mental status, and autonomic dysfunction. All typical and atypical antipsychotic medications can precipitate the syndrome. NMS has also been associated

with other types of drugs that block central dopamine pathways. All medications implicated in NMS have dopamine D2-receptor antagonist properties. The development of the syndrome is thought to be secondary to decreased dopamine activity in the CNS, either from blockade of D2 receptors or decreased availability of dopamine itself. NMS has features similar to malignant hyperthermia and serotonin syndrome.

The incidence of mortality in cases of NMS is approximately 5-12%. Death usually results from respiratory failure, cardiovascular collapse, myoglobinuric renal failure, arrhythmia, disseminated intravascular coagulation (DIC). Morbidity from NMS includes rhabdomyolysis, pneumonia, renal failure, seizure, arrhythmia, DIC, and respiratory failure.

During treatment with antipsychotic drugs, NMS is more likely to occur soon after initiation of treatment or after an increase in the dose. On average, NMS occurs about 4-14 days after initiation of therapy. Approximately 90% of patients who develop NMS do so within 10 days of beginning antipsychotic treatment.

Chopra 1999
The Neuroleptic Malignant Syndrome: An Indian Experience. The authors discuss 13 cases of NMS treated in an intensive care unit in a large teaching hospital. Mortality rate in these cases was 38%. Patients with NMS had a higher incidence of coexisting medical and neurological illness and a higher mean antipsychotic dose than matched patients treated with antipsychotic medications. Higher potency antipsychotic drugs were also implicated.

Christensen 2002
Fluvoxamine inhibits CYP1A2 and CYP2C19

Craig 2006
'Rhabdomyolysis'
Pathophysiology: rhabdomyolysis is the breakdown of muscle fibers with leakage of potentially toxic cellular contents into the systemic circulation. The final common pathway of rhabdomyolysis may be a disturbance in myocyte calcium homeostasis. Clinical sequelae of rhabdomyolysis include the following:

- Hypovolemia (sequestration of plasma water within injured myocytes)
- Hyperkalemia (release of cellular potassium into the systemic circulation)
- Metabolic acidosis (release of cellular phosphate and sulfate)
- Acute renal failure (nephrotoxic effects of liberated myocyte components)
- Disseminated intravascular coagulation (DIC)

In the U.S., rhabdomyolysis accounts for an estimated 8-15% of cases of acute renal failure. The overall mortality rate for patients with rhabdomyolysis is approximately 5%; however, the mortality rate of any single patient is dependent upon the underlying etiology and any existing comorbidities. Usually presents with muscle pain, and sometimes dark urine. Common risk factors include alcohol abuse, soft tissue

compression, and seizure. Other causative factors include trauma, exertion, drug abuse, metabolic abnormalities, hypothermia, viral illness, flulike illness, burns, sepsis, ischemia, polymyostis, hereditary disorders, drug overdose, and gangrene.

Deng 1990
NMS in Chinese inpatients exposed to neuroleptics.

Friedman 1988
Neuroleptic Malignant Syndrome: The results of a 6-month prospective study of Incidence in a state psychiatric hospital. Just one single case out of 495 patients exposed to antipsychotic medication.

Gelenberg 1988
A Prospective Survey of Neuroleptic Malignant Syndrome in a Short-Term Psychiatric Hospital. Only one patient developed NMS out of 1,470 patients treated with antipsychotic medication (rate of 0.07% per year). The low rate may be due to use of relatively low doses of neuroleptic medication.

Gelenberg 1989- people with history of NMS and rechallenge.

Granfors 2004: ciprofloxacin inhibits CYP1A2

Granfors 2005a: fluvoxamine inhibits CYP1A2

Granfors 2005b: oral contraceptives containing ethinyl estradiol and gestodene inhibits CYP1A2 (markedly increases tizanidine concentrations)

Hermesh 1992
Risk for NMS. Two series of consecutive psychiatric inpatients. At higher risk: patients with Bipolar Disorder and patients treated with injections (higher potency).
Bipolar risk may be at least partly related to lithium exposure and high level of agitation.

Kapur 2001
Dopamine D2 receptor antagonism and their role in the activity of atypical antipsychotic drugs

Keck 1987
Frequency and Presentation of NMS (a prospective study)

Keck 1989
Ditto.

Keck 1991
Declining Frequency of NMS: increased awareness, diagnosis, intervention, treatment, less use of intramuscular medications.

Khan 2001
Placebo treatment and symptom reduction and suicide risk in FDA databases of clinical trials in acute Schizophrenia. Suicide and suicide attempts did not differ significantly. In the placebo group, there was almost no improvement of symptoms.

Mackay 1998
Drug Safety Research Unit, United Kingdom. The DSRU is the centre for prescription event monitoring (PEM). PEM studies are noninterventional observational cohort studies that monitor the safety of newly marketed drugs.

Marder 1997
The effect of risperidone on the five dimensions of Schizophrenia derived by factor analysis: combined results of the North American Trials. Positive symptoms, negative symptoms, disorganized thinking, uncontrolled hostility and excitement, and anxiety/depression. Dr. Marder and colleagues state that risperidone has important over haloperidol. Risperidone produced greater improvements on all five dimensions of Schizophrenia. Especially negative symptoms, uncontrolled hostility and excitement, and anxiety/depression.

Meltzer 1996
Marked elevations of creatine kinase activity associated with antipsychotic drug treatment: markedly elevated serum CK occurred in about 10% of patients treated with the six antipsychotic drugs. May be related to increased permeability of cell membrane. This may be related to serotonergic activity. The increases were not related to NMS. Only one of these patients had rhabdomyolysis as evidenced by myoglobinuria.

Nolte 1991
Rhabdomyolysis associated with cocaine use. Skeletal muscle necrosis without vasulitis.

Roth 1988
Acute rhabdomyolysis associated with cocaine intoxication. Rhabdomyolysis, renal failure, severe liver dysfunction, disseminated intravascular coagulation.

Siris 2001
Suicide and Schizophrenia. Studies estimate that approximately 10% of schizophrenic patients complete suicide. Risk factors include being young, male, early in the course of illness, high socioeconomic background, high intelligence, having high expectations, recently discharged from the hospital, depressive symptoms, and AKATHISIA.
Dr. Siris knows.

Teraro 1999
CPK can be benign

Tohen 1999
Olanzapine treats acute mania

Tohen 2000
Olanzapine treats acute mania

Venkatakrishnan 2005
CYP2D6 inhibited by paroxetine

Muscal 2007
Rhabdomyolysis.
Myalgia, muscle weakness, and dark urine. The triad is rarely observed together. Life-threatening renal failure and disseminated intravascular coagulation are the most dreaded complications. Correct fluid and electrolyte abnormalities.

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Formulation:

Asenapine tablets are available in two strengths (5 mg and 10 mg). It is intended for sublingual administration. Tablets are manufactured by suspending asenapine maleate into an aqueous solution of gelatin and mannitol, followed by freeze-drying the suspension. Dosing: for Schizophrenia, begin with 5 mg to 10 mg BID, starting with 5 mg BID. For acute mania, begin with 10 mg BID.

Asenapine was initially developed as an oral formulation, but, due to extremely low bioavailability (< 2%), the oral formulation was discontinued in favor of a fast-dissolving tablet for sublingual administration. The low bioavailability of orally administered asenapine is due to extensive first-pass metabolism in the liver (and probably the gut as well). Therefore, a sublingual formulation was developed to circumvent the hepato-gastrointestinal first-pass metabolism. The bioavailability of asenapine after sublingual dosing is considerably higher (35%) than after oral dosing.

Potential problems with formulation and route of administration:
(sublingual is necessary, due to the extremely low bioavailability of asenapine. There is significant loss of a dose if it is swallowed.

Metabolite assessment (per Ron: “commendable”); the assessment was detailed and thorough.

- Parent drug is the active moiety
- Many metabolites ~38; exposures to each are quite low; none are highly prevalent
- None are > 7% of urine radioactivity
- CYP1A2 has some role; fluvoxamine inhibition ↑exposure ~30%
- CYP1A2 induction by carbamazepine ↓ exposure by ~18%
- The smoking induction didn’t really do much, because the subjects were smokers.
- With severe hepatic impairment, AUC increases 7-fold
- With supratherapeutic doses, subjects had acute dystonia
- Tablet administration results in asenapine dissolution of 4 mg/mL

- Sublingual administration yields a mean (across studies) bioavailability of ~36%
- Sublingual bioavailability may be significantly variable, depending on the amount of saliva, swallowing, anticholinergic status, food and water intake
- Look at the three-way administration study: sublingual, supralingual, buccal

APPENDIX 4 INVESTIGATORS AND CLINICAL SITES

----------Appendix for 041004----------

Investigators and Sites

01- George Ainslie, M.D., Department of Veterans Affairs Medical Center, Coatesville, PA
02- Ronald Brenner, M.D., Neurobehavioral Research, Inc. Lawrence, NY
03- George Chappell, M.D., Providence St. Peter Hospital, Olympia, WA
04- Paul Keck, M.D., Univ. of Cincinnati College of Medicine, Cinc., OH
05- Carlos Figueroa, M.D., BHC Alhambra Hospital, Rosemead, CA
07- Clifford Goldman, M.D., ClinCearch, Kenilworth, NJ
08- Robert Horne, M.D., North Las Vegas, NV
09- Adel Wassef, M.D., UT Health Sciences Center, Houston Texas
11- Michael Lesem, M.D., Claghorn-Lesem Clinical Research, Bellaire, TX
12- Robert Litman, M.D., Center for Behavioral Health, Rockville, MD
13- Rick Mofsen, D.O., Clinical Research Associates, St. Louis, MO
14- Steve Potkin, M.D., Univ. of California Irvine Medical Center, Orange, CA
15- Clifford Roberson, M.D., Tennessee Christian Medical Center, Madison, TN
16- David Sack, M.D., Institute for Psychopharmacology Research, Cerritos, CA
17- Scott Segal, M.D., North Miami, FL
18- Seeth Vivek, M.D., Jamaica Hospital Medical Center, Jamaica, NY
19- Tram Tran-Johnson, M.D., California Neuropsychopharmacology Clinical Research Institute, San Diego, CA
20- Cherian Verghese, M.D., Albert Einstein Medical Center, Philadelphia, PA
24- Robert Litman, M.D., Washington Hospital Center, Washington, DC
25- Mohammed Bari, M.D., Synergy Clinical Research, Chula Vista, CA
27-David Brown, M.D., Community Clinical Research, Austin, TX

Site #	Site Name	Randomized (n)	Treated (n)	ITT analysis (n)	Per Protocol analysis (n)
01	Coatesville, PA	3	3	2	0
02	Lawrence, NY	6	6	6	5
03	Olympia, WA	2	2	2	2
04	Cincinnati, OH	3	3	3	2
05	Rosemead, CA	9	9	9	5
07	Kenilworth, NJ	4	3	3	0
08	North Las Vegas, NV	1	1	1	0
09	Houston, TX	9	9	9	5
11	Houston, TX	21	21	21	17
12	Rockville, MD	6	6	6	5
13	St. Louis, MO	14	14	13	13
14	Orange, CA	9	9	8	6
15	Madison, TN	9	9	9	6

16	Cerritos, CA	18	17	16	13
17	North Miami, FL	12	12	12	10
18	Jamaica, NY	9	9	9	8
19	San Diego, CA	20	20	20	18
20	Philadelphia, PA	6	6	6	4
24	Washington, DC	6	6	6	1
25	Chula Vista, CA	9	9	7	5
27	Austin, TX	6	6	6	5
All	Total	182	180	174	130

Combining sites for the ITT analysis:

Twenty sites were planned for the trial. Three sites failed to recruit subjects, and three additional sites were used. A total of 21 sites recruited subjects. To determine potential treatment by site interactions, a minimum of 6 ITT population subjects were required from each center. However, not all centers had 6 ITT subjects. Therefore, for the purposes of analysis, sites 01, 03, 04, 07, and 08 were combined into a composite center with 11 subjects in the ITT population.

Investigators and Sites for Study 041021

01- Scott Aaronson- Sheppard Pratt Health System, Baltimore, MD
02- Jose Alvarez* (did not enroll subjects)
03- Jeffrey Borenstein- Holliswood Hospital, Holliswood , NY
04- Ronald Brenner- Neurobehavioral Research Inc., Floor, Lawrence, NY
05- Toni Carman- Research Strategies Inc., Chagrin Falls, OH
06- Leslie Citrome- Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY
07- Robert Horne- Montevista Hospital, Las Vegas, NV
08- James Knutson- Eastside Therapeutic Resource, Kirkland WA
09- Angelos Halaris- VA Medical Center, Hines IL
10- Robert Litman- Centers for Behavioral Health LLC, Baltimore MD
11- Adam Lowy- Comprehensive NeuroScience Inc., Washington, DC
12- Andrew Cutler- Florida Clinical Research Center LLC, Bradenton FL
13- Denis Mee-Lee- Hawaii Clinical Research Center, Honolulu HI
14- Robert Dahmes- Louisiana Research Associates, New Orleans LA
15- Bradley Diner- Arkansas Psychiatric Clinic PA
16- William Fuller- Avera Research Institute, Sioux Falls SD
17- Clifford Roberson*(did not enroll subjects)
18- Lev Gertsik- California Clinical Trials, Glendale CA
19- Morteza Marandi- Comprehensive Neuroscience Inc., Cerritos CA
20- Steven Holroyd- Research Strategies Inc., Reno NV
21- Mary Knesevich- University Hills Clinical Research, Irving TX
22- Jelena Kunovac- Excell Research, Oceanside CA
23- David Walling- CNS Network, Garden Grove CA
24- Henry Nasrallah- University of Cincinnati Medical Center, Cincinnati OH
25- Stephen Mohaupt- California Clinical Trials, Anaheim CA
26- Rajaprabhakaran Rajarethinam*(did not enroll subjects)
27- Suhas Shanbhag- ClinSearch Inc, Kenilworth NJ
28- Kenneth Sokolski- Clinical Innovations, Santa Ana, CA
29- Nicholas Vatakis- Social Psychiatry Research Institute, New York, NY
30- Alexander Miller- University of Texas Health Science Center at San Antonio
31- Larry Ereshefsky- California Clinical Trials, Culver City CA
32- David Feifel – University of California at San Diego Medical Center
33- Michael Levy*(did not enroll subjects)
34- Duong Nguyen- Woodland International Research Group LLC, Little Rock AR

35- Douglas Dolnak- California Clinical Trials, San Diego CA
36- Leonid Bardenstein- City Psychiatric Hospital #15, Moscow Russia
37- Galina Panteleyeva- Mental Health Research Centre of RAMS, Moscow Russia
38- Margarita Morozova- City Psychiatric Hospital #14, Moscow Russia
39- Anatoly Smulevich- City Psychiatric Hospital #1, Moscow Russia
40- Isaak Gurovich- Moscow Scientific Research Institute of Psychiatry, Moscow Russia
41- Iryna Y. Vlokh- Lviv State Medical University, Lviv Ukraine
42- Oleg S. Chaban- Ukrainian Research Institute of Social, Forensic Psychiatry and Drug Abuse, Kiev Ukraine
43- Vladyslav A. Demchenko- Kiev City Psychoneurological Hospital #2, Kiev Ukraine
44- Valeriy S. Bitensky- Odessa Medical University, Department of Psychiatry, Odessa Ukraine
45- Vitaliy Y. Pishel- Ukrainian Research Institute of Social, Forensic Psychiatry and Drug Abuse, Kiev Ukraine
46- Svitlana Y. Kazakova- Lugansk State Medical University, Department of Psychiatry, Lugansk Regional Psychoneurological Hospital, Lugansk Ukraine
47- Svitlana M. Moroz- Psychosomatic Center of Dnepropetrovsk, Dnepropetrovsk Ukraine
48- Viktor P. Samokhvalov- Crimean State Medical University Department of Psychiatry, Psychotherapy, Narcology, Simferopol Ukraine
49- Lyudmyla N. Yur'yeva- Dnepropetrovsk State Medial Academy, Curanive-preventive Amalgation Interoblast Clinical Psychjneurological Center, Dnepropetrovsk Ukraine

Investigators and Clinical Sites for Study 041022

Title of the clinical trial

A multicenter, randomized, double-blind, flexible -dose, 6-week trial of the efficacy and safety of asenapine compared with placebo using olanzapine positive control in subjects with an acute exacerbation of schizophrenia

Investigators

1) Mohammed Bari
2) Tram Trans-Johnson
3) Steven Potkin
4) Robert Manning
5) Douglas Dolnak
6) Michael Plopper
7) David Marks
8) Madeleine Valencerina
9) Edward Burdick
10) Sohail Punjwani
11) Mark Lerman
12) Ricky Mofsen
13) Joseph McEvoy
14) Steven Glass
15) Jose Canive
16) Miranda Chakos
17) Rakesh Ranjan
18) Mark Novitsky
19) Michael Lesem
20) David Brown
21) Jason Baron
22) Rajinder Shiwach
23) Charles Bailey
24) Mikhail Burdukovsky
25) Nikolay Neznanov
26) Svitlana Kazakova
27) Svitlana Moroz
28) Viktor Samokhvalov
29) Lyudmyla Yur´yeva
30) Oleksandr Napryeyenko
31) Evgenia Reprova [a]
32) Seeth Vivek [a]
33) Philip Janicak [a]

Thirty (30) sites randomized subjects.

[a] Sites did not randomize subjects.

Clinical trial centers

1) Synergy Clinical Research, 5577 University Avenue, Chula Vista, CA 92105
2) CNRI - San Diego LLC, 9466 Black Mountain Road, Suite 100, San Diego, CA 92126
3) UCI Medical Center, 101 The City Drive Way, Orange, CA 92868
4) CNRI – Los Angeles LLC, 8309 Telegraph Road, Pico Rivera, CA 90660
5) California Clinical Trials, 3625 Ruffin Road, Suite 100, San Diego, CA 92123
6) Sharp Mesa Vista Hospital, 7850 Vista Hill Ave., San Diego, CA 92123
7) Optimum Health Services, 7200 Parkway Drive, Suite 116, La Mesa, CA 91942
8) Kedren Community Mental Health Center, 4211 South Avalon Boulevard, Los Angeles, CA 90011
9) Segal Institute for Clinical Research, 1065 N.E. 125th Street, Suite 417, North Miami, FL 33161
10) Segal Institute for Clinical Research, 1065 N.E. 125th Street, Suite 417, North Miami, FL 33161
11) Comprehensive NeuroScience Inc., 1721 Moon Lake Blvd., Suite 109, Hoffman Estates, IL 60194
12) Clinical Research, Inc., 2639 Miami Street, St Louis, MO 63118
13) John Umstead Hospital, 1003 12th Street, Bldg. 32 Ward 321, Butner, NC 27509
14) CNS Research Institute (CRI), 130 White Horse Pike, Clementon, NJ 08021
15) VA Medical Center, 1501 San Pedro SE, Psychiatry Service 116A, Albuquerque, NM 87108
16) SUNY Downstate Medical Center, 450 Clarkson Avenue, Box 1203, Brooklyn, NY 11238
17) Rakesh Ranjan M.D. and Associates Inc., 600 East Smith Road, Suite H, Medina, OH 44256
18) Quantum Clinical Services, 111 North 49th Street, Kirkbride Center, Philadelphia, PA 19139
19) Claghorn-Lesem Research Clinic, Inc., 6750 West Loop South, Suite 1050, Bellaire, TX 77401
20) Community Clinical Research, Inc., 12151 Hunters Chase, Austin, TX 78729
21) MedLabs Research of Houston Inc., 6260 Westpark, Suite 250, Houston, Tx 77057
22) InSite Clinical Research, 2000 Old Hickory Trial, DeSoto, TX 75115
23) Accurate Clinical Trials, 206 Park Place Blvd, Suite 247, Kissimmee, FL 34741
24) City Psyciatric Hospital No4, 75, Obvodny Canal Embankment, 191119, St. Petersburg, Russia

25) City Psyciatric Hospital No6, 13, Obvodny Canal, 193167, St. Petersburg, Russia
26) Lugansk State Medical University, Department of Psychiatry, Lugansk Regional Psychoneurological Hospital, 22, 50 let Oborony Luganska str., Lugansk, 91045 Ukraine
27) Psychosomatic Center of Dnepropetrovsk regional clinic, 14, Oktyabrskaya sq., Dnepropetrovsk, 49616 Ukraine
28) Crimean State Medical University, Department of Psychiatry, Psychotherapy, Narcology Crimean Republican Clinical Psychoneurological Hospital No1, 27, R. Luxemburg str., Simferopol, 95006, Ukraine
29) Dnepropetrovsk State Medical Academy, Curanive-preventiveAmalgation Interoblast Clinical Psychjneurological Center, MoH Ukraine, Dep. Of Psychiatry of Post Graduate Education, 1, Behtereva str., Dnepropetrovsk, 9115, Ukraine
30) National Medical University, Department of Psychiatry, City Clinical Psychonevrological Hospital No1, 103 Frunze Str., Kiev, Ukraine
31) City Psyciatric Hospital No3 named after Skvortsov-Stepanov, 36, Fermskoe shosse, 197341, St. Petersburg, Russia
32) Jamaica Hospital Medical Center, 8900 Van Wyck Expressway, Jamaica, NY 11418
33) Rush University Medical Center, 1720 West Polk, Office 111, Chicago, Il 60612

Investigators and Clinical Sites for Study 041023

Title of the clinical trial

A multicenter, randomized, double-blind, fixed-dose, 6-week trial of the efficacy and safety of asenapine compared with placebo using haloperidol positive control in subjects with an acute exacerbation of schizophrenia (041023)

Investigators

1) Gary Booker
2) Daniel Anderson
3) Saroj Brar
4) David Flaherty
5) Joseph Kwentus
6) Carlos Figueroa
7) Herbert Meltzer
8) Donald Garcia
9) Robert Reisenberg [a]
10) Anantha Shekhar
11) Richard Jaffe
12) Franco Sicuro
13) Bart Sloan
14) Cherian Verghese [b]
15) Daniel Zimbroff
16) Guy Brannon
17) Norman Costigan
18) Alan Jacobson [a]
19) Mohammed Alam [a]
20) Scott Segal
21) Himasiri De Silva
22) Ramanath Gopalan
23) T. P. Sudhakar
24) J. K. Trivedi [a]
25) Ramanathan Sathianathan
26) Sanjay Phadke
27) N. N. Raju
28) Rajesh Nagpal
29) P. S. V. N. Sharma
30) Lakshman Dutt
31) Mikhail Sheifer
32) Alexander Mouzitchenko
33) Alexander Reznik
34) Elena Grigorieva
35) Yuri Alexandrovsky
36) Alexander Kociubynski
37) Mikhail Popov
38) Lala Kasimova
39) Kausar Yakhin
40) Mikhail Burdukovsky [b]
41) Evgenia Rebrova
42) Nikolay Neznanov
43) Victoria Burtea
44) Irina Dan
45) Dan Prelipceanu
46) Petru Boisteanu
47) Monica Ienciu
48) Daniel Vasile
49) Gheorghe Oros

Forty-three (43) sites randomized subjects.
[a] Site was shipped drug but did not screen or randomize any subjects. [b] Site did not randomize any subjects.

Clinical trial centers

1) 851 Olive Street, Shreveport, LA 71104 USA
2) AVI Clinical Research, 3250 Lomita Blvd, Suite 107, Torrance, CA 90505 USA
3) Deaconess Medical Arts Building, 4255 Pearl Road, Suite 105, Cleveland, OH 44109 USA
4) Segal Institute for Clinical Research, 1065 N.E. 125th Street, Suite 417, North Miami, FL 33161 USA
5) Precise Clinical Research, 3531 Lakeland Drive, Brentwood Plaza Suite 1060, Flowood, MS 39232 USA
6) Research Strategies, Inc., 180 N. San Gabriel Blvd., Suite 201, Pasadena, CA 91107 USA
7) Psychiatric Hospital at Vanderbilt, Frank Luton Center, 1601 23rd Avenue South, Suite 306, Nashville, TN 37212 USA
8) Future Search Trials, 4200 Marathon Bldv., Suite 200, Austin, TX 76756 USA
9) Atlanta Center for Medical Research, 811 Juniper Street NE, Atlanta, GA 30308 USA
10) Indiana University, Larue D. Carter Memorial Hospital, 2601 Cold Spring Road, Indinanapolis, IN 46222 USA
11) Belmont Center for Comprehensive Treatment, 4200 Monument Road, Philadelphia, PA 19131 USA
12) Millennium Psychiatric Associates, 12303 De Paul Dr., St. Louis, MO 63044 USA
13) Research Center for Clinical Studies, 17 Old Kings Highway South, Suite 1-2, Darien, CT 06820 USA
14) Keystone Clinical Studies, LLC, 1401 Dekalb Street, Suite 201, Norristown, PA 19401 USA
15) Pacific Clinical Research Medical Group, 1317 W. Foothill Boulevard, Suite 200, Upland, CA 91786 USA
16) Brentwood Research Institute, 1002 Highland Avenue, Suite 400, Shreveport, LA 71101 USA
17) Red Deer Mental Health Clinic, 4733-49 Street, Red Deer, AB T4N 1T6 CANADA
18) Allied Clinical Trials, Inc, 9480 S.W. 77 Avenue, Miami, FL 33156 USA

19) American Medical Research, Inc, 1200 Harger Road, Suite 415, Oak Brook, Il 60523 USA
20) Segal Institute for Clinical Research, Professional Clinical Research, Inc., 1065 N.E. 125th Street, Suite 417, North Miami, FL 33161 USA
21) Clinical Innovations, 801 N. Tustin Ave., Suite 600, Santa Ana, CA 92705 USA
22) Comprehensive Neuroscience, 1010 N. Glebe Rd., Suite 400, Arlington, VA 22201 USA
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27) Government Hospital for Mental Care, Department of Psychiatry, China Waltair, Visakhapatnam, ANDH PRAD 530017 INDIA
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30) Sheth Vadilal Sarabhai Municipal Hospital, Department of Psychiatry, Ellis Bridge, Ahmedabad, GUJARAT 380006 INDIA
31) Samara Psychiatric Hospital, 78 Nagornaya str., Samara 443 016 RUSSIA
32) City Psychiatric Hospital 14, Psychiatry, 15 Bekhtereva str., Moscow 193019 RUSSIA
33) Moscow Region Psychiatric Hospital #5, Psychiatry, Abramtzevskoe shosse, 1a, Hotkovo, Sergiev-Posad district 142601 RUSSIA
34) Yaroslavl State Medical Academy, Psychiatry Department, Regional Clinical Psychiatric Hospital, Zagorodniy sad, 6, Yaroslavl 150003 RUSSIA
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36) Bekhterev Psychoneurological Research Institute, Outpatient Psychiatry, 3 Bekhterev Str., St. Petersburg 193019 RUSSIA
37) City Psychiatric Hospital #3 of Skvortsov-Stepanov, Department #7, Fermskoye shosse, 36, St. Petersburg 194214 RUSSIA
38) City Psichiatric Hospital #1, 41, Ulyanova str, Nizhniy Novgorod 603 155 RUSSIA
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Investigators and Clinical Sites for Study A7501004

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10. Prof. Hyun-Sang Cho
11. Mohd Daud Dalip and Ahmad Hatim Sulaiman (Previous PI)
12. Kim Kah Lau
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61. Toni L. Carman*
62. Steven Holroyd*
63. Mohammed Abdul Bari
64. Craig Alan Ginsberg*
65. Charles Edward Bailey Jr.
66. Duong Huu Nguyen
67. Eduardo Cifuentes

* Did not randomize subjects

1. University Hospital Sv. Naum, Second Psychiatric Clinic, Sofia, 1113 BULGARIA
2. Varna University Hospital "Sveta Marina", Third Psychiatric Clinic, 1, "Hristo Smirnenski" Varna, 9010 BULGARIA
3. Department of Psychiatry, Justice K.S. Hegde Charitable Hospital, K.S. Hegde Medical Sciences Complex, Deralkatte, Karnataka, Mangalore 574 160 INDIA
4. Madras Medical College and Government General Hospital, Department of Psychiatry, Chennai, Tamil Nadu 600 003 INDIA
5. Poona Hospital and Research Centre, 27 Sadashiv Peth, Pune, 411 030 INDIA
6. Institute of Human Behavior & Allied Sciences, Department of Psychiatry, New Delhi, 110095 INDIA
7. Sri Venkateshwara Medical College, Department of Psychiatry, Tirupati, Andhra Pradesh 517507 INDIA
8. Spandana Nursing Home, No. 549/46, 6th Main, Rajajinagar, 4th Block, Bangalore, Karnataka 560 010 INDIA
9. The Catholic University of Korea, St. Mary's Hospital, 62 Yeouido-dong, Yeongdeungop-gu, Seol KOREA, REPUBLIC OF
10. Severance Mental Health Hospital, Department of Psychiatry, 696-6 Tanbeol-dong, Gwangju-si, Gyeonggi-do 464-100 KOREA, REPUBLIC OF
11. Hospital Mesra Bukit Padan, P.O. Box 11342, Kota Kinabalu, Sabah 88140 MALAYSIA
12. Jabatan Psikiatri, Hospital Pulau Pinang, Jalan Residensi, Pulau Pinang, 10990 MALAYSIA
13. Hospital Bahagia U/U Kinta, Tanjung Rambutan, Perak Darul Ridzuan 31250 MALAYSIA
14. Philippine General Hospital, Department of Psychiatry, Taft Avenue, Manila PHILIPPINES
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/s/

Robert Levin
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Gwen Zornberg
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CMC review was completed 11 APR 2008 recommending AE. Dr. Levin reported to me today verbally that no major toxicities including cases of aplastic anemia evident in clinical data. The data supporting acute efficacy in SZ and BP appear satisfactory.

ADDENDUM: CORRECTION OF CLINICAL REVIEW

Application Type:	NDA
Submission Number:	22-117
Letter Date:	August 29, 2007
Stamp Date:	August 29, 2007
PDUFA Goal Date:	June 29, 2008
Reviewer Name:	Robert L. Levin, M.D.
Addendum Date:	May 15, 2008
Established Name:	Asenapine Maleate
Proposed Trade Name:	Saphris
Therapeutic Class:	Atypical Antipsychotic
Applicant:	Organon
Priority Designation:	S
Formulation:	Sublingual rapidly disintegrating tablets
Dosing Regimen:	Twice daily
Indications:	Schizophrenia; Bipolar Disorder; Acute Manic Episode
Intended Population:	Adults

Correction of Executive Summary (Written on May 1, 2008)

In the last sentence of the excerpt of Executive Summary of the Clinical Review below, (completed and filed on May 1, 2008), I had mistakenly written that Study 041004 was a failed study. Study 041004 was, in fact, a positive study, which is one of the two pivotal Schizophrenia studies that were positive. However, in the second sentence of the excerpt below, I had correctly stated that Study 041004 demonstrated the efficacy of asenapine 5 mg BID SL. In other sections of the review, it is clear that my conclusion was that Study 041004 was a positive study. The Executive Summary should be corrected to state that Study 041021 was the failed study.

Below is an excerpt of the Executive Summary of the Clinical Review, 1.3.2 Efficacy:

The primary objective of the controlled, short-term Schizophrenia trials was to evaluate the efficacy of asenapine (5-10 mg BID) compared to placebo, as measured by the Positive and Negative Syndrome Scale (PANSS). Two of these studies (041004 and 041023) demonstrated the efficacy of asenapine 5 mg BID SL. However, 10 mg BID was not demonstrated to be efficacious in Study 041023, as determined by the pre-specified primary statistical analysis plan (last observation carried forward). However, the results of a non-primary statistical analysis plan (mixed-model repeated measure) suggested that the 10 mg BID dose was efficacious in the treatment of Schizophrenia. In two other similarly designed studies (041021 and 041022), asenapine was not efficacious in either fixed doses of 5 mg BID or 10 mg BID or as flexible doses of 5-10 mg BID. Study 041022 was negative, as the active control (olanzapine) demonstrated efficacy. Study 041004 was a failed study; neither asenapine nor the active control (olanzapine) demonstrated efficacy.

The last sentence of the section above should state: “Study 041021 was a failed study; neither asenapine nor the active control (olanzapine) demonstrated efficacy.

Robert L. Levin, M.D., May 15, 2008
Medical Officer,
FDA CDER ODE1 DPP HFD 130

cc: IND 22-108
HFD 130
T Laughren
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Robert Levin
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MEDICAL OFFICER

22-117 Asenapine: Addendum to Clinical NDA Review

NDA:	22-117
Drug:	Asenapine
Submission date:	August 29, 2007
Date of Addendum:	June 26, 2008
Subject of Addendum:	Review of Deaths, Serious Adverse Events, and Selected Adverse Events
Medical Officer:	Robert L. Levin, M.D.

I. Introduction

This review will discuss specific safety items in more detail. Topics will include: 1) review of all deaths in the asenapine program; 2) review of completed suicides and an analysis of suicidality; 3) review of most of the medical serious adverse events that were not related to the illnesses under treatment (Schizophrenia, Schizoaffective Disorder, and Bipolar Disorder, Manic Episode); 4) review of cases of rhabdomyolysis, hyponatremia, neutropenia, and selected cardiovascular adverse events.

The safety data reviewed herein derive from: 1) the original NDA submission (with the data cutoff date of January 15, 2007); and 2) the 4-Month Safety Update Report (with the data cutoff date of October 31, 2007). Currently, the total number of newly exposed subjects and the total exposures in person-years since the January 15, 2007 cutoff date is unavailable.

II. Deaths in the Asenapine Clinical Program

The deaths listed and discussed below had all been reported in the NDA submission and briefly discussed in the original clinical NDA review, except for two cases (**2544-121503** and **A7501021-1016002**, which were newly reported in the 4 month safety update report). The line listing and the narratives of deaths below takes into account all of the deaths in the asenapine clinical Schizophrenia and Bipolar Mania programs. Compared to the original NDA review, this addendum contains more details about all of the deaths in all treatment groups. In the original review, there were 15 deaths in the completed studies and 9 deaths in ongoing studies. The treatments in the ongoing studies had been blinded; however, in the 4-month safety update, the treatment assignments had been unblinded. Thus, there were 24 deaths discussed in the original review. Two additional deaths are discussed in this review. The total number of deaths in all treatment groups in the asenapine program is 26.

A. Line Listing of Deaths

Deaths in Cohort E (Controlled and non-controlled Schizophrenia and Mania Studies)		
1. **041013-28**	asenapine	Laryngeal dystonia, epiglottitis
2. **041013-48**	asenapine	Pulmonary embolism
3. **041021-125010**	olanzapine	Completed suicide
4. **041023-363015**	placebo	Malignant thymoma
5. **25517-115024**	asenapine	Completed suicide
6. **25517-127004**	asenapine	Completed suicide
7. **25517-130013**	asenapine	Completed suicide
8. **25517-131010**	asenapine	Completed suicide
9. **25517-186007**	asenapine	Pneumonia
10. **25517-204011**	olanzapine	Completed suicide
11. **25517-242020**	asenapine	Cardiac failure
12. **25517-248014**	asenapine	Completed suicide
13. **A7501006-40031005**	asenapine	Drug overdose
14. **A7501004-40111002**	asenapine	Completed suicide
15. **A7501004-41331009**	olanzapine	Completed suicide
16. **041513-315504**	asenapine	Respiratory failure
17. **041513-368509**	asenapine	Completed suicide
18. **25543-125005**	asenapine	Completed suicide
19. **25543-125006**	asenapine	Completed suicide
20. **A7501007-50281012**	olanzapine	Completed suicide
21. **A7501007-51241008**	asenapine	Neonatal death; asenapine exposure pregnancy
22. **P25520-132017**	asenapine	Death- unexplained
23. **P25520-241041**	asenapine	Pulmonary embolism
24. **P25520-246021**	asenapine	Cardiac failure
25. **2544-121503 ****	asenapine	Myocardial infarction
26. **A7501021-1016002 ****	asenapine	Cardiopulmonary arrest

** These two deaths were newly reported in the 4-month safety update report

Death post-clinical pharmacology (hepatic impairment) study		
A7501018-10021006	asenapine	Post hepatic impairment study: A 55 y.o. male with severe hepatic impairment had a planned surgery for umbilical hernia 10 days after a single dose of asenapine. Death from complications of the surgery occurred 2 months later.

B. Narratives of Deaths

1. **041013-28**: The subject was a 49 year-old male with Schizophrenia who was treated with low dose asenapine (600-1200 ug) for 4 days. He continued to be acutely psychotic and agitated. Study drug was discontinued, and the subject was treated with **olanzapine and haloperidol**. Details suggest that the subject developed **acute laryngeal dystonia**. He developed acute respiratory distress and died of cardiopulmonary arrest. Autopsy revealed severe edema and erythema of the laryngopharynx and epiglottitis as well as tracheitis. The subject also had

significant coronary artery disease and renovascular disease consistent with his history of hypertension. The death was probably unrelated to asenapine.

2. **041013-48**: The subject was a 57 y.o. with Schizophrenia and AIDS, COPD, pyrexia, leukopenia, and cachexia. He was treated with low dose **asenapine** (600-3200 ug) for 41 days. The subject was found dead in his bed. Autopsy revealed **pulmonary embolism**, which was reported as the cause of death. The death was probably unrelated to treatment with asenapine.

3. **041021-125010**: The subject was a 33 y.o. male with Schizophrenia who was treated with **olanzapine** for 37 days. The cause of death was **completed suicide** by a multi-drug overdose. The death was probably unrelated to treatment with olanzapine.

4. **041023-363015:** This schizophrenic subject treated with **placebo** died from complications of a malignant thymoma.

5. **25517-115024**: The subject was a 25 y.o. male with Schizophrenia who was treated with asenapine 10-20 mg for 18 days. On day 18 he had an exacerbation of psychotic symptoms, and he **completed suicide** by hanging. The only preceding adverse event reported was hypertension. There were no reports of akathisia, mania, depression, or agitation during the study. The death does not appear to be related to treatment with asenapine.

6. **25517-127004**: The subject was a 32 y.o. male with Schizophrenia who was treated with **asenapine** 10-20 mg/day for 152 days. He **completed suicide** by hanging. There were no preceding adverse events reported such as akathisia, anxiety, mania, or agitation. Worsening of delusions and mild depression had been reported during the study. The death did not appear to be related to treatment with asenapine.
7. **25517-130013**: The subject was a 32 y.o. male with Schizophrenia who was treated with **asenapine** 10-20 mg/day for 256 days. He developed an exacerbation of Schizophrenia, and he **completed suicide** by hanging. There were no adverse events reports such as agitation, violent behavior, akathisia, anxiety, depression, or mania. The death does not appear to be related to treatment with asenapine.

8. **25517-131010**: The subject was a 25 y.o. male with Schizophrenia who was treated with **asenapine** 10-20 mg/day for 33 days. He **completed suicide** by hanging. There were no adverse events such as exacerbation of psychosis, depression, mania, agitation, akathisia, anxiety, or substance use. The death was probably not related to treatment with asenapine.

9. **25517-186007**: The subject was a 52 y.o. male with Schizophrenia who was treated with **asenapine** 10-20 mg for 45 days. On day 39, he developed a productive cough, fever, and shortness of breath. He was diagnosed with left lower lobe pneumonia, and he began treatments with i.v. ampicillin and oxygen. The

cause of death was lobar **pneumonia**. Other adverse events included worsening of Schizophrenia and fever. There were no reports of dysphagia or dystonia. The death was probably not related to treatment with asenapine.

10. **25517-204011**: The subject was a 41 y.o. with Schizophrenia who was treated with olanzapine for 375 days. He **completed suicide** by hanging while hospitalized.

11. **25517-242020**: The subject was a 50 y.o. male subject with Schizophrenia who was treated with **asenapine** 10-20 mg/day for 5 days. He was found dead in the hospital. Autopsy findings suggested that the subject died from **cardiac arrest** and **cerebrovascular accident**. Agitation was reported on the first day of study treatment. The death was probably not related to treatment with asenapine.

12. **25517-248014**: The subject was a 21 y.o. male with Schizophrenia who was treated with **asenapine** 10-20 mg/day for 7 days. The subject **completed suicide** by jumping from a building. No other medical history or adverse events were reported. There were no other details provided. The death was not related to treatment with asenapine.

13. **A7501006-40031005:** The subject was a 32 y.o. male with Bipolar Disorder and polysubstance abuse who was treated with asenapine 10-20 mg/day for 44 days. He was found dead in his home. He had a fresh puncture wound in his neck. Toxicology examination was positive for methadone, cocaine, diazepam, and diphenhydramine. The cause of death was accidental multiple drug overdose. The death does not appear to have been related to treatment with asenapine.

14. **A7501004-40111002**: The subject was a 49 y.o. male with Schizophrenia who was treated with **asenapine** 10-20 mg/day for 10 days. He **completed suicide** by jumping from a bridge and drowning. During the 10 days on treatment, the subject became stabilized and was discharged home. There was no evidence of suicidality or acute mood or psychotic symptoms before discharge. There were no adverse events such as suicidal ideation, mania, depression, akathisia, agitation, psychosis, or anxiety. Adverse events included sedation, dry mouth, hyperglycemia, and hypersalivation. The death did not appear to be related to treatment with asenapine.

14. **A7501004-41331009**: The subject was a 40 y.o. female treated with olanzapine for 12 days. She **completed suicide** by ingesting organophosphorous.

16. **041513-315504:** The subject was a 37 y.o. male with Schizophrenia who was treated with **asenapine** for 204 days. The subject was reported to have lost consciousness after an apparent seizure. The cause of death reported is **respiratory failure**. There are no other details available currently. The death was probably unrelated to treatment with asenapine.

17. **041513-368509:** The subject was a 23 y.o. male who was treated with **asenapine** for 96 days. The subject **completed suicide** by overdosing with clozapine. Other adverse events reported during the study included worsening of Schizophrenia, CPK increase, and extrapyramidal symptoms. The death was probably unrelated to treatment with asenapine.

18. **5543-125005:** The subject was a 64 y.o. male with Schizophrenia who was treated with **asenapine** for 31 days. The subject **completed suicide** by unknown method. No other details were provided for the case. The investigator judged that the death was possibly related to treatment with asenapine, but it is not clear what the rationale was.

19. **25543-143006: The death was unrelated to treatment with asenapine.** The subject was a 67 y.o. male with Schizophrenia who was treated with asenapine for 92 days. The cause of death was metastatic lung cancer. Three days after beginning study drug treatment, the subject was hospitalized because of abnormal findings on chest radiograph. The subject was a chronic smoker. The subject was diagnosed with mycobacterium tuberculosis. The subject had persistent respiratory symptoms as well as anemia. Further work-up revealed metastatic lung carcinoma.

20. **A7501007-50281012:** The subject was a 24 y.o. male with Bipolar Disorder who was treated with **olanzapine** for 178 days. He **completed suicide** by a gun shot wound to the head. No other details are available. The death was probably unrelated to treatment with olanzapine.

21. **A7501007-51241008:** A neonatal death occurred for a pregnant subject treated with asenapine. The subject, had 3 previous premature deliveries, and she delivered at 32 weeks gestation. No other details are available. The death was possibly related to treatment with asenapine.

22. **P25520-132017**: The subject was a 44 y.o. woman with Schizophrenia who was treated with **asenapine** for approximately 521 days. She was **found dead** in her home several days after her last study visit. The precise date of death and the cause of death are uncertain. Clinical laboratory findings included a low

    hemoglobin concentration and hematocrit at Weeks 52 and 64 and a low WBC at Week 64. The lymphocyte count was low at Weeks 40, 52, and 64. The neutrophil counts were normal, as were the platelets, Monocytes, Eosinophils, and basophils. There was no evidence of aplastic anemia or netropenia or agranulocytosis. Creatinine was mildly elevated at the Week 40 visit. On an unspecified date, the peripheral blood smear revealed hypochromia, anisocytosis, and poikylocytosis.

23. **P25520-241041**: The subject was a 57 y.o. woman with Schizophrenia who was treated with **asenapine** for 470 days. She died 4 days after her last dose of asenapine. The subject developed sudden **respiratory failure** and required treatment on a ventilator. The cause of death was **pulmonary embolism**. Other adverse events reported during the study were worsening of Schizophrenia and insomnia. The death was probably not related to treatment with asenapine.

24. **P25520-246021**:
The subject was a 57 y.o. male with Schizophrenia and depression who was treated with **asenapine** for 430 days. The death was attributed to **cardiac failure**. No other details were provided on the case report form.

25. **5443-121503:** The subject was a 59 y.o. male with Schizophrenia who was treated with **asenapine** for 363 days. 80 days after the last dose, he developed epigastric pain and hematemesis. Cause of death was **myocardial infarction**. The death was probably not related to treatment with asenapine.

26. **A7501021-1016002**: The subject was a 76 y.o. female with Schizophrenia. On the 28th day after her last dose of **asenapine**, she **died suddenly** after slumping in a chair. The death was attributed to cardio-respiratory arrest; however, no autopsy was performed. The death was probably not related to treatment with asenapine.

III. Completed Suicide and Suicidality Analysis

There was not an excess of completed suicides in the asenapine group, compared to the olanzapine group when adjusted for exposure. There were 8 suicides in the asenapine group and 4 in the olanzapine group. There were no suicides in the other treatment groups (placebo, risperidone, and haloperidol). For the involved studies with suicides, only one study had a placebo group (A7501004: a controlled, short-term mania study). All of the other involved studies were long-term, double-blind, active-control studies, without a placebo group.

The total asenapine exposure in the Schizophrenia and Mania programs was 625.5 person-years. There were 8 suicides in the asenapine group. Thus, the rate of suicide adjusted for asenapine exposure was 1.279 suicides per 100 person-years. The total olanzapine exposure in the Schizophrenia and Mania programs was 298.1 person-years. There were 4 suicides in the olanzapine group. Thus, the rate of suicide adjusted for olanzapine exposure was 1.342 suicides per 100 person-years. Thus, the adjusted rate in the olanzapine group was 1.049 times the rate in the asenapine group.

For the combined Schizophrenia program, there were 7 suicides in the asenapine group and 2 suicides in the olanzapine group. The total asenapine exposure in the Schizophrenia program was 573.3 person years. The total olanzapine exposure was 234.1 person-years. Thus, the adjusted rates of suicide were 1.22 suicides per 100 person-years in the

asenapine group and 0.854 suicides per 100 person-years in the olanzapine group. The rate in the asenapine group was 1.428 times the rate in the olanzapine group.

In the combined Mania program, there was one suicide in the asenapine group and 2 suicides in the olanzapine group. The total exposures in person-years were 51.2 and 64 in the asenapine and olanzapine groups, respectively. The suicide rates adjusted for exposure were 1.953 in the asenapine group and 3.125 in the olanzapine group (per 100 person-years of exposure.

Controlled Schizophrenia Trials

There were no completed suicides in the placebo-controlled trials in the asenapine, placebo, olanzapine, risperidone, or haloperidol groups. In the placebo-controlled Schizophrenia trials, the exposures in person-years were: 67.6 for asenapine, 15.3 for olanzapine, 38.8 for placebo, 9.8 for haloperidol, and 9.0 for risperidone.

Controlled Mania Trials

In the placebo-controlled Mania trials, there was one suicide in the asenapine group and one suicide in the olanzapine group. There were no suicides in the placebo group. In Study A7501004, the suicide in the asenapine group occurred at Day 12, and the suicide in the olanzapine group occurred at Day 13.

The exposures in the acute mania studies were 17.2 person-years for asenapine and 20 person-years for olanzapine. (The placebo exposure was 9 person-years). The exposure-adjusted rate of suicide per 100 person years was 5.81 for asenapine and 5.0 for olanzapine. Thus, the rate in the asenapine group was 1.16 times the rate in the olanzapine group.

Long-term, Double-blind, Active-controlled Schizophrenia Studies (no placebo group)

In the long-term, active-controlled Schizophrenia studies, there were 7 suicides in the asenapine group and 2 suicides in the olanzapine group. In Study 25517, there were 5 suicides in the asenapine group and one suicide in the olanzapine group. The study design was as follows: Study 25517 was a large, 52-week, double-blind, active-controlled (olanzapine) study, without a placebo control. There were 908 subjects in the asenapine group and 311 subjects in the olanzapine group. In the asenapine group, the suicides occurred on days 8, 18, 33, 152, and 257. In the Olanzapine group, the suicide occurred on Day 376.

In Study 041513, there was one suicide in the asenapine group (Day 96) and none in the haloperidol group. There was no olanzapine group. This study was a 52-week, double-blind, active-controlled (haloperidol) study without a placebo control.

In Study 25543, one subject in the asenapine group completed suicide (on Day 31), and one subject in the olanzapine group completed suicide (Day 191). Study 25543 was a long-term, active-controlled (olanzapine) study of negative symptoms in Schizophrenia.

The exposure for the long-term Schizophrenia studies was 505.7 person-years for the asenapine group and 218.8 person-years in the olanzapine group. The suicide rates adjusted for exposure were 1.384 suicides per 100 person-years of exposure in the asenapine group and 0.941 suicides per 100 person-years of exposure in the olanzapine group. Thus, the adjusted rate in the asenapine group was 1.47 times the rate in the olanzapine group.

Long-term, Double-blind, Active-controlled Mania Studies (no placebo group)

In the long-term Mania studies, there was one suicide in the Olanzapine group. There were no suicides in the asenapine group. The total asenapine exposure was 34 person-years, and the total olanzapine exposure was 44 person-years. The adjusted rate of suicide in the olanzapine group in these studies was 2.27 suicides per 100 person-years.

Sponsor's Suicidality Adverse Events Analysis

Based on review of suicidality adverse event data presented in the tables below, treatment with asenapine (10-20 mg/day) does not appear to be associated with an increase in suicidality, compared to placebo or olanzapine.

Table 83 Adverse events related to suicidality (combined phase 2/3 studies, cohort E)

Adverse Event SOC/ Preferred Term n (%)	Placebo (N=706)	Asenapine			Risp 3 mg BID (N=120)	Halo 4 mg BID (N=115)	Olan 5-20 mg QD (N=899)
		<5 mg BID (N=298)	5-10 mg[a] BID (N=1953)	All (N=2251)			
Psychiatric disorders							
Suicidal and self-injurious behaviours	7 (1.0)	9 (3.0)	37 (1.9)	46 (2.0)	3 (2.5)	0	18 (2.0)
SAEs	2 (0.3)	3 (1.0)	33 (1.7)	36 (1.6)	2 (1.7)	0	17 (1.9)
Discontinuations	4 (0.6)	2 (0.7)	15 (0.8)	17 (0.8)	2 (1.7)	0	7 (0.8)
Completed suicide	0	0	6 (0.3)	6 (0.3)	0	0	2 (0.2)
Intentional self injury	1 (0.1)	1 (0.3)	2 (0.1)	3 (0.1)	0	0	2 (0.2)
Self injurious ideation	0	0	1 (0.1)	1 (0.04)	0	0	0
Suicidal behaviour	1 (0.1)	1 (0.3)	0	1 (0.04)	0	0	1 (0.1)
Suicidal ideation	5 (0.7)	8 (2.7)	22 (1.1)	30 (1.3)	2 (1.7)	0	6 (0.7)
Suicide attempt	1 (0.1)	0	9 (0.4)	9 (0.4)	1 (0.8)	0	7 (0.8)
Patient exposure years	52	34	611	645	21	10	285
Cases of completed suicide	0	0	6	6	0	0	2
Incidence[b]	0	0	0.98	0.93	0	0	0.70
Cases of suicidal and self-injurious behaviours	7	9	37	46	3	0	17
Incidence[b]	13.49	26.24	6.06	7.13	14.29	0	5.97
Cases of suicidal ideation	5	8	22	30	2	0	6
Incidence[b]	9.63	23.32	3.60	4.65	9.52	0	2.11
Cases of suicidal attempt	1	0	9	9	1	0	7
Incidence[b]	1.93	0	1.47	1.40	4.76	0	2.46

[a] fixed and flexible doses
[b] incidence /100 exposure years
Risp=risperidone, Halo=haloperidol, Olan=olanzapine
Source: 2.7.4 Appendix Tables 2.2.E, 2.18.E, 2.26.2.E, and 2.30.E

Table 84 Adverse events related to suicidality (6-week and long-term schizophrenia studies, cohorts A and B)

Adverse Event	Placebo (N=503)	Asenapine			Risp 3 mg BID (N=120)	Halo 4 mg BID (N=115)	Olan 5-20 mg QD (N=505)
		<5 mg BID (N=298)	5-10 mg[a] BID (N=1480)	All (N=1778)			
Patient exposure years	42.9	34.3	559.0	593.3	21.0	9.8	234.1
Cases of suicidal and self-injurious behaviours	5 (1.0)	9 (3.0)	27 (1.8)	36 (2.0)	3 (2.5)	0	11 (2.2)
Incidence[b]	11.66	26.24	4.83	6.07	14.29	0	4.70
Cases of completed suicide	0	0	5 (0.3)	5 (0.3)	0	0	1 (0.2)
Incidence[b]	0	0	0.89	0.84	0	0	0.43
Cases of suicidal ideation	4 (0.8)	8 (2.7)	15 (1.0)	23 (1.3)	2 (1.7)	0	3 (0.6)
Incidence[b]	9.32	23.32	2.68	3.88	9.52	0	1.28
Cases of suicidal attempt	1 (0.2)	0	8 (0.5)	8 (0.5)	1 (0.8)	0	5 (1.0)
Incidence[b]	2.33	0	1.43	1.35	4.76	0	2.14

a fixed and flexible doses
b incidence/100 exposure years
Risp=risperidone, Halo=haloperidol, Olan=olanzapine
Source: 2.7.4 Appendix Table 2.26.2.1.E

Table 85 Adverse events related to suicidality (3-week and 12-week bipolar mania studies, cohorts C and D)

	Placebo (N=203)	Asenapine 5-10 mg BID flexible dose (N=379)	Olanzapine 5-20 mg QD flexible dose (N=394)
Patient exposure years	9.0	51.6	50.8
Cases of suicidal and self-injurious behaviours	2 (1.0)	10 (2.6)	6 (1.5)
Incidence[a]	22.22	19.38	11.81
Cases of completed suicide	0	1 (0.3)	1 (0.3)
Incidence[a]	0	1.94	1.97
Cases of suicidal ideation	1 (0.5)	7 (1.9)	3 (0.8)
Incidence[a]	11.11	13.57	5.91
Cases of suicidal attempt	0	1	2
Incidence[a]	0	1.94	3.94

[a] incidence/100 exposure years
Source: 2.7.4 Appendix Table 2.26.2.2.E

Intersept Scale for Suicidal Thinking

Combined Acute and Long-term Schizophrenia and Mania Studies

An analysis of the Intersept Scale for Suicidal Thinking (ISST) was performed for some studies. The results for the available combined Phase 2/3 data demonstrate a decrease in the mean total score for all treatment groups throughout the study and at endpoint (-0.1 placebo, -0.1 asenapine 5-10 mg BID, -0.2 haloperidol, and -0.2 olanzapine). There appears to be no significant differences among the treatment groups.

Controlled Schizophrenia Studies

An analysis of the ISST data was performed for 3 controlled, short-term Schizophrenia studies (041021, 041022, and 041023). There was a small increase in the mean total score in all treatment groups at endpoint (0.4 for placebo, 0.5 for all asenapine 5-10 mg BID, 0.2 for haloperidol, and 0.6 for olanzapine). There were no significant differences among the treatment groups.

Mania Study (12-week)

An analysis of the ISST data was performed for the 12-week Bipolar Mania study. The results of the mean total score and change from baseline on Day 28, Day 63, and endpoint show a small increase in the mean total score across all treatment groups at endpoint (0.4 for asenapine 9- week, 0.1 for asenapine 12-week, and 0.2 for olanzapine 12-week). The results were similar between the olanzapine and asenapine groups.

Conclusion

An analysis of the Intersept Scale for Suicidal Thinking (ISST) showed there were no differences in scores among the treatment groups.

IV. Selected Serious Adverse Events and Other Adverse Events of Interest

This section contains a discussion of most of the medical serious adverse events in the asenapine programs for Schizophrenia and Mania. The majority of serious adverse events in all treatment groups in the asenapine program were psychiatric adverse events related to the illnesses under treatment (Schizophrenia, Schizoaffective Disorder, and Bipolar Disorder). The table below illustrates this finding. In the asenapine groups, 94% of all serious adverse events were psychiatric adverse events.

Serious adverse events in cohort E: proportion of SAE that were psychiatric				
Asenapine	Placebo	Olanzapine	Risperidone	haloperidol
306/325 (94%)	51/61 (84%)	77/87 (89%)	17/21 (81%)	8/8 (100%)

A. Cardiovascular Adverse events

25501-1. A 22 y.o. healthy volunteer with a resting HR of 58 bpm received a 30-mg oral dose of asenapine. Approximately 2.5 hours after the dose, the subject sat up in bed and felt dizzy and nauseated. The ECG telemetry strip showed a HR slowing and an 8.7-second pause. This was followed by heart block and nodal bradycardia., which spontaneously converted to sinus rhythm. He had a similar episode 2 hours later. He recovered from the episodes.

Neurally Mediated Reflex Bradycardia

The subject above probably experienced neurally mediated reflex bradycardia (NMRB). NMRB is not unexpected with a drug that has alpha-1-adrenergic antagonist properties. The Cardiorenal consultants discuss this phenomenon. The consultants agree with the sponsor's interpretation that the cardiovascular adverse event was related to NMRB. There were several similar cases in healthy volunteers who received asenapine in the clinical pharmacology studies. There was one possible case of NMRB in a subject with Schizophrenia who was treated with asenapine. Neurally Mediated Reflex Bradycardia (NMRB) is a benign, self-limiting event, and the most common cause of vasovagal syncope. It involves central hypovolemia, vasodepression, and bradycardia. Bradycardia can be accompanied by periods of asystole that are due to either sinus pause or heart block. NMRB can occur with or without sinus pause and is typically associated with postural challenge. Healthy, young volunteers with a high resting vagal tone display a higher incidence of NMRB than do psychiatric patients.

041033-101012
The subject was a 44 y.o. healthy volunteer who was treated with asenapine (one dose) and fluvoxamine (6 doses). The subject developed bradycardia and sinus pauses during sleep while on telemetry. He was wakened and remained asymptomatic. The subject recovered. The event was thought to be related to study drug treatment. This was probably a case of neurally mediated reflex bradycardia related to treatment with asenapine.

A7501001-10020007:
The subject was a 51 y.o. male with Schizophrenia who participated in a dedicated QT study. He was treated with one dose of asenapine. About 1.5 hours after the dose, he experienced **severe bradycardia**, and he was taken to an emergency room. He had ECG changes suggestive of myocardial infarction. He did not have chest pain. He was treated with oxygen, atropine, aspirin, metoprolol, tenectplase, lidocaine, and magnesium, and he was admitted to a cardiac care unit. Coronary angiogram was negative. He developed atrial fibrillation which resolved spontaneously. The event was possibly related to treatment with asenapine. This was possibly a case of neurally mediated reflex bradycardia.

Arrhythmias

The Cardiorenal consultants note the following:

In Cohort E (combined Phase 2/3 for Bipolar Mania and Schizophrenia), the incidence of tachycardia (17), sinus tachycardia (5) sinus bradycardia (13), ventricular extrasystoles (2) were higher than in the placebo group but comparable to olanzapine. There was 1 case of atrial fibrillation in the placebo group. There were 2 cases of "cardiac flutter" and 1 case of WPW syndrome with asenapine. The proportion of patients who experienced heart blocks was similar in the asenapine (BBB-1, LBBB-2, and RBBB-3) and olanzapine groups.

The most common arrhythmias seen in all studies were tachycardia and bradycardia and occurred in the subjects dosed between 5-10 mg b.i.d. Narratives for the patients with cardiac flutter and WPW syndrome were not available for review. However, the number of cases of atrial fibrillation/flutter was similar in active and placebo groups in all cohorts.

In Study A75016, (per protocol), healthy subjects were monitored by ECG telemetry. There were asymptomatic episodes of the following: bradycardia (15); tachycardia (24); sinus pause (18); junctional rhythm (4); bradycardia with junctional rhythm (4); extrasystole (1); sinus bradycardia (1) There were no deaths, serious adverse events, or discontinuations due to adverse events in this study.

25517-192001: The subject was a 38 y.o. male with Schizophrenia who was treated with asenapine 10-20 mg/day for 365 days. He had a history of chest pain and hypertension. From day 18-21, he had chest pain. Cardiology consult findings included a positive troponin test. Angiogram demonstrated coronary artery occlusion. The diagnosis was **myocardial infarction**. Treatment with asenapine was resumed, and the subject recovered. The SAE was probably not related to treatment with asenapine.

25517-22003: The subject was a 50 y.o. male with Schizoaffective Disorder who was treated with asenapine 10-20 mg/day for 281 days. On Day 151, he was hospitalized due to chest pain and shortness of breath. The diagnosis was **cardiac failure**. The subject continued taking asenapine in the study. The SAE was probably not related to treatment with asenapine.

041021-138010: The subject was a 32 y.o. male with Schizophrenia who was treated with asenapine 5 mg/day for 42 days. He was asymptomatic, but the planned ECG showed marked bradycardia, supraventricular complexes and intraventricular conduction delay (RBBB). He was hospitalized for observation, and study medication was discontinued. The subjects recovered. Other adverse events included weight gain and increased appetite.

041033-101018:
The subject was a 44 y.o. healthy volunteer who was treated with asenapine (one dose) and fluvoxamine. The subject had acute onset of chest pain and dyspnea. A ventilation-perfusion scan confirmed the diagnosis of **pulmonary embolism**. Two relatives had a history of pulmonary embolism. The event was unlikely to have been related to treatment with study drugs.

041001-20 The subject was a 33 y.o. male with Schizophrenia who was treated with low-dose asenapine (400 mcg) for 7 days. While on telemetry per protocol, he developed asymptomatic non-sustained (10 beats/4 seconds) **ventricular tachycardia** (150 bpm). He continued study medication after evaluation by a cardiology team. It was thought that the event was unlikely to be related to treatment with asenapine.

25525-101029:
A healthy subject developed atrial fibrillation during treatment with asenapine and paroxetine as part of a drug-drug interaction study. The event was probably related to treatment with either one or both drugs. The subject had chemical cardioversion and recovered.

25517-192001: The subject was a 38 y.o. male with Schizophrenia who was treated with asenapine 10-20 mg/day for 365 days. He had a history of chest pain and hypertension. From day 18-21, he had chest pain. Cardiology consult findings included a positive troponin test. Angiogram demonstrated coronary artery occlusion. The diagnosis was **myocardial infarction**. Treatment with asenapine was resumed, and the subject recovered. The SAE was probably not related to treatment with asenapine.

25517-22003: The subject was a 50 y.o. male with Schizoaffective Disorder who was treated with asenapine 10-20 mg/day for 281 days. He was hospitalized due to chest pain and shortness of breath. The diagnosis was **cardiac failure**. The subject continued taking asenapine in the study. He had a history of coronary artery disease, congestive heart failure, hypertension, smoking, subarachnoid hematoma, obesity, and adrenal adenoma, hypercholesterolemia. Other adverse events reported during the study were hematuria, hyperuricemia, and headache, aggravation of psychotic disorder. The SAE was probably not related to treatment with asenapine

41512-224505: The subject was a 55 y.o. female with Schizophrenia and a history of hypertension. She had discontinued treatment with antihypertensives and developed an acute episode of **hypertension**. She resumed antihypertensive medication and became stable. The SAE was probably not related to treatment with asenapine.

Syncope:

25517-109003. The subject was a 46 y.o. male with a diagnosis of Schizophrenia. He was treated with asenapine 10-20 mg BID for 46 days. On Day 46, the subject had an episode of **syncope**. He had been on a long walk in the heat, and he appeared to be dehydrated.

He was evaluated in a hospital, and no specific cause of the syncope was discovered. He had a history of gout and anxiety. Preceding adverse events during the trial included sweating, hyperglycemia, insomnia, agitation, diarrhea, depression, paranoia, anxiety, and shivering.

25517-137002. The subject was a 22 y.o. male with a history of Schizophrenia. H was treated with asenapine 10-20 mg/day for 28 days. One day after the last dose, he experienced **syncope** (witnessed). He was unconscious for less than a minute. The subject reported that he had felt dizzy immediately prior to the syncope. He was hospitalized for a work up of the syncopal episode. No specific abnormality was found. The subject reported that he had a low intake of fluids for several days before the event. Other adverse events during the study included dizziness, sedation, nausea, and vomiting.

A7501006-50041001. The subject was a 58 y.o. female with Bipolar Disorder who was treated with asenapine 10-20 mg/day for 2 days. The subject awoke one morning feeling dizzy, hot, weak, thirsty, and hungry. The subject fell and might have lost consciousness. It was presumed that this was an episode of **syncope.** Medical history was significant for hypothyroidism, hypercholesterolemia, smoking, and insomnia. Preceding adverse events included headache, somnolence, hot flashes, and depressed mood.

A7501021-10231002: The subject was a 75 y.o. male with Schizophrenia who was treated with asenapine. Patient developed uremia and acute mental status changes and syncope 3 days after beginning treatment with asenapine. Subject had a history of coronary artery disease, hypertension, and peripheral artery disease, and patent foramen ovale.

25517-247010.
The subject was a 43 y.o. female with Schizophrenia who was treated with one dose of asenapine 5 mg. She experienced nausea, vomiting, dizziness, **syncope** and angioneurotic edema on the same day. The syncope occurred approximately 40 minutes of the dose. The subject did not have any known drug allergies or significant medical history. The investigator concluded that the events were probably related to treatment with asenapine.

B. Hematologic Adverse Events

1. Neutropenia

In the asenapine program, there were 9 subjects who had the adverse event neutropenia. For the cases of neutropenia, there were 4 in the asenapine group, 2 in the placebo group, and 3 in the olanzapine group. None of the cases in the asenapine group were serious adverse events. One olanzapine case was a serious adverse event. One asenapine case and 2 olanzapine cases of neutropenia led to discontinuation of treatment.

25517-189002. The subject was a 21 y.o. Black female with Schizophrenia who was treated with **asenapine** 10-20 mg/day. At screening, her absolute neutrophil was in the low normal range (1.9; lower limit of normal = 1.8). Throughout most of the study, her ANC was in the normal range; however, the ANC was low on one occasion (1.5 at Week 16). Her ANC was 2.5 on subsequent assessments, and she completed the study (through Week 32). There were no adverse events such as fever or infection. Medication was not discontinued.

P25520-238006. The subject was a 25 y.o. white male with Schizophrenia who was treated with **asenapine** 10-20 mg/day. At baseline, his ANC was 2.4. At Week 100, his ANC was low (1.3). Subsequently, the ANC fluctuated between 1.5 and 1.7. It was thought that the low ANC was not due to treatment with asenapine, and asenapine was continued. The subject did not have any adverse events consistent with infection. He completed the study through Week 148.

P25520-181037. The subject was a 48 y.o. white male with Schizophrenia who was treated with **asenapine** 10-20 mg/day. He had the adverse event of neutropenia on Day 621 (ANC = 1.5), which resolved on Day 626 (ANC = 2.5).

041002-1212: The subject was a 41 y.o. African American female with Schizophrenia, treated with **asenapine**. On the planned lab assessment on Day 7, it was noted that she had a decrease in WBC and neutrophil count. At screening, the WBC was 3720 and the ANC was 2630. On Day 7, the WBC was 3130 and the ANC was 750. Study medication was discontinued. On Day 8, the subject developed a fever. On follow-up lab assessment 7 days later, the WBC and ANC had increased to 3420 and 1260. Also of note, the patient was treated concomitantly with mirtazapine which has a risk of neutropenia and agranulocytosis. There were no other reported adverse events.

There were 3 cases of asenapine-treated subjects with an AND < 500. None of these were reported as an adverse event, and none of these led to discontinuation of treatment with asenapine. Most of the cases of ANC between 500 and 1500 were not associated with clinical symptoms. Generally, the low neutrophil count values were isolated and transient. There were no cases of agranulocytosis. Most of these cases were not reported as adverse events, as the investigators did not consider the laboratory findings clinically relevant. In several cases, there were concomitant medications or comorbid medical conditions present known to cause neutropenia.

2. Anemia

25517: 221005: The subject was a 47 y.o. female with Schizophrenia who was treated with **asenapine** 10-20 mg/day for 367 days. On Day 42 lab assessment, she was found to have a decreased hemoglobin and hematocrit. She was hospitalized and diagnosed with **anemia**. Five weeks later, the anemia resolved. She continued study treatment with asenapine. The subject had a history of anemia and hematuria. Other adverse events

during the study: hematuria and decreased appetite. The SAE was probably not related to treatment with asenapine.

3. Thrombocytopenia

There was one asenapine case of thrombocytopenia reported as an adverse event. This was not a serious adverse event, and it was not associated with discontinuation of study treatment. Currently, the details of the case and the subject identification number and are not available. We could request additional information from the company.

C. Hepatotoxicity

There were no Hy's Law cases in the asenapine program. While there were cases of transaminase elevation > 3 times normal, the cases were not associated with elevations of bilirubin > 2 times the normal. There were no cases of elevated bilirubin reported as adverse events, serious adverse events, or as reasons for discontinuation

25517-174001: The subject was a 43 y.o. female with Schizophrenia who was treated with asenapine 10-20 mg/day for 26 days. On Day 16, it was noted that the subject had elevated ALT. The highest **ALT** was 90, and the highest AST was 44. Study treatment with asenapine was discontinued. The SAE was possibly related to treatment with asenapine.

D. Rhabdomyolysis Cases

There were several cases of rhabdomyolysis reported as adverse events in the asenapine, and there was one in the olanzapine group. The cases do not suggest that asenapine causes muscle injury. In all of the cases, there were other factors that appear to have contributed to adverse events.

1. Subject 25517-204006 (asenapine)

The subject was a 35-year-old female who started treatment with asenapine (5-10 mg BID) on 7 June 2004. On 21 August 2004 she drank about 5 to 6 liters of water and was hospitalized on the same day after having a convulsive seizure associated with a sudden episode of loss of consciousness with dystonic movements and loss of urinary sphincter control. Afterward, the subject remained hyporeactive, and without psychomotor agitation. Dizziness, nausea, and vomiting also occurred and resolved spontaneously. Abnormal levels of sodium, chloride, potassium, calcium, and magnesium were noted together with increased levels of urea. She was treated with hypertonic saline, dextrose, and furosemide and was diagnosed with hypo-osmolar hyponatremia secondary to primary polydipsia.

Twenty-four hours later, the subject was found to have increased levels of CPK and hepatic enzymes. She was subsequently diagnosed with rhabdomyolysis with a peak CPK value of 30,402 U/L. After treatment, the subject's plasma sodium resolved, the subject

felt more reactive and developed a fever. Twenty-four hours later, osmolality normalized and the subject remained without fever and was conscious. The CPK was noted to be decreasing at the time of the discharge, and the subject eventually recovered. Study medication was interrupted on 22 August 2004. Study medication was restarted on the same day, and it was permanently discontinued on 24 August 2004. This event was considered by the investigator to be possibly related to study medication.

A summary of her sodium, CPK, creatinine, and BUN values are summarized in Table 1.

Table 1. Laboratory Values for Patient 204006, Study 25517

	21-Aug-04	22-Aug-04	23-Aug-04	24-Aug-04	25-Aug-04	27-Aug-04	1-Sep-04
Sodium (Na)	114	134		141	140	140	140
CPK		1,444	30,341		30,402	8,376	197
Creatinine	0.6	0.7					
BUN	6.2	6.8					

Note: Shaded areas denote post-treatment period. Treatment period was from 7 June 2004, to 24 August 2004.

The laboratory values show a sodium value below normal (114 mmol/L) on the day she was reported to have had excessive water intake, and a subsequent seizure; her CPK values rose thereafter. There was no muscle-related adverse events reported or apparent renal involvement. From the details of this case, the precipitating event of her CPK elevations was likely due to her seizure and/or excessive water intake and hyponatremia, which could have precipitated the seizure; however, details are lacking to substantiate this. CPK elevations in this case appear may be more likely due to the patient's excessive water intake and hyponatremia/seizure rather than due to study medication.

2. Subject 25517-102009 (asenapine)

This 68-year-old female subject started asenapine (5-10 mg BID) on 24 September 2004. She could not be contacted by telephone for 2 days, and on 26 November 2004, the staff of the study hospital and the police checked on the subject. The subject was found collapsed in her home. She was taken to the emergency department. Upon admission, vital signs were stable, but she had a widespread expiratory wheeze. She also had signs of bruising. A cerebrovascular accident was ruled out by MRI, and she was diagnosed with rhabdomyolysis, acute renal failure, collapse, hyponatremia, left ventricular failure (secondary to aggressive hydration), and a urinary tract infection (E. coli). Serotonin syndrome and delirium were initially suspected, but eventually not confirmed.

Study medication was permanently discontinued on 26 November 2004. During the hospitalization, the following medications were administered: salbutamol, normal saline, omeprazole, sodium hydrogen carbonate, haloperidol, furosemide, heparin, docusate sodium, temazepam, sodium bicarbonate, paracetamol, risperidone, citalopram hydrobromide, levothyroxine sodium, and acetylsalicylic acid. During hospitalization, the subject was alert and oriented. She improved gradually, and on 3 December 2004, she

had recovered and was discharged from the hospital. This event was considered by the investigator to be possibly related to study medication.

Table 2 is a summary of her sodium, CPK, creatinine, and BUN values:

Table 2. Laboratory Values for Patient 102009, Study 25517

	17-Sep-04	20-Sep-04	1-Oct-04	2-Oct-04	15-Oct-04	18-Oct-04	5-Nov-04	8-Nov-04	26-Nov-04	27-Nov-04	28-Nov-04	29-Nov-07	30-Nov-04	1-Dec-04	2-Dec-04
Sodium (Na)	141	141	138	138	141	141	139	139	113	122	132	133	134	137	13
CPK									82303	10137	76880	44808	15184	5079	
Creatinine	70	70	80	80	80	80	80	80	121	168	138	111	70	74	
BUN	6.6		4.9		6.2		6.8		8.9	13.7	13.5	7.6	3.4	3.6	

Note: Shaded areas denote pre-treatment and post-treatment periods. Treatment period was 24 September 2004 to 26 November 2004. BUN = blood urea nitrogen. CPK = creatine phosphokinase.

3. Subject CNS-9241-61402 (asenapine)

This 44-year-old male began treatment with asenapine on 15 June 1993 (oral formulation, 2-3 mg BID). On 29 June 1993, the subject had from polydipsia. Disturbed consciousness (delirium) and incontinence of urine following polydipsia were observed on 27 July 1993; water intoxication was considered as a diagnosis. Water drinking was limited. On the same day, the subject fell and sustained a laceration on the head that required suturing. Mild dysbasia, dysarthria, and increased CPK were observed on 28 July 1993. Study medication was continued since both dysbasia and dysarthria were improved. There was no disturbance in consciousness, hyperthermia, muscle rigidity, shaking palsy, autonomic nervous system symptoms, muscle swelling, or pain.

On 30 July 1993, asenapine was discontinued due to abnormally high CPK concentrations. An abnormal urinalysis (i.e., urine glucose 2+, urine protein 1+, and urine occult blood 3+) was observed on the same day.

Rhabdomyolysis following water intoxication was considered by the investigator, and an infusion of 1,500 ml/day was started. His laboratory data normalized and his urine glucose, protein, and occult blood became negative on 4 August 1993. The subject subsequently withdrew from the trial, after an administration period of 46 days, due to the rhabdomyolysis; relationship to study medication was not reported by the investigator.

Table 3 is a summary of his sodium, CPK, creatinine, and BUN values.

Table 3. Laboratory Values for Patient 61402, Study CNS-9241, 1993

	15-Jun-93	29-Jun-93	13-Jul-93	28-Jul-93	30-Jul-93	31-Jul-93	2-Aug-93	4-Aug-93	6-Aug-93	9-Aug-93	11-Aug-93	18-Aug-93
Sodium (Na)	140	135	140	131	142	140	140	141	143	141	143	140
CPK	81	151	257	3640	50490	54200	29810	6840	971	304	284	133
Creatinine	0.9	0.9	1.0			0.7				0.8		
BUN						13.1				19.5		

Note: Shaded areas denote post-treatment periods. Treatment period was from 15 June 1993 to 30 July 1993. BUN = blood urea nitrogen. CPK = creatine phosphokinase.

Review of the laboratory values shows a low sodium value (131 mmol/L) the day after he was reported to have polydipsia, possible water intoxication, disturbed consciousness and

a fall resulting in a head laceration. Although CPK values were elevated (257 U/L) 15 days prior to the events, CPK started to rise substantially after his excessive water intake, disturbed consciousness, and fall. There was no evidence of renal impairment, and no muscle-related adverse events were reported. The CPK elevations may be related to the fall and subsequent head trauma. It is possible that the CPK elevations were due to study medication.

4. Subject 041-002-0525 (asenapine)

The subject was a 53-year-old male with a history of intermittent hyponatremia and a history of alcohol dependence (in remission). He was treated with asenapine (0.8 mg BID) from 7 May 1999 to 10 June 1999. On 23 June 1999, 13 days after his last dose of asenapine, the subject was found unconscious on the floor of his apartment. He was admitted to the hospital and diagnosed with (b) (4) (according to the investigator). He was treated with levofloxacin, potassium chloride, Neutra-Phos, multivitamins (MVI), thiamine, and folic acid. The subject recovered and was discharged from the hospital on (b) (4). This event was not considered by the investigator to be related to study medication.

Table 4 summarizes the subject's sodium, CPK, creatinine, and BUN values.

Table 4. Laboratory Values for Patient 0525, Study 041-002, 1999

	30-Apr-99	13-May-99	20-May-99	27-May-99	3-Jun-99	10-Jun-99	23-Jun-99	24-Jun-99	25-Jun-99	26-Jun-99	27-Jun-99	28-Jun-99	29-Jun-99	30-Jun-99	2-Jul-99	3-Jul-99
Sodium (Na)	122	132	128	129	125	126	117	123	125	123	125	128	122	126	127	126
CPK							7832	6766	3493	2861	1559	1007				
Creatinine	0.6	0.7	0.7	0.6	0.5	0.4										
BUN	9	10	13	15	12	8										

Note: Shaded areas denote pre-treatment and post-treatment periods. Treatment period was from 7 May 1999 to 10 June 1999. BUN = blood urea nitrogen. CPK = creatine phosphokinase.

The subject had a history of hyponatremia, and he had low sodium values throughout the study. His lowest sodium value of 117 mmol/L occurred 13 days after his last dose of asenapine and coincident to his collapse. CPK started to rise at the same time. From the case details, the CPK elevations appear to be more likely due to his collapse/hyponatremia than to study medication.

5. Subject A7501004-40231005 (olanzapine)

The subject was a 39-year-old male with a history of polysubstance abuse (crack cocaine, alcohol, marijuana). He was hospitalized on (b) (4), due to an exacerbation of Bipolar Disorder, and was started on olanzapine treatment on 2 August 2005 (15 mg QD). He was discharged from the hospital on (b) (4) and the next day (b) (4) (b) (4) presented to the emergency room with lower abdominal pain and gastrointestinal bleeding. He was hospitalized and was diagnosed with acute renal failure and rhabdomyolysis (according to the investigator) secondary to cocaine use. Olanzapine was

discontinued on 9 August 2005. He recovered and was discharged from the hospital on (b) (4). This event was considered by the investigator to be unrelated to study medication.

Table 5 summarizes his sodium, CPK, creatinine, and BUN values.

Table 5. Laboratory Values for Patient 40231005, Study A7501004

	29-Jul-05	30-Jul-05	2-Aug-05	11-Aug-05	13-Aug-05
Sodium (Na)	141	141	141	144	144
CPK	85	85	153	269	269
Creatinine	1.1	1.1	1.0	0.9	0.9
BUN	16		16	9	

Note: Shaded areas denote pre-treatment and post-treatment periods. Treatment period was from 2 Aug 2005 to 9 Aug 2005. BUN = blood urea nitrogen

Review of his available laboratory values reveals a mild CPK elevation (269 U/L) with no evidence of renal impairment (although the case details indicate renal failure). No muscle-related adverse events were reported. The events of this case appear to be secondary to his cocaine use rather than to study medication.

E. Seizure

041002-102. The subject was a 36 y.o. female with a diagnosis of Schizophrenia. She was treated with low dose asenapine (400 mcg/day). On Day, she had a witnessed generalized seizure. A CT scan and EEG were normal. There were no other reported adverse events. The subject was discontinued from the study. The subject had a history of headache, hypothyroidism, and insomnia.

25517-146005. The subject was a 49 y.o. male with Schizophrenia. He was treated with asenapine 10-20 mg/day for 6 days. Two days after his last dose of asenapine, he was hospitalized due to a seizure. He later resumed treatment with asenapine. Ten days later, he had 3 more seizures in one day. Asenapine was discontinued. Medical history included high blood pressure, overweight, pulmonary edema, hypercholesterolemia, diabetes mellitus. There were no other adverse events reported during the study.

25517-219008. The subject was a 33y.o. female with a history of Schizoaffective disorder who was treated with asenapine 10-20 mg/day for 39 days. She had a single generalized seizure. She had a history of seizure two years previously, treated with valproate. She also had a history of diabetes mellitus. Depression was also reported during the study.

25517-223011. The subject was a 34 y.o. female with a history of Schizoaffective Disorder. She was treated with asenapine 10-20 mg/day for 176 days. The subject had neurological symptoms and EEG findings consistent with focal seizure (temporal lobe). She was discontinued from the study and treated with carbamazepine. Other adverse events included auditory hallucinations, insomnia, headache, and sedation.

V. Recommendations

It would probably be useful to request the following additional information from the sponsor:

- The total number of unique subjects exposed to asenapine and other treatments in the asenapine program
- The total exposure to asenapine and other treatments in person-years.
- Narratives of cases of anemia and thrombocytopenia that are referred to in the safety summaries (case numbers are not available).

_____

Robert Levin, M.D., June 27, 2008
Medical Officer,
FDA CDER ODE1 DPP HFD 130

cc: NDA 22-117
HFD 130
T Laughren
M Mathis
G Zornberg
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Levin
6/27/2008 04:12:37 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA/Serial Number:	22-117 (N000)
Drug Name:	Sycrest® (asenapine maleate)
Indication:	schizophrenia
Applicant:	Organon
Dates:	Date of Document: 8/30/2007
	PDUFA Due Date: 6/30/2008
Review Priority:	Standard
Biometrics Division:	Biometrics I, HFD-710
Statistical Reviewer:	Yeh-Fong Chen, Ph.D.
Concurring Reviewers:	Peiling Yang, Ph.D.
	H. M. James Hung, Ph.D.
Medical Division:	Division of Psychiatry Drug Products, HFD-130
Clinical Team:	Clinical Reviewer: Robert Levin, M.D.
	Clinical Team Leader: Gwen Zornberg, M.D.
Project Manager:	Keith Kiedrow

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1. EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

The sponsor submitted four completed studies to evaluate asenapine's efficacy in treatment of schizophrenia. On the face, only two studies (Studies 41004 and 41023) showed statistically significant efficacy findings. After evaluation, this reviewer determined that only data for asenapine 5 mg BID from Study 41023 showed clearly statistically significant findings. Even though the analysis results for Study 41004 seemed to suggest a statistically significant difference in comparison with placebo, the strength of evidence for asenapine's efficacy based on this study may be weak due to the very high dropout rate. In particular, the dropout rates between the asenapine and placebo groups were very different. Regarding Study 41023, the fact that asenapine 10 mg BID performed numerically worse than asenapine 5 mg BID also adds difficulty to the interpretion of the asenapine's efficacy finding.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

In this NDA submission, the sponsor included results of trials to demonstrate asenapine's efficacy in two different indications. They were treatment of schizophrenia and treatment of acute manic or mixed episodes associated with bipolar I disorder. In this statistical review, only evaluation for schizophrenia trials were performed and reported. The statistical evaluation for the bipolar I disorder trials was performed and reported in another separate review.

In this submission, the sponsor only focused only on the four schizophrenia trials. They are trials 041004, 041023, 041021 and 041022, where only trials 041004 and 041023 showed statistically significant results.

The primary endpoint for these studies was defined as the change in the PANSS total score from baseline to endpoint (LOCF). In addition to the LOCF analysis results, the sponsor also performed the MMRM analysis, which they later proposed to replace the LOCF as the primary analysis. According to the results, the sponsor concluded that asenapine was statistically significantly superior to placebo in the primary efficacy variable in two of the trials with an effective fixed dose regimen (041004 and 041023), but not in the third fixed dose trial (041021). The flexible dose trial (041002) is considered a failed trial because neither asenapine nor the active comparator olanzapine was statistically significantly different from placebo on any efficacy measure. They further emphasized that in both positive trials, 5 mg BID has been demonstrated to be statistically significantly superior to placebo in reducing total PANSS scores and also 10 mg BID in Study 041023 according to the proposed MMRM analyses results.

1.3 STATISTICAL ISSUES AND FINDINGS

Study 41004

Study 41004 was a phase II study with a 60% dropout rate. Although both LOCF and MMRM analysis results appeared to demonstrate the efficacy finding of asenapine 5 mg, this reviewer had the following concerns:

- The study had an overall 60% dropout rate and the rates between the asenapine and placebo groups were very different. Thus, the positive findings based on both LOCF and MMRM analysis results could be too much biased to be convincing.

- It could be due to especially high dropout rate in placebo patients, the placebo response of this study was much smaller than those in other asenapine studies.

- It was noted that patients randomized to the asenapine treatment group seemed to be sicker than patients in the other two treatment groups (i.e., risperidone and placebo) according to their PANSS total scores. To patients who were randomized to the active comparator, risperidone, where their average baseline PANSS total scores was similar to placebo patients, the analysis for change from baseline to the endpoint on PANSS total scores did not show statistically significant difference.

Study 41021

This is a completely negative study where the study drug did not show any efficacy but the active control did.

Study 41022

This is a failed study. Not only did the study drug and the active control fail to show any efficacy findings, but patients in the placebo group even performed numerically better than those in the study drug group.

Study 41023

Although the sponsor mentioned in the clinical overview file of the submission that the MMRM analysis had replaced the LOCF analysis as the primary analysis for all studies, the LOCF analysis was actually the primary analysis and the MMRM analysis was a post-hoc analysis. Based on the protocol specified primary analysis, data only showed statistically significant findings for asenapine 5 mg BID. This reviewer plotted the visit-wise LOCF and OC analysis results and noted that the LOCF analysis results do not seem to be unacceptable. After all, the observed effect size for 10 mg was smaller than that for the 5 mg regardless of analysis methods.

2. INTRODUCTION

2.1 OVERVIEW

In this NDA submission, the sponsor included results of trials to demonstrate asenapine's efficacy in two different indications. They were treatment of schizophrenia and treatment of acute manic or mixed episodes associated with bipolar I disorder. In this statistical review, however, only evaluation for schizophrenia trials were performed and reported. The statistical evaluation for the bipolar I disorder trials were performed and reported in another separate review.

The sponsor's asenapine schizophrenia clinical development program comprises a total of 19 trials, of which 10 were completed and 9 were ongoing as of the data cut-off date of January 15, 2007. Six of the ten completed trials were short-term (6-week of treatment) studies. These trials were performed as adequately powered and well controlled trials (randomized, double-blind, placebo-controlled) of asenapine in subjects who met DSM-IV (Phase II) or DSM-IV-TR (Phase III) diagnostic criteria for schizophrenia and who were acutely exacerbated at the time of enrollment.

Three of the short-term trials explored the efficacy of asenapine fixed doses ≥5 mg BID, one trial explored 5 mg BID of asenapine (041004), and 2 trials (041021 and 041023) investigated asenapine 5 mg BID and 10 mg BID in fixed dose designs. An additional fourth Phase III trial (041022) with a flexible dose regimen (5-10 mg BID) and a design similar to that of 041021 and 041023 in all aspects other than the administered doses was performed. In this submission, the sponsor only focused on the four schizophrenia trials. They are trials 041004, 041023, 041021 and 041022, where only trials 041004 and 041023 showed significant results.

The following Table 2.1 shows the sponsor's analysis results for the primary endpoint for the aforementioned four studies. The primary endpoint for these studies was defined as the change in the PANSS total score from baseline to endpoint visit (LOCF). In addition to the LOCF analysis results, the sponsor also performed the MMRM analysis, which they later proposed to replace the LOCF as the primary analysis. According to the results, the sponsor concluded that asenapine was statistically significantly superior to placebo in the primary efficacy variable in two of the trials with an effective fixed dose regimen (041004 and 041023), but not in the third fixed dose trial (041021). The flexible dose trial (041002) is considered a failed trial because neither asenapine nor the active comparator olanzapine were statistically significantly different from placebo on any efficacy measure. They further emphasized that in both positive trials, 5 mg BID has been demonstrated to be statistically significantly superior to placebo in reducing total PANSS scores and also 10 mg BID in Study 041023 according to the proposed MMRM analyses results.

Note that in the following four trials only two seemly positive studies (Studies 41004 and 41023) that the sponsor determined were described in detail in this statistical review.

Table 2.1 Sponsor's Results for Mean Change from Baseline to Study Endpoint Visit

NOP	Methods	Treatment	Placebo	Asenapine 5 mg BID	Risperidone
041004	LOCF	Mean Change	-4.64	-14.37	-10.05
		S.E.	2.53	2.58	2.59
		Diff. vs. placebo	-	-9.72	-5.41
		SE (Diff)	-	3.53	3.51
		P-value		0.007	0.125
	MMRM	Mean Change	-8.5	-19.8	-16.2
		S.E.	3.41	3.25	3.28
		Diff. vs. placebo	-	-11.33	-7.72
		SE (Diff)	-	4.68	4.69
		P-value		0.018	0.104

NOP	Methods	Treatment	Placebo	Asenapine 5 mg BID	Asenapine 10 mg BID	Olanzapine
041021	LOCF	Mean Change	-11.14	-14.51	-13.44	-16.54
		S.E.	1.64	1.59	1.63	1.64
		Diff. vs. placebo	-	-3.38	-2.30	-5.40
		SE (Diff)	-	2.21	2.24	2.24
		P-value		0.128	0.305	0.017
	MMRM	Mean Change	-13.2	-16.4	-17.1	-19.9
		S.E.	1.95	1.83	1.93	1.9
		Diff. vs. placebo	-	-3.12	-3.88	-6.68
		SE (Diff)	-	2.66	2.73	2.71
		P-value		0.241	0.157	0.015

NOP	Methods	Treatment	Placebo	Asenapine 5-10 mg BID	Olanzapine
041022	LOCF	Mean Change	-9.89	-9.44	-11.20
		S.E.	1.74	1.73	1.72
		Diff. vs. placebo	-	0.45	-1.31
		SE (Diff)	-	2.36	2.36
		P-value		0.848	0.579
	MMRM	Mean Change	-15.6	-11.6	-15.9
		S.E.	2.03	2.11	2.12
		Diff. vs. placebo	-	3.99	-0.25
		SE (Diff)	-	2.92	2.93
		P-value		0.174	0.932

NOP	Methods	Treatment	Placebo	Asenapine 5 mg BID	Asenapine 10 mg BID	Haloperidol
041023	LOCF	Mean Change	-10.7	-16.2	-14.9	-15.4
		S.E.	1.57	1.66	1.69	1.63
		Diff. vs. placebo	-	-5.48	-4.11	-4.70
		SE (Diff)	-	2.23	2.25	2.21
		P-value		0.014	0.068	0.034
	MMRM	Mean Change	-14.6	-21.3	-19.4	-20.0
		S.E.	1.61	1.70	1.68	1.70
		Diff. vs. placebo	-	-6.77	-4.86	-5.47
		SE (Diff)	-	2.33	2.32	2.33
		P-value		0.004	0.038	0.020

Model for LOCF data: response=BL + Treatment + Center;
Model for MMRM: response=BL + Treatment +Center + Visit + Treatment*Visit with covariance structure UN;
P-values were not adjusted by any multiple comparison procedures.

Source: Sponsor's Table 3 of Module 5.3.5.3.

2.2 DATA SOURCES

This NDA submission was stored in the center's electronic document room (EDR) by the following directory: \\Cdsesub1\evsprod\NDA022117\0000.

3. STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

The following description is based on the sponsor's clinical study report. Any discrepancy between the study report and study protocol will be discussed in the section of statistical reviewer's comments.

3.1.1 Description of Study 041004

3.1.1.1 Study Objectives

The primary objective of the trial was to compare the effectiveness of Org 5222 5 mg twice daily with risperidone 3 mg twice daily and placebo twice daily to treat the symptoms of schizophrenia as measured by the total score on the Positive and Negative Syndrome Scale (PANSS).

Secondary objectives were to evaluate the comparative effects of additional measures of efficacy (the 3 subscales of the PANSS, the Calgary Depression Scale, the Clinical Global Impression Scale [CGI], and the cognitive assessment battery), and all safety measures (findings from physical examinations, laboratory evaluations, electrocardiograms, and AEs, including extrapyramidal symptoms).

Another secondary objective was to characterize the population pharmacokinetics of Org 5222 and a major metabolite of Org 5222 (Org 30526).

3.1.1.2 Study Design

This was a double-blind, three-arm, fixed-dose, placebo-controlled trial in subjects with acute exacerbation of their schizophrenic illness. The trial included a screening period, a washout period (a minimum of 3 days and a maximum of 7 days), a treatment period (including a 21-day inpatient phase and a 21-day outpatient phase), and for subjects who did not enter the 041502 trial, a follow-up visit.

Subjects who met the screening criteria were admitted to the hospital for the single-blind washout period. At the completion of the washout period, subjects who met the entrance criteria specified on the baseline checklist were randomized to one of the following treatment groups: Org 5222 5 mg twice daily, risperidone (3 mg) twice daily, or placebo twice daily.

Subjects were treated with trial medication according to their randomized treatment group. Subjects randomized to the Org 5222 5 mg group received trial medication according to the following schedule: 1 mg twice daily on Day 1, 2 mg twice daily on Day 2, 3 mg twice daily on Day 3, 4 mg twice daily on Day 4, and 5 mg twice daily on Days 5 through 42. Subjects randomized to the risperidone group received trial medication according to the following schedule: 1 mg twice daily on Day 1, 2 mg

twice daily on Day 2, and 3 mg twice daily on Days 3 through 42. Subjects randomized to the placebo group received placebo twice daily throughout the treatment period.

Assessments during the treatment period were conducted weekly, except for vital sign assessments which were conducted daily during the inpatient phase.

3.1.1.3 Efficacy Variables and Analyses

The primary efficacy variable was the change from baseline in the total PANSS score at the endpoint visit. The secondary efficacy variables included PANSS subscales, CGI-Severity of Illness and CGI-Clinical Global Improvement. Other efficacy variables included CGI-Quality of Life, living status and employment status.

A last-observation-carried-forward (LOCF) analysis was performed for all variables at all time-points. In an LOCF approach, all missing data on a specific post-baseline efficacy assessment within the scheduled treatment period plus the allowed time frame of 3 days was replaced by the last available observed post-baseline value before that specific visit. The LOCF approach was the primary approach.

For all analyses, group differences were tested using an ANOVA with treatment and site as factors, and the comparison between the Org 5222 5 mg group and the placebo group was performed using t-test. The 95% confidence intervals for the difference in the means also was calculated using t-test and the model based estimated standard error. The treatment by site interaction was examined. Comparison of risperidone group with the placebo group also was performed using the same method as described above.

Reviewer's Note: Although the sponsor claimed that in the study overview that the MMRM has replaced the LOCF analysis as the primary analysis for this study, the MMRM analysis was a post-hoc analysis. This study was conducted from August 2001 to May 2002 and the study overview was written in July 2007 after the sponsor had a Pre-NDA meeting with the FDA on February 22, 2007. Based on the study protocol, the LOCF analysis was specified as the primary analysis.

3.1.2 Efficacy Results for Study 41004

3.1.2.1 Patient Disposition and Baseline Demographic Characteristics

Table 3.1.2.1 shows the disposition of subjects by treatment group. A total of 182 subjects were randomized in the trial: Org 5222 5 mg, 60 subjects; risperidone 3 mg, 60 subjects; and placebo, 62 subjects. Of these subjects, 180 received study medication (Org 5222, 59 subjects; risperidone, 59 subjects; and placebo, 62 subjects). The 2 randomized subjects who did not receive study medication were Subject 0072 (refused washout medication and withdrew consent) and Subject 0096 (decompensated during washout period and was withdrawn from the study).

Table 3.1.2.1 Disposition of Subjects by Treatment Group for Study 41004

	Org 5222 5 mg	Risperidone 3 mg	Placebo	Total
All-Subjects-Randomized	60	60	62	182
All-Subjects-Treated	59	59	62	180
Discontinued	32	34	41	107
Completed Trial	27	25	21	73

Note that only a total of 73 subjects completed the trial; Org 5222, 27 subjects; risperidone, 25 subjects; and placebo, 21 subjects. Table 3.1.2.2 provides the number (%) of subjects who discontinued by reason for discontinuation and treatment group for the All-Subjects-Treated Group. Overall, the percentage of subjects who discontinued due to an AE/SAE was relatively low (10%), with a greater percentage of subjects discontinuing due to lack of efficacy (24%) or other reasons (26%). The most common reason for discontinuation in the "other reasons" category was withdrawal of consent in all 3 treatment groups.

Table 3.1.2.2 Number (%) of Subjects Who Discontinued by Reason for Discontinuation and Treatment Group for Study 41004

	Org 5222 5mg (N=59)		Risperidone 3mg (N=59)		Placebo (N=62)		Total (N=180)	
	n	%	n	%	n	%	n	%
AE/SAE	7[a]	12	4	7	7	11	18	10
Lack of Efficacy	9	15	16	27	18	29	43	24
Other Reasons	16	27	14	24	16	26	46	26
Total	32	54	34	58	41	66	107	60

[a] Included in this count is Subject 0040; however, this subject was incorrectly classified as discontinuing due to an AE/SAE (i.e., Adverse Event/Serious Adverse Event)

Table 3.1.2.3 shows baseline characteristics by treatment group for the all subjects-treated group.

Table 3.1.2.3 Baseline Characteristics by Treatment Group for All-Subject-Treated Group for Study 41004 (Reported are Means and Standard Deviation)

Variable	Org 5222 5mg (N=59)	Risperidone 3mg (N=59)	Placebo (N=62)	Total (N=180)
Age (years)	38.22 (59)	42.73 (59)	42.10 (62)	41.03 (10.86)
Weight (kg)	88.90 (21.48)	84.97 (20.64)	90.13 (23.60)	87.99 (21.93)
Height (cm)	172.39 (10.03)	171.46 (11.01)	172.48 (9.06)	172.12 (10.01)

Source: Sponsor's Table 10 of CSR.

3.1.2.2 Sponsor's Efficacy Results for Primary Parameter

The primary efficacy parameter was the total PANSS score. Table 3.1.2.4 shows the sponsor's by visit and treatment analysis results for total PANSS score using the LOCF analysis for the Intent-to-Treat population. As shown in the table, mean baseline total PANSS scores were similar among the three treatment groups (Org 5222, 96.48; risperidone, 92.18; placebo, 92.43). There was a nominally statistically significant decrease in total PANSS score for Org5222 subjects compared with placebo subjects at Visits 2, 3, 4, 5, and 6. There were no statistically significant

differences between risperidone and placebo at any of the visits, although the risperidone subjects did have a greater mean reduction in total PANSS score at each visit compared with placebo subjects.

In addition, it was noted that results of the LOCF analysis for mean baseline score and mean change from baseline score for the per-protocol group were consistent with results of the LOCF analysis for the Intent-to-Treat Group. The sponsor did not make any comment regarding the OC analysis results although this analysis results were performed and reported (Table 3.1.2.5).

Table 3.1.2.4 Sponsor's Analysis Results for Mean Change from Baseline to All Visits for Total PANSS Scores for Study 41004 (LOCF Analysis)

Visit		Org 5222 5mg (N = 58)	Risperidone 3mg (N = 56)	Placebo (N = 60)
Baseline	n	58	56	60
	Mean	96.48	92.18	92.43
	SE	2.16	2.05	1.93
Visit 1	n	58	56	60
	Mean	-6.22	-5.61	-3.88
	SE	1.67	1.81	1.45
	P-value	0.2767	0.3922	NA
Visit 2	n	58	56	60
	Mean	-11.31	-8.25	-5.52
	SE	1.99	2.36	1.64
	P-value	0.0319	0.3447	NA
Visit 3	n	58	56	60
	Mean	-16.91	-10.77	-6.38
	SE	2.38	2.75	2.07
	P-value	0.0010	0.2023	NA
Visit 4	n	58	56	60
	Mean	-16.88	-10.25	-6.55
	SE	2.51	2.74	2.28
	P-value	0.0025	0.3048	NA
Visit 5	n	58	56	60
	Mean	-15.98	-10.50	-4.70
	SE	2.59	2.71	2.18
	P-value	0.0012	0.1013	NA
Visit 6/ET	n	58	56	60
	Mean	-15.86	-10.93	-5.27
	SE	2.62	2.67	2.30
	P-value	0.0024	0.1186	NA

Source: Sponsor's Table 16 of CSR.

Table 3.1.2.5 Sponsor's Visit-wise OC Analysis Results for Change of Total PANSS from Baseline for Study 41004

Visit	Treatment	N	L.S. Treatment Difference vs. Placebo (SE)	P-value (vs. Placebo)
1	Org5222 5mg	56	-2.33 (2.29)	0.3105
	Risperidone 3mg	56	-1.62 (2.30)	0.4820
	Placebo	57		
2	Org5222 5mg	47	-6.73 (2.83)	0.0191
	Risperidone 3mg	50	-4.15 (3.81)	0.1425
	Placebo	48		
3	Org5222 5mg	42	-14.3 (3.39)	0.0001
	Risperidone 3mg	44	-5.62 (3.42)	0.1037
	Placebo	43		
4	Org5222 5mg	32	-7.51 (4.36)	0.0895
	Risperidone 3mg	30	-3.38 (4.41)	0.4462
	Placebo	27		
5	Org5222 5mg	29	-7.08 (4.85)	0.1496
	Risperidone 3mg	28	-3.97 (4.99)	0.4291
	Placebo	25		
6	Org5222 5mg	27	-7.13 (5.00)	0.1592
	Risperidone 3mg	25	-5.74 (5.11)	0.2657
	Placebo	22		

Source: Sponsor's Tables 6.#.1.2 and 6.F.2 of Appendix F of CSR.

3.1.2.3 Sponsor's Efficacy Results for Secondary Parameters

The secondary parameters included the 3 subscales of the PANSS: the Positive PANSS, Negative PANSS, and General Psychopathology PANSS, as well as the CGI-Severity of Illness and CGI-Global Improvement. Table 3.1.2.6 summarizes the sponsor's LOCF analysis results for these secondary parameters. For all these secondary parameters, Org 5222 5 mg appeared to beat placebo at the significance level of 0.05.

Table 3.1.2.6 Sponsor's Analysis Results for Secondary Parameters for Study 41004

Variable	Org 5222 5 mg (N=58)	Risperidone 3 mg (N=56)	Placebo (N=60)
Positive PANSS Total Score			
Mean Change from Baseline to Visit 6 (SE)	-5.48 (0.84)	-5.13 (0.95)	-2.50 (0.75)
P-Value (vs. Placebo)	0.01	0.03	
Negative PANSS Total Score			
Mean Change from Baseline to Visit 6 (SE)	-3.21 (0.71)	-1.05 (0.75)	-0.55 (0.74)
P-Value (vs. Placebo)	0.01	0.61	
General Psychopathology PANSS			
Mean Change from Baseline to Visit 6 (SE)	-7.17 (1.34)	-4.75 (1.31)	-2.22 (1.13)
P-Value (vs. Placebo)	0.005	0.17	

Variable	Org 5222 5 mg (N=58)	Risperidone 3 mg (N=56)	Placebo (N=60)
CGI-Severity of Illness Score			
Mean Change from Baseline to Visit 6 (SE)	-0.74 (0.12)	-0.75 (0.13)	-0.28 (0.11)
P-Value (vs. Placebo)	0.007	0.004	
CGI-Global Improvement Score			
Mean (SE)	3.25 (0.15)	3.21 (0.14)	3.73 (0.18)
P-Value (vs. Placebo)	0.04	0.024	

3.1.2.4 Statistical Reviewer's Findings and Comments

1. Based on the sponsor-provided data, this reviewer found that Patients #40 and #108 did not have any post-baseline measurements for the primary endpoint, total PANSS score. Since the primary endpoint was the change from baseline to the endpoint of visit for the total PANSS score, these two patients should be removed from the primary analysis based on the definition of Intent-to-Treat population in the study. After removing these two patients from the primary analysis data set, this reviewer found that the conclusions stay the same. Actually, this reviewer found that in the overview of this NDA submission, the LOCF analysis results that the sponsor reported for Study 041004 were based on the data after excluding these two patients (See Table 3.1.2.6). Thus, based on this analysis results without including Patients #40 and #108, Org 5222 5 mg showed statistically significant efficacy findings in comparison with placebo, but Risperidone 3 mg did not. However, this reviewer had some concerns about the accepting these findings as a confirmatory evidence. The reasons will be explained in the following comments.

2. Although in this study the analysis results for the primary endpoint either based on the LOCF or the MMRM analysis supported the efficacy of Org 5222 5 mg, this reviewer wished to point out that this study had a very high dropout rate (~60% on average) and the dropout rates were quite different between the Org 5222 5 mg group and placebo. As we can see from Table 3.1.2.2, in particular, the placebo group of patients even had 65% dropout rate. So, a reasonable concern is that whether a study with >50% dropout rate can still be accepted as a pivotal study.

   This study was originally planned as a phase II study, so only about 60 patients per treatment arm. With 65% of patients dropped out from the placebo group, only 22 patients completed the study. Based on the reasons of dropouts, 30% of dropouts in placebo group were due to lack of efficacy, but only 15.5% of dropouts in Org 5222 5mg were due to lack of efficacy. When there were many more placebo patients dropped out due to lack of efficacy than Org5222 5mg patients, it is likely that the LOCF (last observation carried forward) analysis could bias the results. Although the MMRM analysis results still showed p-value <0.05, it is well known that the MMRM analysis heavily depends on the missing at random (MAR) assumption. With the very large percentage of dropouts in the study, the likelihood that non-ignorable missing data has an insurmountable impact on the validity of statistical analysis increases a great deal. Thus, it is highly doubtful that the MAR assumption will hold. The OC analysis results, as expected, did not show statistically significant

findings for the change from baseline to the final visit for the comparison between Org 5222 5mg and placebo.

Table 3.1.2.7 shows the sponsor's LOCF, OC and MMRM analysis results which had been confirmed by this reviewer.

Table 3.1.2.7 Sponsor's Analysis Results for Study 41004

Method of Analysis	Treatment	Treatment Difference (vs. Placebo)	SE	P-value
LOCF	Org5222 5mg	-9.72	3.53	0.007
	Risperidone 3mg	-5.41	3.51	0.125
OC	Org5222 5mg	-7.13	5.00	0.1592
	Risperidone 3mg	-5.74	5.11	0.2657
MMRM	Org5222 5mg	-11.33	4.68	0.018
	Risperidone 3mg	-7.72	4.69	0.104

3. As mentioned in Comment #2, this study had a very high dropout rate. To understand the dropout pattern, this reviewer drew plots for visit-wise least square mean changes from baseline (Figure 3.1), and patients' data profiles (Figures 3.2 – 3.4). It was noted that after Visit 3, where there were about 22% patients who dropped out from the study, the differences between Org5222 5mg and placebo's observed data dramatically reduced. However, the difference between Org5222 5mg and placebo's LOCF data were not much affected. According to Figure 3.2, for completers, patients in Org5222 5mg seems to perform similarly to patients in placebo. It appears that the differences between Org5222 5mg and placebo were mainly from those dropouts.

Figure 3.1 Reviewer's Plot for the Visit-Wise Mean Change from Baseline on Total PANSS Score for Study 41004

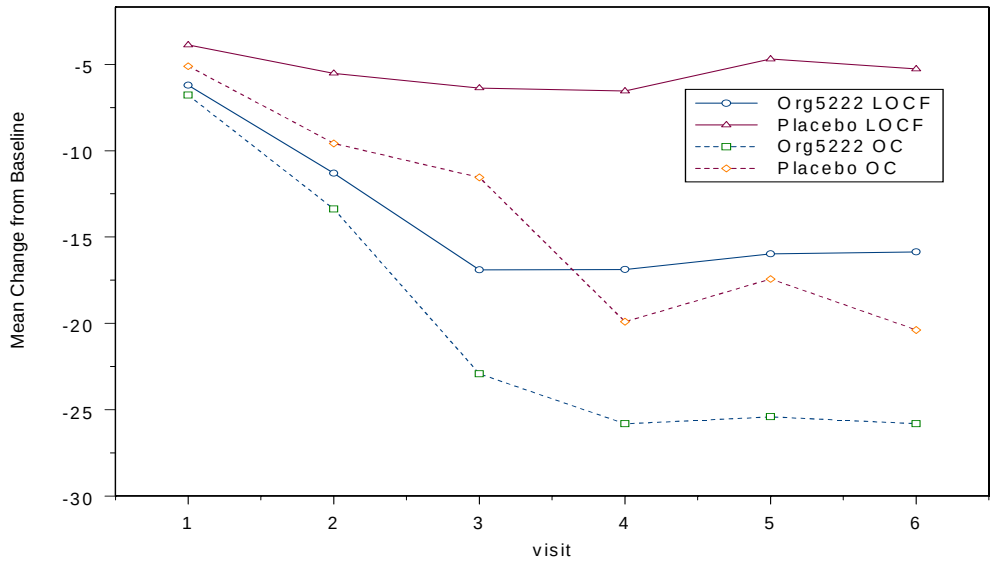


Figure 3.2 Reviewer's Plot of Patient Profile by Total PANSS Score for Study 41004 (Combined Groups) [Blue: Org5222 5mg and Orange: Placebo]

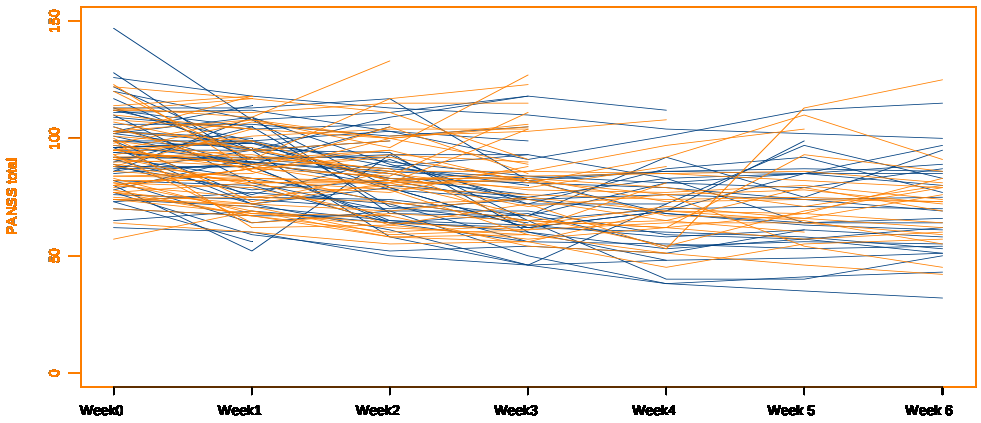


Figure 3.3 Review's Plot of Org5222 5mg Patient Profile by Total PANSS Score for Study 41004

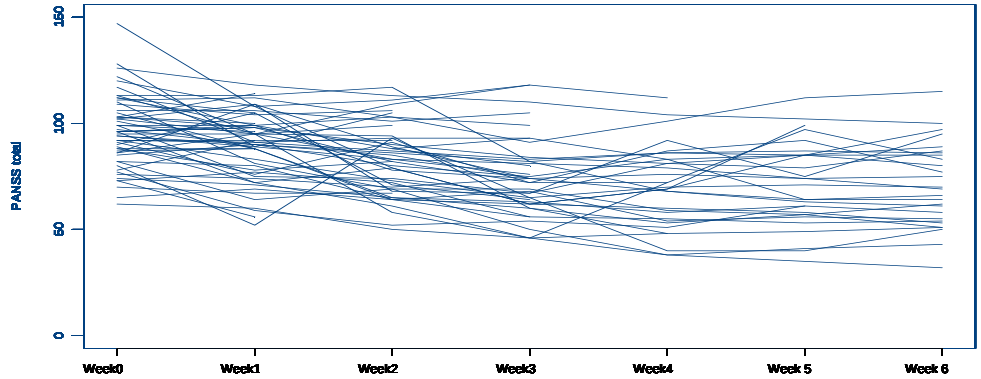
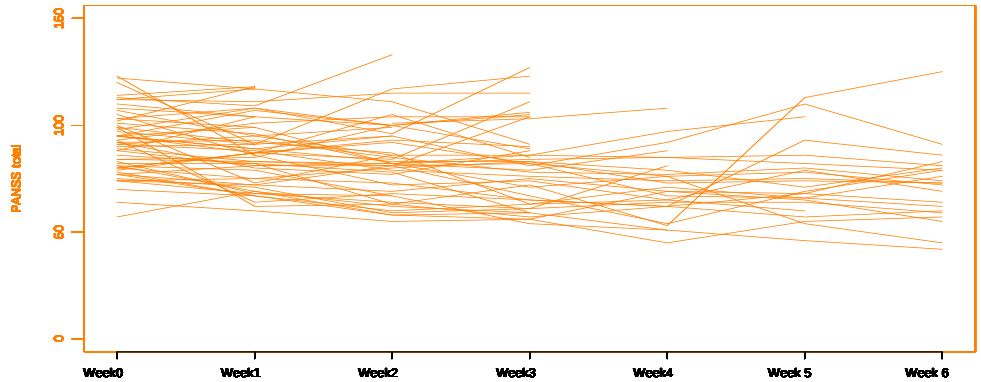


Figure 3.4 Reviewer's Plot of Placebo Patient Profile by Total PANSS Score for Study 41004



4. Observing baseline total PANSS score in each treatment group from Table 3.1.2.3, we note that Org5222 5mg appears to have much larger mean than those in the other two groups. This reviewer found that when the center factor was included into the ANOVA model, the difference between Org5222 5mg and placebo became statistically significant. Nevertheless, the difference between Org5222 5mg and placebo is still statistically significant when the primary endpoint is analyzed with the baseline total PANSS score as a covariate by ANCOVA.

5. The analysis of percent reduction from baseline to the end visit can be a reasonable sensitivity analysis to study the data with the presence of baseline imbalance. The sponsor performed the reduction analysis for at least 20% and 30% reduction, respectively. This reviewer could not confirm the sponsor's analysis results and performed her own results in the following Table 3.1.2.8. As shown in the table, the number of patients who had at least 20% reduction or at least 30% reduction are similar in Org 5222 5mg group and in Risperidone 3 mg group. The p-values for the comparisons between Org 5222 5mg group and placebo and for the comparisons between Risperidone 3 mg and placebo are all bigger than 0.05 for both at least 20% reduction and at least 30% reduction. It appears that the results by the primary ANOVA analysis were not be supported by this percent reduction analysis.

Table 3.1.2.8 This Reviewer's Analysis Results for Percent Reduction from Baseline Score for Total PANSS at Visit 6/Endpoint by Treatment Group for Study 41004

	Org 5222 5 mg (N=57)		Risperidone 3 mg (N=56)		Placebo (N=59)	
	n	%	n	%	n	%
≥20% reduction	23	40	22	39	15	25
P-value (vs. Placebo)*	0.11		0.14		NA	
≥30% reduction	12	21	10	18	7	12
P-value (vs. Placebo)*	0.19		0.35		NA	

* P-values were obtained by CMH stratified by Center

3.1.3 Description of Study 041023

3.1.3.1 Study Objectives

The primary objective of this study was to compare the effectiveness of asenapine 5 and 10 mg BID with placebo in the treatment of schizophrenia.

A secondary objective was to compare the effectiveness of asenapine 5 and 10 mg BID with placebo in the treatment of negative symptoms of schizophrenia.

3.1.3.2 Study Design

The trial was a randomized, double-blind, fixed-dose, placebo- and positive-controlled, multi-center efficacy trial in subjects with a DSM-IV-TR™ (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, 2000) diagnosis of schizophrenia who were acutely exacerbated at the time of admission to the trial.

This trial consisted of screening, a 2-day taper period (eligible severely ill subjects were permitted to be randomized immediately at the discretion of the investigator), and a 6-week active treatment period. The active treatment period was initiated on day 1 following randomization of subjects to one of the following treatments in a 1:1:1:1 distribution: asenapine 5 BID, asenapine 10 mg BID, haloperidol 4 mg BID, or placebo.

Subjects were to be hospitalized for the first 2 weeks (14 days) of the 6-week trial period. Hospitalization beyond 2 weeks was to be approved by the sponsor. For the remainder of the trial, subjects were to continue as outpatients. Subjects who completed the protocol were offered the option of participating in the long-term extension trial (041513), where they would have the opportunity to continue to be treated for an additional 52 weeks. Subjects who did not continue in the extension trial (whether they completed the present 6-week trial or discontinued prematurely) had a follow-up visit 7 days after their end-of-treatment visit. Thirty days after discontinuation, the subject was to be called to determine if any serious adverse events had occurred during this period or to update the status of unresolved serious adverse events.

3.1.3.3 Efficacy Variables and Analyses

The primary efficacy rating scale was the Positive and Negative Syndrome Scale (PANSS). The PANSS is a 30-item clinician-rated instrument for assessing the symptoms of schizophrenia.

Secondary efficacy rating scales included Clinical Global Impression of Severity of Illness (CGI-S), Clinical Global Impression of Improvement (CGI-I), Calgary Depression Scale for Schizophrenia (CDSS), CNS Vital Signs, Readiness for Discharge Questionnaire (RDQ) and InterSept Scale for Suicidal Thinking (Modified Version)(i.e., ISST-Modified).

The primary efficacy endpoint was defined as the change in the PANSS total score from baseline to endpoint (LOCF). The PANSS total score for each subject was calculated as the sum of the ratings assigned to each of the 30 PANSS items. If more than 5 PANSS individual items were missing, the total PANSS scores would not be computed. If 5 or fewer items of the PANSS were missing, then the total PANSS scores will be prorated.

The primary analysis was based on the intent-to-treat group. The ANCOVA model described above was used to assess treatment differences. The primary treatment comparison between groups was based on the differences in the model based least square means (LSMEANS). Missing values for PANSS total score were replaced using the LOCF method described above. Summary statistics were presented by treatment for PANSS total score at baseline and endpoint and for change from baseline in PANSS total score to endpoint. The assumptions of the ANCOVA model were checked as described in the SAP.

In order to assess the robustness of the results against potential bias caused by missing data due to dropouts, supportive analyses based on the intent-to-treat group were conducted using two methods:

- The previously defined ANCOVA model using observed cases (OC)
- A mixed model analysis using repeated measures

All hypothesis testing was conducted using two-sided tests with alpha = 0.05 level of significance. The primary comparisons for assessing the efficacy of treatment with asenapine on symptoms of schizophrenia were between each asenapine treatment group and the placebo group for the primary endpoint. A Hochberg adjustment method was used to adjust the two comparisons. The haloperidol group versus placebo group comparison was made for assessing assay sensitivity only. Comparisons between each asenapine group and the placebo treatment group for all other efficacy endpoints were considered secondary and were used to support the findings of the primary analysis.

3.1.4 Efficacy Results for Study 41023

3.1.4.1 Patient Dispositions and Baseline Demographic Characteristics

A total of 513 subjects were screened to determine their eligibility for entry into the trial. Of the 513 screened subjects, 55 subjects were withdrawn before randomization, including 32 subjects who did not meet the entry criteria, 21 subjects who withdrew consent, 1 subject who had an adverse event, and 1 subject who was lost to follow-up. The remaining 458 subjects were randomized to treatment with placebo (N=123), asenapine 5 mg BID (N=114), asenapine 10 mg BID (N=106), or haloperidol 4 mg BID (N=115).

Of the 458 randomized subjects, 455 subjects were treated and comprised the all subjects-treated group (123, placebo; 111, asenapine 5 mg BID; 106, asenapine 10 mg BID; 115, haloperidol). The intent-to-treat group consisted of 448 subjects (122, placebo; 109, asenapine 5 mg BID; 105, asenapine 10 mg BID; 112, haloperidol).

Table 3.1.4.1 shows the sponsor's summary of subject disposition and Table 3.1.4.2 shows patients' demographic characteristics. The proportions of subjects in the placebo, asenapine 5 mg BID, asenapine 10 mg BID, and haloperidol treatment groups who withdrew from the trial during the double-blind treatment period were 43.1%,

36.9%, 33.0%, and 40.9%, respectively. The most common reason for discontinuation in the asenapine 5 mg BID, asenapine 10 mg BID, and haloperidol treatment groups was withdrawal of consent (18.9%, 10.4%, and 22.6%, respectively). In the placebo treatment group, the most common reason for withdrawing from the trial was lack of efficacy (17.9%).

Table 3.1.4.1 Sponsor's Summary of Subject Disposition for Study 41023

Subject Disposition	Placebo	Asenapine 5mg BID	Asenapine 10 mg BID	Haloperidol 4 mg BID	All Subjects
Randomized, N	123	114	106	115	458
All-Subjects-Treated, N	123	111	106	115	455
Intent-to-Treat, N	122	109	105	112	448
Withdrew from Trial, n (%)	53 (43.1)	41 (36.9)	35 (33.0)	47 (40.9)	176 (38.7)
Adverse Event	13 (10.6)	5 (4.5)	10 (9.4)	12 (10.4)	40 (8.8)
Schizophrenia Worsening	9 (7.3)	2 (1.8)	9 (8.5)	6 (5.2)	26 (5.7)
Lack of Efficacy	22 (17.9)	12 (10.8)	8 (7.5)	4 (3.5)	46 (10.1)
Withdrew Consent	13 (10.6)	21 (18.9)	11 (10.4)	26 (22.6)	71 (15.6)
Lost to Follow-Up	2 (1.6)	3 (2.7)	2 (1.9)	4 (3.5)	11 (2.4)
Other	3 (2.4)	0 (0)	4 (3.8)	1 (0.9)	8 (1.8)
Insufficient Therapeutic Effect	31 (25.2)	14 (12.6)	17 (16.0)	10 (8.7)	72 (15.8)

Source: Sponsor's Table 6 of the CSR.

Table 3.1.4.2 Sponsor's Summary of Demographic and Other Characteristics for All-Subjects-Treated Group for Study 41023

	Placebo (N=123)	Asenapine 5 mg BID (N=111)	Asenapine 10 mg BID (N=106)	Haloperidol 4 mg BID (N=115)	All Subjects (N=455)
Characteristics					
Gender, n (%)					
Male	64 (52.0)	75 (67.6)	67 (63.2)	63 (54.8)	269 (59.1)
Female	59 (48.0)	36 (32.4)	39 (36.8)	52 (45.2)	186 (40.9)
Premenopausal	45 (76.3)	28 (77.8)	33 (84.6)	36 (69.2)	142 (76.3)
Postmenopausal	14 (23.7)	8 (22.2)	6 (15.4)	16 (30.8)	44 (23.7)
Race, n (%)					
Caucasian	76 (61.8)	71 (64.0)	67 (63.2)	68 (59.1)	282 (62.0)
Black	31 (25.2)	22 (19.8)	29 (27.4)	35 (30.4)	117 (25.7)
Asian	11 (8.9)	11 (9.9)	10 (9.4)	12 (10.4)	44 (9.7)
Other	5 (4.1)	7 (6.3)	0 (0.0)	0 (0.0)	12 (2.6)
Age category, n (%)					
18 – 64 years	122 (99.2)	108 (97.3)	104 (98.1)	114 (99.1)	448 (98.5)
≥ 65 years	1 (0.8)	3 (2.7)	2 (1.9)	1 (0.9)	7 (1.5)
Age, years					
Mean (SD)	40.1 (11.61)	38.0 (11.99)	37.1 (10.92)	39.0 (11.18)	38.6 (11.45)
Median	42.0	38.0	37.0	40.0	39.0
Range	18, 70	18, 69	19, 68	18, 67	18, 70
Weight, kg					
Mean (SD)	74.5 (17.08)	77.6 (17.43)	77.8 (21.04)	76.5 (17.42)	76.5 (18.23)
Median	73.5	75.8	76.4	75.5	75.0
Range	45, 120	48, 135	39, 154	42, 128	39, 154
BMI, kg/m^2					
Mean (SD)	26.0 (5.08)	26.7 (5.10)	26.2 (5.77)	26.5 (5.20)	26.3 (5.27)
Median	25.3	26.3	25.4	25.7	25.6
Range	17, 40	18, 39	19, 51	18, 42	17, 51

Source: Sponsor's Table 10 of CSR.

As seen in the above table, the asenapine 5 mg BID and 10 mg BID treatment groups included a higher proportion of males (67.6% and 63.2%, respectively) than the placebo (52.0%) and haloperidol (54.8%) treatment groups. Except for gender, the four treatment groups were well balanced with respect to demographic characteristics at baseline. Most subjects were either Caucasian (62.0%) or Black (25.7%). Subjects ranged in age from 18 to 70 years, and the overall mean (SD) age was 38.6 (11.45) years. Subjects' BMI ranged from 17 to 51 kg/m^2; the mean BMI (SD) was 26.3 (5.27) kg/m^2.

3.1.4.2 Sponsor's Efficacy Results for Primary Parameter

The primary efficacy analysis was a comparison of the LS mean change from baseline to endpoint (LOCF) in the PANSS total score in each asenapine treatment group versus the placebo treatment group using an ANCOVA model. Table 3.1.4.3 shows the sponsor's analysis results for the primary endpoint. As shown from the table, at endpoint, asenapine 5 mg BID showed statistically significantly better performance than placebo but asenapine 10 mg BID did not. Haloperidol also had statistically significantly better performance than placebo.

Table 3.1.4.3 Sponsor's Analysis Results for Change from Baseline in PANSS Total Score Based on LOCF Data for Study 41023

Visit	Placebo N=122	Asenapine 5 mg BID N=109	Asenapine 10 mg BID N=105	Haloperidol 4 mg BID N=112
Baseline, n	122	109	105	112
LS mean [a] (SE)	89.0 (0.92)	88.9 (0.97)	89.4 (0.99)	88.5 (0.96)
95% CI [a]	(87.15, 90.78)	(86.98, 90.81)	(87.43, 91.33)	(86.65, 90.41)
Change from baseline to day 4, n	122	109	105	111
LS mean change [b] (SE)	-3.4 (0.72)	-2.9 (0.76)	-4.4 (0.77)	-3.4 (0.75)
P-value [b]		0.6827	0.3230	0.9819
Change from baseline to day 7, n	122	109	105	112
LS mean change [b] (SE)	-5.9 (0.94)	-7.2 (0.99)	-7.7 (1.01)	-7.3 (0.97)
P-value [b]		0.3487	0.1981	0.2842
Change from baseline to day 14, n	122	109	105	112
LS mean change [b] (SE)	-8.3 (1.14)	-10.5 (1.20)	-10.4 (1.23)	-11.0 (1.18)
P-value [b]		0.1703	0.2100	0.0931
Change from baseline to day 21, n	122	109	105	112
LS mean change [b] (SE)	-9.1 (1.31)	-13.2 (1.38)	-11.6 (1.41)	-13.8 (1.36)
P-value [b]		0.0265	0.1717	0.0106
Change from baseline to day 28, n	122	109	105	112
LS mean change [b] (SE)	-9.4 (1.43)	-14.2 (1.51)	-11.7 (1.53)	-14.4 (1.48)
P-value [b]		0.0184	0.2548	0.0140
Change from baseline to day 35, n	122	109	105	112
LS mean change [b] (SE)	-10.2 (1.48)	-15.3 (1.57)	-13.3 (1.60)	-14.7 (1.54)
P-value [b]		0.0169	0.1390	0.0312
Change from baseline to day 42, n	122	109	105	112
LS mean change [b] (SE)	-10.8 (1.56)	-16.2 (1.65)	-14.7 (1.68)	-15.6 (1.62)
P-value [b]		0.0144	0.0768	0.0296
Change from baseline to Endpoint, n	122	109	105	112
LS mean change [b] (SE)	-10.7 (1.57)	-16.2 (1.66)	-14.9 (1.69)	-15.4 (1.63)
P-value [b]		0.0145	0.0680	0.0342
Adjusted p-value [c]		0.0290	0.0680	

[a] Based on an ANOVA model with fixed effects for treatment and pooled investigative site.

[b] Based on an ANCOVA model with treatment and pooled investigative site as fixed effects and baseline as a covariate. P-values are based on the difference in the LS mean change for active treatment versus placebo.

[c] Adjusted by Hochberg method for testing two asenapine groups versus the placebo group.

Source: Sponsor's Table 16 of CSR.

Note that : The sponsor showed two different analysis results for Week 6; one is the change from baseline to Day 42 and the other one is the change from baseline to Endpoint. This reviewer found that the difference was due to some patients who had the endpoint data after Day 42 and these data were used for the change from baseline to Endpoint analysis but not to Day 42 analysis by the LOCF principal. Two analysis results were very close and yielded the same conclusions.

The observed-case analysis confirmed the findings of the LOCF analysis for asenapine 5 mg BID. The observed-case analysis indicated that asenapine 5 mg BID and 10 mg BID, but not haloperidol, separated from placebo at day 42. Table 3.1.4.4 shows the sponsor's observed case analysis results at Day 42.

Table 3.1.4.4 Sponsor's Observed Case Analysis Results at Day 42 for Study 41023

Variable	Placebo (N=68)	Asenapine 5 mg BID (N=70)	Asenapine 10 mg BID (N=67)	Haloperidol 4 mg BID (N=64)
Change from Baseline in Total PANSS score (SE)	-19.1 (1.46)	-23.9 (1.46)	-23.2 (1.45)	-21.9 (1.49)
P-value (vs Placebo)		0.0171	0.0398	0.1567

Source: Sponsor's Table 11.5.1.1.4 of CSR

3.1.4.3 Sponsor's Efficacy Results for Secondary Parameters

The sponsor's analysis results for some major secondary endpoints are shown in Table 3.1.4.4. As we can see from the table, among these five endpoints, asenapine 5 mg showed nominally statistically significant results on all endpoints except on Negative PANSS Total score but asenapine 10 mg only showed nominally statistically significant results on Positive PANSS total score in comparison with placebo. Haloperidol also showed nominally statistically significant results on Positive PANSS total score in addition to CGI-Severity of Illness score.

Table 3.1.4.4 Sponsor's Analysis Results for Secondary Parameters for Study 41023

Variable	Placebo (N=122)	Asenapine 5 mg BID (N=109)	Asenapine 10 mg BID (N=105)	Haloperidol 4 mg BID (N=112)
Positive PANSS Total Score				
LS Mean Change from Baseline to Endpoint (SE)	-3.7 (0.52)	-5.8 (0.54)	-5.4 (0.55)	-5.8 (0.53)
P-Value (vs. Placebo)		0.0052	0.0243	0.0035
Negative PANSS Total Score				
LS Mean Change from Baseline to Endpoint (SE)	-2.4 (0.40)	-3.4 (0.42)	-3.5 (0.43)	-3.1 (0.42)
P-Value (vs. Placebo)		0.0649	0.0531	0.1878
General Psychopathology PANSS				
LS Mean Change from Baseline to Endpoint (SE)	-4.7 (0.80)	-7.0 (0.85)	-6.0 (0.86)	-6.5 (0.83)
P-Value (vs. Placebo)		0.045	0.2748	0.1259

Variable	Placebo (N=122)	Asenapine 5 mg BID (N=109)	Asenapine 10 mg BID (N=105)	Haloperidol 4 mg BID (N=112)
CGI-Severity of Illness Score				
LS Mean Change from Baseline to Endpoint (SE)	-0.63 (0.092)	-0.93 (0.098)	-0.86 (0.100)	-0.93 (0.096)
P-Value (vs. Placebo)		0.0219	0.0818	0.0220
CGI-Global Improvement Score*				
Responders, n (%)	41 (33.6)	52 (47.7)	46 (44.2)	49 (43.8)
Non-responders, n (%)	81 (66.4)	57 (52.3)	58 (55.8)	63 (56.3)
P-Value (vs. Placebo)		0.0272	0.1348	0.1016

* CGI-I responder was defined as a subject with a CGI-I score of 1 or 2.

3.1.4.4 Statistical Reviewer's Findings and Comments

1. Based on the LOCF analysis results (Table 3.1.4.3), only 5mg BID of asenapine showed statistically significant findings in comparison with placebo although the 10 mg BID of asenapine also showed statistically significant findings from the MMRM analysis results (Table 3.1.4.5). The sponsor made a note in the clinical overview file of the NDA submission that "As the LOCF analysis is considered less appropriate due to this violation for the trials in question, the sponsor proposes that the MMRM analysis be used as the primary statistical analysis utilizing the intent-to-treat (ITT) dataset for the schizophrenia trials and for the bipolar I disorder trials."

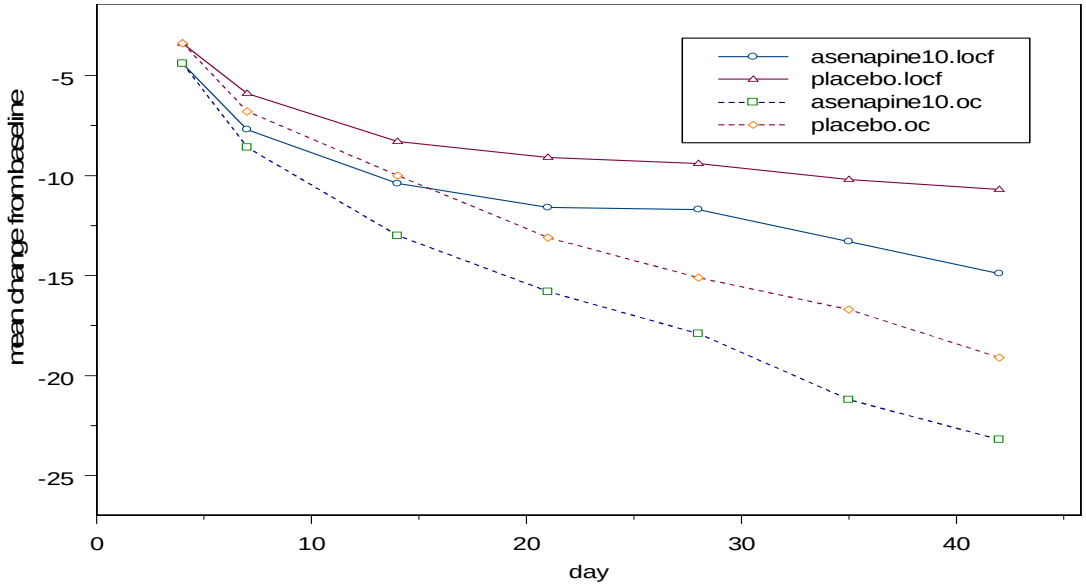
   The sponsor's MMRM analysis results were confirmed by the statistical reviewer. According to the Agency's Pre-NDA Meeting minutes (dated February 22, 2007), although FDA told the sponsor that for the conducted trials, FDA is willing to look at justification that the MMRM is less biased than the LOCF analysis. This reviewer would like to emphasize that this MMRM analysis is indeed a post hoc analysis, (where the clinical study report was written in April of 2007 and the LOCF was still noted as the primary analysis) and the FDA also informed the sponsor that they should stick to the pre-specified primary analysis (LOCF). This reviewer would like to point out that even though the MMRM analysis results showed the statistically significant findings for asenapine 10 mg's efficacy, the observed effect of asenapine 10 mg was still less than asenapine 5 mg, like what was shown by the LOCF analysis.

Table 3.1.4.5 Sponsor's MMRM analysis results for Total PANSS Scores for Study 41023

Variable	Placebo (N=122)	Asenapine 5 mg BID (N=109)	Asenapine 10 mg BID (N=105)	Haloperidol 4 mg BID (N=112)
LS Mean Change (SE)	-14.6 (1.61)	-21.3 (1.70)	-19.4 (1.68)	-20.0 (1.70)
Difference vs. Placebo (SE)		-6.77 (2.33)	-4.86 (2.32)	-5.47 (2.33)
P-value		0.004	0.038	0.020

2. To help examine whether the LOCF analysis results are biased, this reviewer drew the graph of the visit-wise least square means based on the LOCF data and OC data for asenapine 10 mg group and placebo. As we can observe from Figure 3.5, similar to dropout patients from placebo group, dropout patients from asenapine 10 mg group seemed to have worse improvement than patients who completed till the study end. According to Table 3.1.4.1, the top withdrawn reason for patients in asenapine 10 mg group is indeed 'Insufficient Therapeutic Effect'. In this case the OC analysis results which were obtained after removing many patients who did not perform well, was clearly biased. The LOCF analysis results do not seem to be unacceptable.

Figure 3.5 Reviewer's Plot for the Visit-Wise Least Square Mean Change from Baseline on Total PANSS Score for Study 41023



3.2 EVALUATION OF SAFETY

The evaluation of safety was not performed in this review. Please see the clinical review for this evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The sponsor performed the summaries of PANSS total score for the gender, race, age and region (only US and non-US sites) subgroups based on the combined study data (Studies 41004 and 41023). Their results were confirmed by the statistical reviewer.

4.1 GENDER, RACE AND AGE

Tables 4.1.1 to 4.1.3 show the sponsor's summaries of subgroup analysis for gender, race and age. As show in the tables, except patients who were older than 65 years old and in asenapine 10 mg group, PANSS scores in all subgroups decreased from baseline at Day 42 for all treatment groups (i.e., asenapine 5 mg BID, asenapine 10 mg BID, risperidone 3 mg BID, haloperidol 4 mg BID, and placebo). Except Asian patients in asenapine 5 mg group, other subgroups of patients with asenapine performed better than those with placebo.

Table 4.1.1 Sponsor's Summary of PANSS Total Score by Gender for LOCF data for Studies 41004 and 41023

	Placebo	Asenapine 5 mg BID	Asenapine 10 mg BID	Risperidone 3 mg BID	Haloperidol 4 mg BID
Female, n	71	48	39	22	51
Mean Change (SD)	-7.9 (16.92)	-16.6 (18.19)	-13.1 (20.45)	-13.7 (19.33)	-16.5 (17.56)
Male, n	110	118	66	34	61
Mean Change (SD)	-9.2 (19.12)	-15.7 (18.65)	-15.5 (18.71)	-9.0 (20.48)	-13.9 (15.19)

Source: Sponsor's table 8.S of Clinical Summary

Table 4.1.2 Sponsor's Summary of PANSS Total Score by Race for LOCF data for Studies 41004 and 41023

	Placebo	Asenapine 5 mg BID	Asenapine 10 mg BID	Risperidone 3 mg BID	Haloperidol 4 mg BID
Caucasian, n	94	95	67	25	68
Mean Change (SD)	-6.7 (17.29)	-16.6 (19.25)	-14.7 (18.50)	-7.4 (15.88)	-13.8 (16.38)
Black, n	62	49	28	25	32
Mean Change (SD)	-11.7 (17.99)	-16.1 (16.67)	-9.9 (18.49)	-10.7 (23.36)	-14.8 (17.02)
Asian, n	11	11	10	1	12
Mean Change (SD)	-18.4 (20.99)	-11.3 (19.15)	-27.2 (22.97)	-19.0 (.)	-23.4 (11.82)
Other, n	14	11	0	5	0
Mean Change (SD)	-1.2 (20.12)	-14.6 (20.37)	NA	-27.2 (16.72)	NA

Source: Sponsor's table 9.S of Clinical Summary

Table 4.1.3 Sponsor's Summary of PANSS Total Score by Age for LOCF data for Studies 41004 and 41023

	Placebo	Asenapine 5 mg BID	Asenapine 10 mg BID	Risperidone 3 mg BID	Haloperidol 4 mg BID
18 to 64 years, n	178	162	103	56	111
Mean Change (SD)	-8.7 (18.39)	-16.1 (18.54)	-15.0 (19.34)	-10.8 (19.99)	-15.0 (16.32)
≥ 65, n	3	4	2	0	1
Mean Change (SD)	-11.3 (6.43)	-10.5 (16.20)	2.5 (3.54)	NA	-27.0 (.)

Source: Sponsor's table 10.S of Clinical Summary

4.2 OTHER SPECIAL/SUBGROUP POPULATIONS

Table 4.1.4 shows the sponsor's subgroup analysis for data in US and non-US Sites. Note that Study 041004 was composed of US sites only and Study 041023 had both US and non-US sites. Risperidone was not used at non-US sites. The results showed that in general, decreases from baseline in the mean PANSS score were observed for all treatment groups in US and non-US sites. However, there were greater decreases from baseline at non-US sites, particularly for 10 mg asenapine and 4 mg haloperidol. In summary, decreases from baseline in mean PANSS score at endpoint was greater for all treatment groups compared to placebo in both regions.

Table 4.1.4 Sponsor's Summary of PANSS Total Score by Region for LOCF data for Studies 41004 and 41023

	Placebo	Asenapine 5 mg BID	Asenapine 10 mg BID	Risperidone 3 mg BID	Haloperidol 4 mg BID
US, n	113	101	45	56	48
Mean Change (SD)	-7.8 (18.26)	-16.4 (17.71)	-9.4 (15.67)	-10.8 (19.99)	-11.9 (16.43)
Non-US, n	68	65	60	0	64
Mean Change (SD)	-10.2 (18.27)	-15.2 (19.71)	-18.6 (20.91)	NA	-17.5 (15.89)

Source: Sponsor's table 10.S of Clinical Summary

5. SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

Study 41004

Study 41004 was a phase II study with a 60% dropout rate. Although both LOCF and MMRM analysis results appeared to demonstrate the efficacy finding of asenapine 5 mg, this reviewer had the following concerns:

- The study had an overall 60% dropout rate and the rates between the asenapine and placebo groups were very different. Thus, the positive findings based on both LOCF and MMRM analysis results could be too much biased to be convincing.

- It could be due to especially high dropout rate in placebo patients, the placebo response of this study was much smaller than those in other asenapine studies.

- It was noted that patients randomized to the asenapine treatment group seemed to be sicker than patients in the other two treatment groups (i.e., risperidone and placebo) according to their PANSS total scores. To patients who were randomized to the active comparator, risperidone, where their average baseline PANSS total scores was similar to placebo patients, the analysis for change from baseline to the endpoint on PANSS total scores did not show statistically significant difference.

Study 41021

This is a completely negative study where the study drug did not show any efficacy but the active control did.

Study 41022

This is a failed study. Not only did the study drug and the active control fail to show any efficacy findings, but patients in the placebo group even performed numerically better than those in the study drug group.

Study 41023

Although the sponsor mentioned in the clinical overview file of the submission that the MMRM analysis had replaced the LOCF analysis as the primary analysis for all studies, the LOCF analysis was actually the primary analysis and the MMRM analysis was a post-hoc analysis. Based on the protocol specified primary analysis, data only showed statistically significant findings for asenapine 5 mg BID. This reviewer plotted the visit-wise LOCF and OC analysis results and noted that the LOCF analysis results do not seem to be unacceptable. After all, the observed effect size for 10 mg was smaller than that for the 5 mg regardless of analysis methods.

5.2 CONCLUSIONS AND RECOMMENDATIONS

The sponsor submitted four completed studies to evaluate asenapine's efficacy in treatment of schizophrenia. On the face, only two studies (Studies 41004 and 41023) showed statistically significant efficacy findings. After evaluation, this reviewer determined that only data for asenapine 5 mg BID from Study 41023 showed clearly statistically significant findings. Even though the analysis results for Study 41004 seemed to suggest a statistically significant difference in comparison with placebo, the strength of evidence for asenapine's efficacy based on this study may be weak due to the very high dropout rate. In particular, the dropout rates between the asenapine and placebo groups were very different. Regarding Study 41023, the fact that asenapine 10 mg BID performed numerically worse than asenapine 5 mg BID also adds difficulty to the interpretion of the asenapine's efficacy finding.

_____

Yeh-Fong Chen, Ph.D.
Mathematical Statistician

cc: NDA 22-117
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-117 / N000
Drug Name:	Asenapine
Indication(s):	Bipolar I
Applicant:	Organon
Date(s):	Initial submission date: August 30, 2007
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	George Kordzakhia, Ph.D.
Concurring Reviewers:	Peiling Yang, Ph.D.; H.M. James Hung, Ph.D.
Medical Division:	Division of Psychiatry Products
Clinical Team:	Robert Levin, M.D., Reviewer Gwen Zornberg, M.D., Team Leader
Project Manager:	Mr. Keith Kiedrow
Key Words	ANCOVA, MMRM

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1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

At flexible doses of 5 to 10 mg BID (with 10 mg as the starting dose and the option to downtitrate to 5 mg), the asenapine group was statistically significantly superior to placebo in treatment of patients with manic or mixed episodes associated with Bipolar I as measured by the change from baseline in Y-MRS score on Day 21(primary endpoint, Intent-to-treat population) and CGI-BP severity of mania score on Day 21 (key secondary endpoint, Intent-to-treat population).

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

The development program was designed to investigate in parallel asenapine's efficacy in 2 different indications: treatment of schizophrenia and treatment of acute manic or mixed episodes associated with bipolar I disorder. Two pivotal studies (A75011004 and A7501005) were submitted in support of efficacy of asenapine compared with placebo in treatment of subjects with manic or mixed episodes associated with bipolar I disorder. This reviewer evaluated the bipolar I indication. For studies in support of schizophrenia indication, please refer to a separate statistical review by Dr. Yeh-Fong Chen.

Studies 1004 and 1005 were 3-week randomized, placebo and olanzapine controlled, double-blind, double-dummy, multicenter, international studies with identical design. A total of 611 patients at 61 centers entered Study1004, 488 patients were randomized and 342 patients completed the study. The most common reasons for discontinuing the study were withdrew consent and lack of efficacy. There were 654 enrolled patients at 55 centers in Study1005, 489 patients were randomized and 338 patients completed the study. The most common reasons for discontinuing the study were withdrew consent and lack of efficacy.

1.3 STATISTICAL ISSUES AND FINDINGS

In studies 1004 and 1005, YMRS and CGI-BP total scores were statistically significantly improved (ie, decreased) in the asenapine treatment group compared with the placebo treatment group. Based on the LOCF ANCOVA analysis, the p-values for asenapine vs. placebo with respect to YMRS total score were <0.001 in both studies. The p-values for asenapine vs. placebo with respect to CGI-BP total score were 0.0116 (study 1004) and 0.0017 (study 1005).

In study 1004, the observed asenapine treatment effect compared with placebo appears to be mainly driven by the non US patients subgroup (see Table 14). The observed treatment differences between asenapine and placebo for US and non US subgroups were respectively 0.13 (SE 1.63) and -8.73 (SE 2.32). For study 1005, the observed treatment effects appeared to be consistent across the US and non US subgroups.

One of the inclusion criteria required that to be eligible for the studies a patient had to have YMRS total score ≥20 at screening and at baseline. In both studies there were several patients included in the ITT population with baseline YMRS total score of 18 and 19. However, the primary efficacy results were not affected by the data from these patients.

INTRODUCTION

1.4 OVERVIEW

The development program was designed to investigate in parallel asenapine's efficacy in 2 different indications: treatment of schizophrenia and treatment of acute manic or mixed episodes associated with bipolar I disorder. Two pivotal studies (A75011004 and A7501005) were submitted in support of efficacy of asenapine compared with placebo in treatment of subjects with manic or mixed episodes associated with bipolar I Disorder. This reviewer evaluated the bipolar indication. For studies in support of schizophrenia indication, please refer to a separate statistical review by Dr. Yeh-Fong Chen.

1.5 DATA SOURCES

Data used for review are from the electronic submission received on August 30, 2007. The network path is \\Cdsesub1\evsprod\NDA022117\0000\ in the EDR.

2 STATISTICAL EVALUATION

2.1 EVALUATION OF EFFICACY

2.1.1 OBJECTIVE

The primary objective of trials 1004 and 1005 was to demonstrate the efficacy of asenapine compared with placebo in treatment of subjects with manic or mixed episodes associated with bipolar I disorder.

2.1.2 STUDY DESIGN

Studies 1004 and 1005 were 3-week randomized, placebo and olanzapine controlled, double-blind, double-dummy, parallel-group, multicenter, international studies to investigate efficacy of asenapine in treatment of adult patients with manic or mixed episodes associated with bipolar I disorder. Subjects were randomly assigned to receive asenapine, olanzapine, or placebo treatment in a ratio of 2:2:1.

To be eligible for the studies a patient had to have a primary diagnosis of bipolar I disorder, current episode manic (DSM-IV 296.4x), or mixed (DSM-IV 296.6x) as determined by a structured clinical interview (MINI) at screening; had a YMRS score ≥20 at screening and at baseline; had a current manic or mixed bipolar I episode that must have begun no more than 3 months prior to the screening visit; had a documented history of at least one previous moderate-to-severe mood episode with or without psychotic features (manic or mixed).

The trial included (up to) a 7-day single-blind placebo run in period during which subjects experiencing a manic or mixed episode received single-blind placebo (placebo olanzapine). After placebo run in, the active treatment period was initiated on Day 1 with placebo, asenapine 10 mg BID, or olanzapine 15 mg QD. Thereafter, treatment continued with flexible dosing (asenapine

5- 10 mg BID, olanzapine 5-20 mg QD, or placebo). Subjects remained confined to an inpatient research facility for at least the first 7 days of active treatment (through Day 7), and were subsequently discharged if deemed clinically stable by the investigator. Subjects completing the trial were eligible for enrollment in an extension trial, Protocol A7501006.

Table 1. Chart for Studies 1004 and 1005.

Screening/Placebo Run-In	Treatment Phase	Extension protocol A7501006
Up to 7 days	3 weeks	9 weeks
Placebo	Placebo, 5-10 mg asenapine, 5-20 mg olanzapine	5-10 mg asenapine, 5-20 mg olanzapine

Source: Corresponds to Figure 1 (pg 37), Clinical Study Report A7501004 and Figure 1(pg 35), Clinical Study Report A7501005.

Screening evaluations were conducted between 7 days prior to and the day immediately before the first double-blind dose. After performing all screening procedures, subjects began (up to) 7 days of single-blinded placebo run-in to allow for time to obtain clinical laboratory results and washout of excluded medications, including mood stabilizers. Eligibility determinations were made by the investigator using local or central laboratory results. In case of any unexpected, clinically relevant abnormal values, including the presence of mood stabilizers at levels higher than those outlined in the exclusion criteria, additional samples were to be obtained and analyzed prior to randomization. Lorazepam for the treatment of agitation was allowed at a maximum dose of 4 mg/day during the screening phase and for the first 7 days following the baseline assessment. The use of benzodiazepines after Day 7 was not permitted.

Remark: The Y-MRS, an 11-item, clinician-rated instrument used for assessing the symptoms of mania, was the primary efficacy variable. The Y-MRS was evaluated at screening and Days 1, 2, 4, 7, 14, and 21 (study endpoint).

2.1.3 PATIENT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Study 1004

This trial was carried out from 30 November 2004 until 29 April 2006. The study was conducted at 61 centers, including 32 in the US, 2 in Bulgaria, 6 in India, 2 Korea, 3 Malaysia, 3 Philippines, 2 Romania, 4 Russia, and 7 in the Ukraine.

A total of 488 subjects were randomized to trial medication: 185 subjects to asenapine, 205 subjects to olanzapine, and 98 subjects to placebo (see Table 2). All randomized subjects received at least 1 dose of trial medication. A total of 342 subjects completed the trial. The proportion of patients who withdrew due to an adverse event/SAE related to the disease under study (bipolar disorder) appears to be higher in asenapine group (9.2%) compared with olanzapine group (3.4%) and placebo (4.1%).

Table 2. Study 1004 Summary of subject disposition and discontinuation

	Placebo	Asenapine	Olanzapine	All Subjects
Patients Randomized	98	185	205	488
Intent-to-treat Population	94	183	203	480
Withdrawn during double-blind, n (%)	41 (41.8%)	61 (33.0%)	44 (21.5%)	146 (29.9%)
Adverse Event/SAE	4 (4.1%)	17 (9.2%)	7 (3.4%)	28 (5.7%)
Lack of Efficacy	14 (14.3%)	14 (7.6%)	13 (6.3%)	41 (8.4%)
Withdrew consent	13 (13.3%)	25 (13.5%)	15 (7.3%)	53 (10.9%)
Lost to follow-up	4 (4.1%)	1 (0.5%)	6 (2.9%)	11 (2.3%)
Other	6 (6.1%)	4 (2.2%)	3 (1.5%)	13 (2.7%)
Completed double-blind	57 (58.2%)	124 (67.0%)	161 (78.5%)	342 (70.1%)

Source: Clinical Study Report A7501004, Table 5 (pg. 77)

All treatment groups appear comparable with respect to age, race, weight, and baseline YMRS total score. The proportion of male subjects was higher in the olanzapine group (57.1%) than in the asenapine (49.7%) or placebo (49.0%) groups (see Table 3). There were two patients randomized to asenapine group and included in the ITT population with baseline YMRS total score of 18.

Table 3. Study 1004 Summary of demographics and baseline characteristics (all randomized patients)

Characteristics	Placebo N=98	Asenapine N=185	Olanzapine N=205	All subjects N=488
Gender				
Male	48 (49.0%)	92 (49.7%)	117 (57.1%)	257 (52.7%)
Female	50 (51.0%)	93 (50.3%)	88 (42.9%)	231 (47.3%)
Race				
Caucasian	55 (56.1%)	104 (56.2%)	110 (53.7%)	269 (55.1%)
African	16 (16.3%)	38 (20.5%)	41 (20.0%)	95 (19.5%)
Asian	22 (22.4%)	40 (21.6%)	44 (21.5%)	106 (21.7%)
Other	5 (5.1%)	3 (1.6%)	10 (4.9%)	18 (3.7%)
Age Category				
18-64 years	95 (96.9%)	179 (96.8%)	204 (99.5%)	478 (98.0%)
>=65 years	3 (3.1%)	6 (3.2%)	1 (0.5%)	10 (2.0%)
Age, years				
Mean (SD)	38.1 (12.49%)	39.1 (12.26)	38.4 (10.82)	38.6 (11.71)
Median	38.0	40.0	39.0	39.0
Range	18, 69	18, 76	18, 66	18, 76
Weight, kg				
Mean (SD)	78.1 (19.82)	75.9 (19.20)	77.9 (19.99)	77.2 (19. 65)
Median	77.3	72.6	77.3	75.4
Range	41, 166	38, 144	38, 136	38, 166
YMRS (at baseline)				
Mean (SD)	28.2 (6.27)	29.4 (6.68)	29.7 (6.61)	29.3 (6.58)
Median	26.5	28.0	28.0	28.0
Range	20, 48	18, 54	20, 56	18, 56

Source: Clinical Study Report A7501004, Table 12 (pg 86).

Study 1005

This trial was carried out from 30 November 2004 until 29 April 2006. The study was conducted at 55 centers, 29 in the US, 2 in Bulgaria, 6 in India, 3 in Korea, 1 in Malaysia, 2 in the Philippines, 2 in Romania, 4 in the Russian Federation, 2 in Turkey, and 4 in Ukraine.

A total of 489 subjects were randomized to trial medication: 194 subjects to asenapine, 191 subjects to olanzapine, and 104 subjects to placebo (see Table 4). Of these, 488 subjects received at least 1 dose of trial medication. A total of 338 subjects completed the trial. In the asenapine and olanzapine treatment groups, the most common reason for withdrawal was withdrawal of consent. It appears that the proportion of patients who withdrew due to an adverse event/SAE is higher in the asenapine group: 10.3% asenapine-treated subjects, 4.2% olanzapine-treated subjects, and 6.7% placebo-treated subjects (see Table 4).

Table 4. Study 1005 Summary of subject disposition and discontinuation

	Placebo	**Asenapine**	**Olanzapine**	**All Subjects**
Patients Randomized	104	194	191	489
Intent-to-treat Population	103	189	188	480
Withdrawn during double-blind, n (%)	40 (38.55%)	72 (37.1%)	39 (20.4%)	151 (30.9%)
Adverse Event/SAE	7 (6.7%)	20 (10.3%)	8 (4.2%)	35 (7.2%)
Lack of Efficacy	17 (16.3%)	16 (8.2%)	11 (5.8%)	44 (9.0%)
Withdrew consent	13 (12.5%)	28 (14.4%)	16 (8.4%)	57 (11.7%)
Lost to follow-up	2 (1.9%)	5 (2.6%)	2 (1.0%)	9 (1.8%)
Other	1 (1.0%)	3 (1.5%)	2 (1.0%)	6 (1.2%)
Completed double-blind	64 (61.5%)	122 (62.9%)	152 (79.6%)	338 (69.1%)

Source: Clinical Study Report A7501005, Table 5 (pg. 74)

All treatment groups were comparable with respect to age, race, and weight. The proportion of male subjects was higher in the olanzapine (60.0%) and asenapine groups (58.8%) than in the placebo (50.0%) groups (see Table 5). There was one patient with YMRS baseline score of 3 randomized to asenapine group. The patient was not included in the ITT population. Two patients with YMRS total score of 18 (placebo) and one patient with baseline YMRS total score of 19 (olanzapine group) were included in the ITT population.

Table 5. Study 1005 Summary of Demographics and Baseline characteristics (all patients treated)

Characterisitcs	Placebo N=104	Asenapine N=194	Olanzapine N=190	All subjects N=488
Gender				
Male	52 (50%)	114 (58.8%)	114 (60%)	280 (57.4%)
Female	52 (50%)	80 (41.2%)	76 (40%)	208 (42.6%)
Race				
Caucasian	59 (56.7%)	122 (62.9%)	114 (60%)	295 (60.5%)
African	19 (18.3%)	31 (16.0%)	31 (16.3%)	81 (16.6%)
Asian	19 (18.3%)	35 (18.0%)	34 (17.9%)	88 (18.0%)
Other	7 (6.7%)	6 (3.1%)	11 (5.8%)	24 (4.9%)
Age				
18-64 years	103 (99.0%)	193 (99.5%)	186 (97.9%)	482 (98.8%)
>=65 years	1 (1.0%)	1 (0.5%)	4 (2.1%)	6 (1.2%)
Age, years				
Mean (SD)	39.4 (11.99)	38.7 (11.88)	40.1 (11.30)	39.4 (11.67)
Median	41.5	40.0	40.0	40.0
Range	18, 66	18, 68	19, 67	18, 68
Weight, kg				
Mean (SD)	78.2 (19.17)	77.7 (19.11)	79.7 (19.88)	78.6 (19.41)
Median	77.1	75.5	79.2	77.1
Range	43, 181	41, 146	33, 145	33, 181
YMRS at baseline				
Mean (SD)	29.0 (6.11)	28.1 (5.77)	28.5 (5.89)	28.5 (5.89)
Median	29.0	28.0	28.0	28.0
Range	18, 47	3, 46	19, 51	3, 51

Source: Clinical Study Report A7501005, Table 12 (pg 82).

2.1.4 STATISTICAL METHODOLOGIES

The primary efficacy endpoint, change from baseline to Day 21 on the Y-MRS total score, was analyzed by a fixed-effects analysis of covariance (ANCOVA) using the LOCF method. The primary model used the ITT population with the baseline score as a covariate and allowed for variability due to center and treatment. Small centers were pooled for analysis. The intent-to-treat (ITT) analysis set consisted of all subjects who were randomly assigned to treatment, received at least 1 dose of trial medication, and had at least 1 post-baseline YMRS score.

During the conduct of the trials, it was learned that a small number of subjects, particularly in certain geographic areas within the US with more than one study site in the trial A7501004 or trial A7501005, had enrolled into the trials at more than one study site. That is, these subjects were “repeat” patients and had violated the exclusion criterion 14 (previously participated in an asenapine trial). Prior to blind break, the statistical analysis plan was amended to include efficacy data from these subjects’ initial participation in the trial only in the ITT population. Safety data for these subjects were not excluded from analyses or summary tables.

The robustness of the results against potential bias caused by missing data was checked by a mixed-model analysis using repeated measures. Secondary analyses included analysis of change from baseline in Y-MRS at all assessed time points.

Pooling algorithm for centers: For non-US sites, all investigative sites within a country with fewer than 10 randomized subjects will be combined into a single pooled site for analysis purposes. If a resulting pooled site still has fewer than 10 randomized subjects, then this pooled site will be further combined with the smallest unpooled site within that country. If there is not another unpooled site within that country, then the pooled site will be combined with the smallest pooled site from another country. This pooling process will continue until there are at least 10 randomized subjects in each pooled site. For US sites, all investigative sites within a geographic region with fewer than 10 randomized subjects will be combined into a single pooled site for analysis purposes. If a resulting pooled site still has fewer than 10 randomized subjects, then this pooled site will be further combined with the smallest unpooled site within that region. If there is not another unpooled site within that region, then the pooled site will be combined with the smallest pooled site from another region within the US. This pooling process will continue until there are at least 10 randomized subjects in each pooled site.

2.1.5 RESULTS OF EFFICACY ANALYSES

Primary Analysis

Based on the LOCF ANCOVA analysis, Y-MRS total scores were statistically significantly improved (i.e. decreased) from baseline to Day 21 in the asenapine and olanzapine treatment groups compared with the placebo treatment group. The results are presented in Table 6. For Study 1004, the LS mean change from baseline to Day 21 was -11.5, -7.8, and -14.6 for the asenapine, placebo, and olanzapine treatment groups, respectively ($p=0.0065$ for asenapine vs. placebo and $p<0.0001$ for olanzapine vs. placebo). For Study 1005, the LS mean change from baseline to Day 21 was -10.8, -5.5, and -12.6 for the asenapine, placebo, and olanzapine treatment groups, respectively ($p<0.0001$ for both comparisons with placebo).

Table 6. YMRS Total Score LS mean Change from Baseline to Endpoint (ITT Population)

	Placebo	**Asenapine**	**Olanzapine**
Study 1004			
Number of Patients	94	183	203
Baseline Mean (SD)	28.3 (6.32)	29.4 (6.72)	29.7 (6.64)
Day 21 Mean (SD)	20.4 (12.70)	17.7 (11.91)	14.9 (10.47)
Mean Change from Baseline (SD)	-7.9 (11.46)	-11.7 (11.34)	-14.8 (10.37)
LS Mean Change from Baseline (SE)	-7.8 (1.11)	-11.5 (0.80)	-14.6 (0.76)
P-value vs. Placebo		0.0065	<0.0001
Study 1005			
Number of Patients	103	189	188
Baseline Mean (SD)	29.0 (6.14)	28.3 (5.53)	28.6 (5.88)
Day 21 Mean (SD)	23.5 (12.57)	17.7 (11.29)	16.1 (9.43)
Mean Change from Baseline (SD)	-5.5 (10.63)	-10.5 (11.13)	-12.5 (9.71)
LS Mean Change from Baseline (SE)	-5.5 (1.01)	-10.8 (0.75)	-12.6 (0.76)
P-value vs. Placebo		<0.0001	<0.0001

Source: Clinical Study Report A7501004, Table 18 (pg 96);
Clinical Study Report A7501005, Table 18 (pg 91)
Note: The reported p-values are nominal and are not adjusted for multiplicity.

Supportive analysis

As an exploratory analysis, the same ANCOVA model was applied to analyze change from baseline in Y-MRS at all assessed time points using LOCF method (see Table 7 and Table 8). The results supported the results on the primary endpoint.

Table 7. Study 1004: YMRS Total Score LS Mean Change from Baseline by Day

Visits	Placebo	Asenapine	Olanzapine
Day 2			
Number of Patients	93	175	200
LS mean Change from Baseline (SE)	-1.7 (0.54)	-3.2 (0.40)	-4.4 (0.37)
P-value vs. Placebo		0.0222	<0.0001
Day 4			
Number of Patients	94	183	203
LS mean Change from Baseline (SE)	-3.6 (0.65)	-5.5 (0.46)	-7.4 (0.44)
P-value vs. Placebo		0.0164	<0.0001
Day 7			
Number of Patients	94	183	203
LS mean Change from Baseline (SE)	-5.4 (0.80)	-7.6 (0.58)	-9.7 (0.55)
P-value vs. Placebo		0.0240	<0.0001
Day 14			
Number of Patients	94	183	203
LS mean Change from Baseline (SE)	-6.7 (1.02)	-10.4 (0.74)	-13.3 (0.70)
P-value vs. Placebo		0.0027	<0.0001
Day 21			
Number of Patients	94	183	203
LS mean Change from Baseline (SE)	-7.8 (1.11)	-11.5 (0.80)	-14.6 (0.76)
P-value vs. Placebo		0.0065	<0.0001

Source: Clinical Study Report A7501004, Table 19 (pg 98)
Note: The reported p-values are nominal and are not adjusted for multiplicity. P-values are based on the difference in the LS means for asenapine and olanzapine treatments versus placebo.

Table 8. Study 1005 YMRS Total Score LS Mean Change from Baseline by Day

Visits	Placebo	Asenapine	Olanzapine
Day 2			
Number of Patients	101	183	182
LS mean Change from Baseline (SE)	-1.5 (0.47)	-3.0 (0.35)	-3.4 (0.35)
P-value vs. Placebo		0.0077	0.0010
Day 4			
Number of Patients	103	189	188
LS mean Change from Baseline (SE)	-3.0 (0.56)	-5.5 (0.41)	-6.6 (0.42)
P-value vs. Placebo		0.0003	<0.0001
Day 7			
Number of Patients	103	189	188
LS mean Change from Baseline (SE)	-3.1 (0.72)	-6.9 (0.53)	-8.2 (0.54)
P-value vs. Placebo		<0.0001	<0.0001
Day 14			
Number of Patients	103	189	188
LS mean Change from Baseline (SE)	-5.1 (0.92)	-9.2 (0.68)	-10.1 (0.69)
P-value vs. Placebo		0.0003	<0.0001
Day 21			
Number of Patients	103	189	188
LS mean Change from Baseline (SE)	-5.5 (1.01)	-10.8 (0.75)	-12.6 (0.76)
P-value vs. Placebo		<0.0001	<0.0001

Source: Clinical Study Report A7501005, Table 19 (pg 92)
Note: The reported p-values are nominal and are not adjusted for multiplicity. P-values are based on the difference in the LS means for asenapine and olanzapine treatments versus placebo.

Sensitivity Analysis

This reviewer conducted sensitivity analysis on the primary efficacy measure. Change from baseline in YMRS Total score was analyzed by mixed effect repeated measures model. The model included therapy, pooled center, visit (day), and interaction of therapy by visit as fixed effects, and baseline as a covariate. The unstructured variance-covariance matrix was used. The results confirmed the results on the primary analysis.

Table 9. Mixed model for repeated measures analysis of change from baseline in YMRS total score

	Study A7501004			Study A7501005		
Visit	**Placebo**	**Asenapine**	**Olanzapine**	**Placebo**	**Asenapine**	**Olanzapine**
	N=94	N=183	N=203	N=103	N=189	N=188
Day 2						
LS Mean Change (SE)	-1.7 (0.55)	-3.2 (0.4)	-4.3 (0.37)	-1.5 (0.47)	-3.1 (0.35)	-3.5 (0.35)
p- value		0.0202	0.0001		0.0054	0.0007
Day 4						
LS Mean Change (SE)	-3.7 (0.66)	-5.8 (0.47)	-7.4 (0.45)	-3.2 (0.56)	-5.7 (0.41)	-6.8 (0.41)
p- value		0.0079	<0.0001		0.0002	<0.0001
Day 7						
LS Mean Change (SE)	-6.2 (0.93)	-8.6 (0.68)	-10.2 (0.62)	-3.8 (0.84)	-7.7 (0.61)	-8.8 (0.6)
p- value		0.0313	0.0003		0.0002	<0.0001
Day 14						
LS Mean Change (SE)	-8.2 (1.06)	-12 (0.76)	-14 (0.69)	-6.9 (0.97)	-10.9 (0.71)	-11.0 (0.69)
p- value		0.0255	0.0003		0.0009	0.0006
Day 21						
LS Mean Change (SE)	-10.8 (1.22)	-14.2 (0.85)	-16.1 (0.77)	-7.4 (1.14)	-13.1 (0.82)	-13.9 (0.78)
p- value		0.0255	0.0003		0.0001	<0.0001

Source: Module 2.7.3 Bipolar Summary of Clinical Efficacy, Table 13 (pg 40)
Note: The reported p-values are nominal and are not adjusted for multiplicity. P-values are based on the difference in the LS means for asenapine and olanzapine treatments versus placebo.

Key Secondary Endpoint

Change from baseline to Day 21 in CGI-BP severity of mania was analyzed by ANCOVA model with treatment and pooled investigative site as fixed effects and baseline as a covariate.
For both studies, improvements in CGI-BP severity of mania from baseline to Day 21 were statistically significantly greater in the asenapine group compared with the placebo group (p=0.0116 in Study 1004, p=0.0017 in Study 1005).

Table 10. CGI-BP Severity Total Score LS mean Change from Baseline to Endpoint (ITT Population)

	Placebo	Asenapine	Olanzapine
Study 1004			
Number of Patients	94	183	203
Baseline Mean (SD)	4.5 (0.79)	4.6 (0.79)	4.6 (0.77)
Day 21 Mean (SD)	3.6 (1.39)	3.3 (1.45)	3.0 (1.24)
Mean Change from Baseline (SD)	-0.8 (1.33)	-1.3 (1.43)	-1.5 (1.28)
LS Mean Change from Baseline (SE)	-0.8 (0.13)	-1.2 (0.10)	-1.5 (0.09)
P-value vs. Placebo		0.0116	<0.0001
Study 1005			
Number of Patients	103	189	188
Baseline Mean (SD)	4.7 (0.79)	4.7 (0.86)	4.6 (0.75)
Day 21 Mean (SD)	4.0 (1.54)	3.5 (1.41)	3.2 (1.16)
Mean Change from Baseline (SD)	-0.7 (1.34)	-1.2 (1.52)	-1.4 (1.20)
LS Mean Change from Baseline (SE)	-0.7 (0.13)	-1.2 (0.10)	-1.4 (0.10)
P-value vs. Placebo		0.0017	<.0001

Source: Clinical Study Report A7501004, Table 22 (pg 101);
Clinical Study Report A7501005, Table 22 (pg 95)
Note: The reported p-values are nominal and are not adjusted for multiplicity.

As an exploratory analysis, this reviewer also considered Cochran-Mantel-Haenszel tests to compare Asenapine versus Placebo. For both studies, improvements in CGI-BP severity of mania from baseline to Day 21 were statistically significantly greater in the asenapine group compared with the placebo group.

Table 11. Cochran-Mantel-Haenszel analysis of change from baseline in CGI-BP Severity Total Score

P-values from Cochran- Mantel-Haenszel Test			
Study 1004		**Study 1005**	
Asenapine vs Placebo	Olanzapine vs Placebo	Asenapine vs Placebo	Olanzapine vs Placebo
0.0117	<0.0001	0.0054	<0.0001

Source: Reviewers results
Note: The reported p-values are nominal p-values and are not adjusted for multiplicity.

2.1.6 REVIEWER'S COMMENTS.

In studies 1004 and 1005, YMRS and CGI-BP total scores were statistically significantly improved (ie, decreased) in the asenapine treatment group compared with the placebo treatment group. Based on the LOCF ANCOVA analysis, the p-values for asenapine vs. placebo with respect to YMRS total score were <0.001 in both studies. The p-values for asenapine vs. placebo with respect to CGI-BP total score were 0.0116 (study 1004) and 0.0017 (study 1005).

One of the inclusion criteria required that to be eligible for the studies a patient had to have YMRS total score ≥20 at screening and at baseline. In both studies there were several patients included in the ITT population with baseline YMRS total score of 18 and 19. However, the primary efficacy results were not affected by the data from these patients.

2.2 EVALUATION OF SAFETY

Not evaluated by this reviewer. Please refer to clinical review of this application for a detailed safety evaluation.

3 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

3.1 GENDER, RACE AND AGE

The reviewer conducted the exploratory analysis for gender and origin subgroups using LOCF ANCOVA model with treatment as a fixed effect and baseline as a covariate. Among all the subgroups, the treatment effect appeared to be numerically in favor of asenapine and olanzapine when compared with placebo. The subgroup analysis by age was not considered since there were too few patients over 65 years of age.

Table 12. Subgroup analysis by gender and race: YMRS total score LS mean change from baseline to endpoint (ITT population)

	Study A7501004			Study A7501005		
	Placebo	**Asenapine**	**Olanzapine**	**Placebo**	**Asenapine**	**Olanzapine**
Gender						
Male; N	47	92	116	51	111	114
Baseline, Mean (SD)	27.5 (5.11)	29.1 (7.03)	29 (6.24)	29.3 (6.74)	27.6 (5.36)	28.4 (5.57)
LS Mean Change from Baseline (SE)	-7.5 (1.53)	-11.1 (1.09)	-15.0 (0.97)	-3.7 (1.31)	-10.6 (0.89)	-12.8 (0.87)
Female; N	47	91	87	52	78	74
Baseline, Mean (SD)	29.1 (7.31)	29.7 (6.41)	30.7 (7.05)	28.8 (5.54)	29.2 (5.67)	28.9 (6.37)
LS Mean Change from Baseline (SE)	-9.2 (1.61)	-12.5 (1.15)	-14.5 (1.18)	-7.1 (1.58)	-10.7 (1.29)	-12.1 (1.33)
Race						
Caucasian; N	52	103	109	58	118	112
Baseline, Mean (SD)	27.0 (5.81)	27.9 (5.59)	28.8 (5.74)	28.0 (5.97)	27.4 (5.22)	28.5 (5.60)
LS Mean Change from Baseline (SE)	-9.7 (1.28)	-10.6 (0.91)	-13.8 (0.89)	-6.9 (1.28)	-9.8 (0.90)	-12.2 (0.92)
Black; N	15	37	40	19	30	31
Baseline, Mean (SD)	30.8 (6.81)	30.1 (6.32)	29.9 (6.64)	27.1 (4.68)	27.9 (3.80)	26.8 (4.58)
LS Mean Change from Baseline (SE)	-8.3 (2.58)	-9.8 (1.64)	-12.8 (1.58)	-6.0 (2.23)	-9.4 (1.78)	-10.1 (1.75)
Asian; N	22	40	44	19	35	34
Baseline, Mean (SD)	30.1 (6.90)	32.5 (8.59)	32.2 (7.94)	34.7 (5.60)	31.3 (7.01)	30.9 (7.73)
LS Mean Change from Baseline (SE)	-4.2 (2.99)	-16.6 (2.21)	-18.6 (2.10)	-0.4 (2.81)	-13.1 (2.04)	-16.3 (2.07)
Others; N	5	3	10	7	6	11
Baseline, Mean (SD)	26.2 (4.09)	30.3 (6.11)	28.0 (7.48)	27.4 (3.69)	29.2 (3.06)	27.0 (2.79)
LS Mean Change from Baseline (SE)	-12.3 (3.90)	-13.5 (5.05)	-16.5 (2.73)	-4.7 (3.49)	-19.6 (3.89)	-10.8 (2.82)

Source: Reviewer's Results
Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

3.2 OTHER SPECIAL/SUBGROUP POPULATIONS

This reviewer conducted exploratory subgroup analysis of efficacy by principal psychiatric diagnosis and region/country (US, non US) using LOCF ANCOVA model with treatment as a fixed effect and baseline as a covariate. The treatment effect appeared to be numerically in favor of asenapine when compared with placebo except for US patients subgroup in study 1004. For this subgroup, the LS mean changes from baseline in YMRS total score were -10.4 (SE 0.93) in the asenapine arm and -10.5 (SE 1.34) in the placebo arm. For patients randomized to olanzapine the LS mean change was - 14.2 (SE 0.89).

Table 13. Subgroup analysis by psychiatric diagnosis: YMRS total LS mean change from baseline to endpoint

	Study A7501004			Study A7501005		
	Placebo	**Asenapine**	**Olanzapine**	**Placebo**	**Asenapine**	**Olanzapine**
Psychiatric Diagnosis						
Manic; N	63	129	139	68	136	130
Baseline, Mean (SD)	28.0 (5.72)	29.6 (6.83)	30.3 (6.20)	30.2 (6.44)	28.8 (5.66)	29.5 (6.08)
LS Mean Change from Baseline (SE)	-7.9 (1.39)	-12.2 (0.97)	-15.4 (0.93)	-4.9 (1.32)	-10.9 (0.93)	-13.0 (0.95)
Mixed; N	31	54	64	35	53	58
Baseline, Mean (SD)	28.9 (7.46)	28.8 (6.46)	28.4 (7.40)	26.9 (4.90)	26.8 (4.94)	26.6 (4.92)
LS Mean Change from Baseline (SE)	-9.0 (1.81)	-10.8 (1.37)	-13.5 (1.26)	-6.3 (1.47)	-9.9 (1.19)	-11.7 (1.14)

Source: Reviewer's Results
Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

Table 14. Subgroup analysis by region/country: YMRS total LS mean change from baseline to endpoint

	Study A7501004			Study A7501005		
	Placebo	**Asenapine**	**Olanzapine**	**Placebo**	**Asenapine**	**Olanzapine**
Psychiatric Diagnosis						
US; N	54	112	121	65	118	122
Baseline, Mean (SD)	27.7 (5.94)	28.8 (6.19)	29.2 (6.22)	27.7 (5.32)	27.2 (4.55)	27.4 (4.82)
LS Mean Change from Baseline (SE)	-10.5 (1.34)	-10.4 (0.93)	-14.2 (0.89)	-6.1 (1.13)	-10.4 (0.84)	-11.6 (0.83)
Non US ; N	40	71	82	38	71	66
Baseline, Mean (SD)	29.1 (6.80)	30.3 (7.42)	30.5 (7.18)	31.4 (6.78)	30.06 (6.50)	30.7 (7.04)
LS Mean Change from Baseline (SE)	-5.3 (1.85)	-14.1 (1.39)	-15.6 (1.29)	-4.2 (1.94)	-11.0 (1.41)	-14.2 (1.47)

Source: Reviewer's Results
Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

4 SUMMARY AND CONCLUSIONS

4.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

In studies 1004 and 1005, YMRS and CGI-BP total scores were statistically significantly improved (ie, decreased) in the asenapine treatment group compared with the placebo treatment group. Based on the LOCF ANCOVA analysis, the p-values for asenapine vs. placebo with respect to YMRS total score were <0.001 in both studies. The p-values for asenapine vs. placebo with respect to CGI-BP total score were 0.0116 (study 1004) and 0.0017 (study 1005).

In study 1004, the observed asenapine treatment effect compared with placebo appears to be mainly driven by the non US patients subgroup (see Table 14). The observed treatment differences between asenapine and placebo for US and non US subgroups were respectively 0.13 (SE 1.63) and -8.73 (SE 2.32). For study 1005, the observed treatment effects appeared to be consistent across the US and non US subgroups.

One of the inclusion criteria required that to be eligible for the studies a patient had to have YMRS total score ≥20 at screening and at baseline. In both studies there were several patients included in the ITT population with baseline YMRS total score of 18 and 19. However, the primary efficacy results were not affected by the data from these patients.

4.2 CONCLUSIONS AND RECOMMENDATIONS

At flexible doses of 5 to 10 mg BID (with 10 mg as the starting dose and the option to downtitrate to 5 mg), the asenapine group was statistically significantly superior to placebo in treatment of patients with manic or mixed episodes associated with Bipolar I as measured by the change from baseline in Y-MRS score on Day 21(primary endpoint, Intent-to-treat population) and CGI-BP severity of mania score on Day 21 (key secondary endpoint, Intent-to-treat population).

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George Kordzakhia
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Peiling Yang
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James Hung
4/18/2008 12:53:00 PM
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Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	22117
Brand Name	Sycrest®
Generic Name	Asenapine (ORG 5222)
Sponsor	Organon USA Inc.
Indication	Treatment of schizophrenia and acute manic or mixed episodes associated with Bipolar I disorder
Dosage Form	Fast dissolving sublingual tablets
Drug Class	Psychotropic agent
Therapeutic Dose	5 to 10 mg b.i.d.
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	20 mg b.i.d.
Application Submission Date	30 August 2007
Review Classification	Standard NDA
Date Consult Received	3 Oct 2007
Clinical Division	DPP / HFD 130
PDUFA Date	30 June 2008

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

This is a positive study by the ICH E14 guideline: the upper 95% confidence interval exceeded 10 ms for all doses.

In this randomized, placebo-controlled, double-blind, multicenter, parallel-group trial, subjects with schizophrenia or schizoaffective disorder received asenapine 5/10 mg b.i.d., asenapine 15/20 mg b.i.d., placebo, or quetiapine 375 mg b.i.d. for 16 days. A dose-response relationship was not observed for asenapine as shown in the following table. We note that with the small sample size (less than 35 subjects pre arm), the study was not powered to detect a dose-response relationship using the primary endpoint.

FDA Analysis: The Point Estimates and 90% CI Corresponding to the Largest Upper Bounds for Asenapine by Dose Group

Treatment	Time, h	Mean ΔΔQTcF, ms	90% CI, ms
Asenapine 5 mg b.i.d., N=30	3	5.0	-1.5, 11.4
Asenapine 10 mg b.i.d., N=27	2	10.5	4.5, 16.5
Asenapine 15 mg b.i.d., N=33	3	8.7	3.0, 14.4
Asenapine 20 mg b.i.d., N=29	4	4.9	-1.9, 11.6

Cross reference: reviewer's analysis in Table 10

An exposure-response analysis conducted by both the sponsor and FDA reviewers showed that asenapine prolonged the QTcF interval in a concentration-dependent manner (described in section 5.2.1.2). The model predicted mean ΔΔQTcF at a mean C_{max} of 10.6 ng/mL, which corresponds to an asenapine dose of 20 mg b.i.d., is 6 ms (8 ms, 90% upper confidence limit). Asenapine 20 mg b.i.d., the maximum tolerated dose in patients with schizophrenia, provides a 2-fold increase in exposure over the highest clinical dose (10 mg b.i.d.) and adequately covers the plasma concentrations observed in phase 2b/3 clinical studies (Figure 1). We note, however, that subjects with severe hepatic impairment have 7-fold increase unbound AUC. The magnitude of QT prolongation in these subjects is not known.

Because asenapine belongs to a pharmacological class of compounds associated with QT/QTc prolongation, the sponsor used quetiapine 375 mg b.i.d. as the positive control. The magnitude of quetiapine effects on the QTc interval is not well characterized. In this study, the difference from placebo in LS mean time-matched QTcF change from baseline at T_{max} was 7 ms (90% CI: 1, 13) on Day 10 and 10 (90% CI: 3, 17) ms on Day 16. The exposure-response relationship for quetiapine was similar to the observed relationship in Study R076477-SCH-1014 in NDA 21,999 (Table 13). Therefore, assay sensitivity with quetiapine could be established.

2 PROPOSED LABEL

The following is our recommendations for labeling. We defer all final labeling decisions to the review division.

5.9 QT Prolongation

The effects of Sycrest® on the QT interval were evaluated in a dedicated QT study [*see CLINICAL STUDIES* (14.3)]. Sycrest® causes a mild ~~(<5 ms)~~ increase in the corrected QT (QTc) interval ~~but the magnitude of the effect is such that it is not expected to be clinically relevant~~. Electrocardiogram (ECG) measurements were taken at various time points during the Sycrest® clinical trial program testing therapeutic doses (5-10 mg b.i.d.) and any post-baseline QT prolongations exceeding 500 ms were reported in comparable rates to placebo in the short-term trials.

Sycrest® should be used cautiously in combination with drugs that are known to prolong the QTc interval including Class 1A (e.g., quinidine, procainamide) or Class 3 (e.g., amiodarone, sotalol) antiarrhythmic medications, antipsychotic medications (e.g., chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other

class of medications known to prolong the QTc interval. Sycrest® should also be used cautiously in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias.

14.3 Thorough QT/QTc Trial

A trial assessing the potential QT/QTc prolonging effect of Sycrest® 5 mg, 10 mg, 15 mg, and 20 mg b.i.d. and placebo was conducted in 151 clinically stable patients with schizophrenia. Electrocardiographic assessments were performed throughout the dosing interval both at baseline and steady state. ~~The mean increase in QTc from baseline at C_{max}, as derived from exposure-response analysis, was 1.9 ms, 3.0 ms, 3.7 ms, and 4.9 ms for Sycrest® 5 mg, 10 mg, 15 mg, and 20 mg b.i.d., respectively; and 7.5 ms for quetiapine 375 mg b.i.d..~~ There was a concentration-dependent increase in QTc interval. ~~Categorical analyses for this study revealed that~~ No patients treated with Sycrest® experienced QTc increases >60 ms from baseline measurements, nor did any patient experience a QTc of >500 ms. Additionally, there were no reports of Torsade de Pointes or any other adverse events associated with delayed ventricular repolarization.

3 BACKGROUND

Asenapine (also referred to as Org 5222) is a psychotropic (psychopharmacologic) agent with a unique receptor binding profile that is available for sublingual administration. Asenapine's pharmacological profile displays potent multi-receptor antagonism for a combination of serotonin, dopamine, noradrenaline, and histamine receptors and no appreciable activity at muscarinic cholinergic receptors. The sponsor believes the compound may be effective in the treatment of various symptom domains in schizophrenia and/or mood disorders, and that it may have low propensity for the induction of extrapyramidal symptoms (EPS).

3.1 MARKET APPROVAL STATUS

Asenapine is not approved for marketing in the USA or elsewhere.

3.2 PRECLINICAL INFORMATION

Source: nonclinical summary

ORG 5222, tested at 0.1, 0.3, and 1 µM concentrations using HEK-293 cells transfected with HERG produced statistically significant and concentration-dependent decreases in hERG current amplitude (30.9 ± 4.3%, 51.2 ± 5.7%, and 69.8 ± 5.8%, respectively) when compared to vehicle control. The IC50 for ORG 5222, the concentration computed from the concentration-response relationship at which 50% of total current was suppressed, was 0.3 µM.

The results of a study in isolated canine Purkinje fibers indicate that asenapine induced mainly decreases in action potential duration, in particular on APD_{50}. These effects were associated with a decrease in the plateau of action potential involving mainly calcium channel current. Decreases in action potential duration were dose-dependent and were more pronounced under low stimulation rate (0.33Hz) than under normal stimulation rates (1Hz). N-desmethylasenapine induced comparable effects (decreased action potential duration, particularly APD_{50}) but at approximately 10 times higher concentrations.

Oral ORG 5222 (1-50 mg/kg) administered to conscious dogs induced dose-dependent negative inotropic and positive chronotropic effects, accompanied by shortening of the PR interval, less marked hypotensive effects and dose-dependently prolonged QTc. The QRS interval was shortened but only at the higher dose. Moderate orthostatic hypotension was observed on tilt which was accompanied by marked and dose-dependent tachycardia. Behavioral excitation was observed at dose levels from 2.5 mg/kg onwards. Sublingual administration of ORG 5222 (0.01-1 mg/kg) induced dose-dependent tachycardia in the absence of negative inotropy and hypotension. QTc was only markedly prolonged by the highest dose used which also lengthened QRS. A similar moderate orthostatic hypotension was seen upon tilt but the accompanying tachycardia was considerably less than after oral administration. Sublingually given Org 5222 caused minor and transient behavioral excitation at the highest dose only, but induced long lasting tranquilization especially at the mid and high doses.

Reviewer's Comment: Non clinical data are suggestive of dose-and concentration-dependent QT prolongation.

3.3 PREVIOUS CLINICAL EXPERIENCE

Source: Clinical Summary

There are 63 trials in the asenapine schizophrenia and bipolar mania clinical development programs that were conducted with the sublingual formulation of asenapine as of the database cut-off of 15 January 2007. The safety information from the completed Phase 2/3 trials was analyzed in five cohorts. As of the January 15, 2007 database cutoff date, there were 11 deaths in the all asenapine group, 1 death in the placebo group, and 3 deaths in the olanzapine group.

One subject in the long-term schizophrenia trial (study 25517) died from aspiration during a *seizure*. The subject, a 33 year old Caucasian female had received asenapine 5-10 mg for one month during the study and was discontinued due to a *seizure*. Three months later, she had another seizure that resulted in death. This death is not included in the tables and listings because it occurred more than 30 days after the last dose.

The most common adverse event leading to death was suicide (6 asenapine 5-10 mg b.i.d. [0.3%], 2 olanzapine [0.2%]). In addition, there were 2 drug overdoses that led to death, 1 in the asenapine 5-10 mg b.i.d. group (accidental overdose) and 1 in the olanzapine group (overdose) neither of the overdose cases was due to asenapine overdose. One subject died of cardiac failure in an ongoing trial

The most common cardiac AEs were bradycardia (3.6%) and tachycardia (2.8%)

A 27 year old male Caucasian healthy volunteer (study 25506), collapsed 15 minutes after the end of a 30 minute intravenous infusion of asenapine (0.7 mg). Just prior to collapse, the subject reported feeling dizzy and unwell and then fell back on the bed. The event was reported as *asystole*; however, this event was considered to be due to neurally mediated reflex bradycardia. The subject recovered.

A 22 year old Caucasian male (resting heart of 58 bpm), received a 30 mg oral dose of asenapine in study 25501. Approximately 2.5 hours after the dose, the subject sat up in bed and felt dizzy and nauseated. The ECG telemetry strip showed heart rate slowing and an *8.7 second pause*. *This was followed by heart block with nodal bradycardia*, which spontaneously converted to sinus rhythm. He had another episode 2 hours later. Both episodes resolved spontaneously without intervention while the subject remained in the supine position.

Vomiting, *syncope*, hypotension were experienced by a 23 year old female (study 25504), following asenapine (4 mg dose) on Day 13, which led to discontinuation from the study (considered related to study drug). Subject recovered the same day.

Grand mal *convulsion* occurred in a 59 year old male (study 25505), following asenapine (2 mg dose) on Day 6, which led to discontinuation from the study. Subject recovered the same day. According to the investigator, the grand mal convulsion was due to hyponatraemia (sodium: 114 mmol/L) secondary to polydipsia and was not related to study drug (see Section 2.7.4.2.1.5.7 on hyponatraemia).

In the long-term schizophrenia study 25517, ECGs were performed at Screening, Weeks 3, 6, 24, and endpoint, and the tracings were read by a central laboratory. Analyses included interval changes from baseline (descriptive statistics), categorical changes, outlier analysis, and post-baseline markedly abnormal changes in morphology. The most frequently reported ECG related AE in the asenapine group (1.2%) was Electrocardiogram QT corrected interval prolonged (0.6% in the olanzapine treatment group).

Reviewers Comment: QT prolongation was also noted in clinical studies. Seizures can be expected in this population due to lowering of seizure threshold due to drug, polydipsia/substance abuse. However, syncope/asystole and an 8.7 sinus pause were noted in young healthy subjects.

3.4 CLINICAL PHARMACOLOGY

Appendix 7.1 summarizes the key features of asenapine's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the following:

- Clinical study report for Study A750-1001 and associated electronic data sets
- Report for Study INT00036960 and associated electronic data sets
- Digital ECGs in the ECG Warehouse for Study A750-1001

4.2 TQT STUDY

4.2.1 Protocol Number and Title

Protocol A7501001: A Double-Blind, Parallel, Multicenter Study to Assess the Effect of Asenapine, Quetiapine (Seroquel®), and Placebo on the QTc Interval in Patients With Schizophrenia

4.2.2 Study Dates

Clinical Trial Start: 29 June 2004
Clinical Trial Completion: 20 December 2004

4.2.3 Objectives

The objectives of this trial were to estimate the effect of asenapine, compared with placebo, on the QTc interval; to estimate the differences between asenapine and

quetiapine on the QTc interval; and to characterize the pharmacodynamic response of asenapine with respect to dose and plasma concentration.

4.2.4 Study Description

4.2.4.1 Design

This was a randomized, placebo-controlled, double-blind, multicenter, parallel-group trial with 2 treatment periods.

Following screening and medication tapering if needed, each subject was evaluated for a minimum of 24 days, consisting of a 5-day single-blind placebo run-in phase, a 16-day treatment phase that included 2 treatment periods, and a post-treatment restabilization period.

4.2.4.2 Controls

The Sponsor used both placebo and active (quetiapine) controls.

4.2.4.3 Blinding

Study drug was administered in a double-blind, double-dummy fashion during periods 1 and 2.

4.2.5 Treatment Regimen

4.2.5.1 Treatment Arms

Subjects were assigned to 1 of 4 treatment groups as shown in Table 1.

Table 1: Treatment Groups

Group	Drug	Period 1: Target Dose (w/Titration)	Period 2: Target Dose (w/Titration)
1	Asenapine	5 mg BID × 10 days	10 mg BID × 6 days
2	Asenapine	15 mg BID × 10 days	20 mg BID × 6 days
3	Quetiapine	375 mg BID × 10 days	375 mg BID × 6 days
4	Placebo	BID × 10 days	BID × 6 days

Sponsor's Table 2, page 26 of CSR for A750-1001

Table 2: Dose Schedule Showing Titration

Day	Placebo	Asenapine		Quetiapine
		5/10 BID	15/20 BID	
1	Placebo BID	5 mg BID	5 mg BID	25 mg BID
2	Placebo BID	5 mg BID	10 mg BID	50 mg BID
3	Placebo BID	5 mg BID	15 mg BID	100 mg BID
4	Placebo BID	5 mg BID	15 mg BID	150 mg BID
5	Placebo BID	5 mg BID	15 mg BID	200 mg BID
6	Placebo BID	5 mg BID	15 mg BID	250 mg BID
7	Placebo BID	5 mg BID	15 mg BID	300 mg BID
8	Placebo BID	5 mg BID	15 mg BID	375 mg BID
9	Placebo BID	5 mg BID	15 mg BID	375 mg BID
10	Placebo BID	5 mg BID	15 mg BID	375 mg BID
11	Placebo BID	10 mg BID	20 mg BID	375 mg BID
12	Placebo BID	10 mg BID	20 mg BID	375 mg BID
13	Placebo BID	10 mg BID	20 mg BID	375 mg BID
14	Placebo BID	10 mg BID	20 mg BID	375 mg BID
15	Placebo BID	10 mg BID	20 mg BID	375 mg BID
16	Placebo BID	10 mg BID	20 mg BID	375 mg BID

Sponsor's Table 5, page 34 of CSR for A750-1001

4.2.5.2 Sponsor's Justification for Doses

The asenapine dose range in the present trial included the lowest effective dose (5 mg b.i.d.) and the maximally tolerated dose (20 mg b.i.d.). This was to allow determination of the dose-response and the construction of a pharmacokinetic/pharmacodynamic model of the QTc effect.

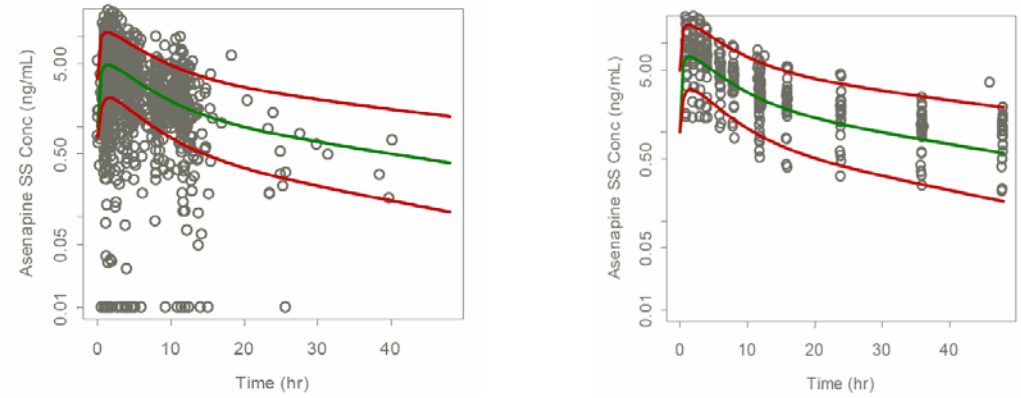
Quetiapine was included to assure assay sensitivity and to make direct comparisons with asenapine. The mean change from baseline in QTc for quetiapine without metabolic inhibition was 4.8 and 5.7 ms for Fridericia's and the population-based correction, respectively. The dose of 750 mg per day approximates the maximally recommended dose, and was the same as in the trial described above.

Reviewer's Comments:

- *Asenapine dose selection for the QT study was reasonable. The exposures achieved with 20mg b.i.d. asenapine reasonably cover the exposures after 10 mg b.i.d. in the phase IIb/III trial in schizophrenia indication (*Figure 1*).*
- *From a dose perspective, administration of quetiapine 375 mg b.i.d. is acceptable as an active control. According to the label, efficacy in schizophrenia was demonstrated in a dose range of 150 to 750 mg/day however, QTc prolongation is not well characterized.*
- *Although quetiapine dose (375mg b.i.d.) was slightly lower than the dose used in another QT study (400 mg b.i.d., NDA 21,999), the exposures achieved are fairly similar.*

- *In subjects with severe hepatic impairment, a 7-fold increase in exposure was observed. The effect on the QT interval with this increase in exposure is not known.*

Figure 1: Asenapine concentrations from phase IIb/III study (Schizophrenia indication; 10mg b.i.d. SS) and QT study (20mg b.i.d. SS)



Source: Sponsor's population PK report (population-pk-phase-2-3-asenapine.pdf) Figures 1 and 3)

4.2.5.3 Instructions with Regard to Meals

Subjects were to have had their meals before dosing and to be finished eating at least 15 minutes before each dose; they were allowed to drink water up to 5 minutes prior to the dose. The timing of meals and medication administration was to be consistent throughout the trial for each subject.

4.2.5.4 ECG and PK Assessments

Serial ECG recordings (triplicates) and corresponding pharmacokinetic (PK) samples were obtained on Days 1, 10, and 16: prior to and 1, 2, 3, 4, 6, 8, and 12 hours following the morning dose of study medication. The ECGs were recorded immediately before the blood draws and the 12-hour postdose ECGs were performed prior to the evening dose of study medication. On Day 16, additional PK samples were obtained at 16, 24, 36, and 48 hours following the morning dose.

4.2.5.5 Baseline

The baselines were defined as the ECGs recorded on the last day of the 5-day single blind placebo run-in phase. Time-matched baselines were used in the primary analysis.

4.2.6 ECG Collection

Digital ECGs (GE Medical MAC 1200 with onscreen display) were performed in triplicate (other than at Screening and Closeout) at the time points specified during the placebo run-in and treatment phases. Subjects were to be supine for at least 10 minutes prior to the 12-lead ECG assessments and a 2-minute period was required between recordings. Study site personnel were instructed to minimize subject stress and anxiety throughout the trial, particularly during the ECG recordings and to minimize environmental sympathetic and autonomic intervention during the ECG recordings.

Electronic data files were sent to a central lab for manual interpretation.

Measured ECGs were interpreted and intervals verified and re-measured onscreen by a cardiologist. All ECGs for a particular subject were overread by the same cardiologist.

All interval measurements were made from a single lead: lead II, or lead I if lead II was not possible, or lead V4 if lead I and lead II were not possible. A complete interpretation was performed. Interval measurements were performed in a digital environment using electronic calipers. Each interval was measured as a single measurement of an averaged complex from the chosen lead, utilizing a validated median template methodology, with a sample of at least 3-5 original complexes.

Machine-interpreted data (PR, QRS, QT, QTc, ventricular rate (VR)) from screening and closeout ECGs was recorded on the 12-lead ECG CRFs.

Reviewers comment: It is unclear if the ECG readers were blinded to time and treatment identifiers.

4.2.7 Sponsor's Results

4.2.7.1 Study Subjects

This trial was designed to evaluate 120 subjects with schizophrenia on Day 10: 30 subjects in each of 4 treatment groups. A total of 151 subjects were enrolled, of whom 148 (114 men, 34 women) took at least 1 dose of study drug (the safety analysis set). Inclusion criteria included normal baseline ECG, age between 18-65 yrs of age and BMI between 17-36 kg/m^2.

The safety analysis set yielded 125 subjects who completed at least 10 days of treatment--the treatment groups at Day 10 ranged in size from 30 to 33 subjects. Thirty-four subjects, 23% of the safety analysis set, discontinued double-blind treatment. The most frequent reason for subject discontinuation was withdrawal of consent (23 subjects, 16%). Eight subjects (5%) withdrew due to adverse events; 7 of these withdrawals were prior to Day 10 and included a withdrawal due to a serious adverse event that began as a PTSS. Subjects in the active treatment groups withdrew consent more often than subjects in the placebo group.

4.2.7.2 Statistical Analyses

4.2.7.2.1 Primary Analysis

The primary endpoint was time-matched change from baseline in QTcF on Day 10 and Day 16 after dosing. Time-matched QTcF was calculated for each subject by subtracting the QTcF at each nominal time on the baseline day from the QTcF at the same nominal time on Day 10 and Day 16. The Sponsor used a repeated measurement Analysis of Variance (ANOVA) to compare asenapine and quetiapine with placebo and used a one-way ANOVA to compare asenapine with quetiapine. The repeated measurement ANOVA for the asenapine with placebo comparisons consisted of treatment, subject within treatment, time, and time by treatment effects.

For all dose combinations of asenapine (5/10 mg b.i.d., 15/20 mg b.i.d.), the largest upper limits of the two-sided 90% Confidence Interval for asenapine vs. placebo differences

after baseline adjustments were above the 10 ms threshold. Analysis of the primary endpoint demonstrated that asenapine had a positive effect on the QTc interval in this trial.

Table 3: Difference in Least Square Means of Asenapine from Placebo of Time Matched Change from Baseline in QTcF (Manually Read)

Treatment Comparison	Time Post-Dose (hour)	N	Difference	90% Lower	90% Upper
Day 10					
Asenapine 5 mg b.i.d. vs Placebo	1	30	0.9	-5.0	6.9
	2	30	2.6	-3.3	8.6
	3	30	5.0	-1.0	**10.9**
	4	30	5.8	-0.2	**11.7**
	6	30	4.1	-1.9	**10.0**
	8	29	5.9	-0.1	**11.9**
	12	29	0.9	-5.1	6.8
Asenapine 15 mg b.i.d. vs Placebo	1	33	5.6	-0.2	**11.4**
	2	33	6.4	0.6	**12.3**
	3	33	8.7	2.9	**14.5**
	4	33	8.0	2.2	**13.8**
	6	33	5.1	-0.8	**10.9**
	8	33	6.1	0.3	**12.0**
	12	32	1.0	-4.8	6.9
Day 16					
Asenapine 10 mg b.i.d. vs Placebo	1	27	3.4	-3.1	**10.0**
	2	27	10.5	3.9	**17.1**
	3	27	-0.4	-6.9	6.2
	4	27	9.3	2.7	**15.9**
	6	26	6.2	-0.4	**12.8**
	8	26	5.2	-1.4	**11.9**
	12	26	0.4	-6.2	7.1
Asenapine 20 mg b.i.d. vs Placebo	1	29	2.6	-3.8	9.1
	2	29	5.2	-1.2	**11.7**
	3	29	-1.1	-7.5	5.4
	4	28	5.1	-1.4	**11.6**
	6	29	-1.3	-7.8	5.1
	8	29	-1.8	-8.2	4.7
	12	29	-1.4	-7.9	5.0

Sponsor's Section 11.1.2.01.01.01, pages236-239 of CSR for A750-1001

Reviewer's Comment: The sponsor used quetiapine as a positive control for the QT study. The following table presented the difference in least square means of quetiapine from placebo of time matched changed from baseline in QTcF.

Table 4: Difference in Least Square Means of Quetiapine from Placebo of Time Matched Change from Baseline in QTcF (Manually Read)

Treatment Comparison	Time Post-Dose (hour)	N	Difference	90% Lower	90% Upper
Day 10					
Quetiapine 375 mg b.i.d. vs Placebo	1	30	2.5	-3.5	8.4
	2	30	6.7	0.8	12.7
	3	30	7.5	1.5	13.4
	4	30	7.9	1.9	13.8
	6	30	2.7	-3.2	8.7
	8	30	10.9	4.9	16.8
	12	30	3.1	-2.8	9.0
Day 16					
Quetiapine 375 mg b.i.d. vs Placebo	1	27	4.1	-2.5	10.7
	2	27	9.9	3.3	16.5
	3	27	6.9	0.4	13.5
	4	27	6.8	0.3	13.4
	6	27	3.1	-3.4	9.7
	8	27	4.9	-1.7	11.5
	12	27	-0.6	-7.2	6.0

Sponsor's Section 11.1.2.01.01.01, pages236-239 of CSR for A750-1001

4.2.7.2.2 Categorical Analysis

A summary of the number of absolute QTcF outliers by day and time is presented in Table 5.

Table 5: Categorization of QTcF Data by Gender and Treatment Group

		Number (Percent) of Subjects by Maximum Post-dose QTcF (msec)								
		---------- Males ----------				---------- Females ----------				
		<430	430-<450	450-<500	≥500		<450	450-<470	470-<500	≥500
Treatment	N	n(%)	n(%)	n(%)	n(%)	N	n(%)	n(%)	n(%)	n(%)
Baseline										
Placebo	28	27 (96.4)	1 (3.6)	0 (0.0)	0 (0.0)	7	7 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asenapine 5 mg	33	33 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	5	5 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asenapine 15 mg	26	26 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	12	12 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Quetiapine 375 mg	27	27 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	10	10 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Day 1[a] through Day 10										
Placebo	28	27 (96.4)	0 (0.0)	1 (3.6)	0 (0.0)	7	6 (85.7)	0 (0.0)	1 (14.3)	0 (0.0)
Asenapine 5 mg	33	29 (87.9)	4 (12.1)	0 (0.0)	0 (0.0)	5	5 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asenapine 15 mg	26	24 (92.3)	1 (3.8)	1 (3.8)	0 (0.0)	12	9 (75.0)	2 (16.7)	1 (8.3)	0 (0.0)
Quetiapine 375 mg	27	26 (96.3)	1 (3.7)	0 (0.0)	0 (0.0)	10	9 (90.0)	1 (10.0)	0 (0.0)	0 (0.0)
Day 11 through Day 16										
Placebo	27	26 (96.3)	1 (3.7)	0 (0.0)	0 (0.0)	5	5 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asenapine 10 mg	24	21 (87.5)	3 (12.5)	0 (0.0)	0 (0.0)	4	4 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asenapine 20 mg	20	20 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	10	8 (80.0)	1 (10.0)	1 (10.0)	0 (0.0)
Quetiapine 375 mg	22	22 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	7	6 (85.7)	1 (14.3)	0 (0.0)	0 (0.0)

Source: 11.1.2.01.01.05
[a] Post dose

Sponsor's Table 36, page 93 of CSR for A750-1001

For the 5 subjects who had QTcF values ≥450 ms (for men) or ≥470 ms (for women), increases from baseline in time matched QTcF ranged from 14 ms to 61 ms. According to the Sponsor, two of these subjects experienced adverse events from the cardiac-disorders system organ class during the trial: Subject 10010016 (hypertension) and Subject 10050009 (increased blood pressure).

During Period 1 (Days 1 through 10), the number of subjects who experienced increases in QTcF ≥30 ms ranged from 7 of 38 subjects (18.4%) in the placebo group to 15 of 37 subjects (40.5%) in the quetiapine group. Three subjects had QTcF increases ≥60 ms. Similarly, the number of subjects who experienced QTcF increases ≥30 ms during Period 2 (Days 11 through 16) ranged from 5 of 32 subjects (15.6%) who received placebo to 9 of 29 subjects (31%) in the quetiapine group; 2 placebo-treated subjects had QTcF increases ≥60 ms. No asenapine treated subject had a QTcF increase ≥60 ms during either treatment period (Table 6).

Table 6: Categorization of QTcF maximum increase from baseline by treatment group

	N (%) of Subjects by Maximum QTcF Increase from Baseline			
Study Day		<30 msec	30-<60 msec	≥60 msec
Treatment	N	n (%)	n (%)	n (%)
Day 1[a] through Day 10				
Placebo	35	27 (77.1%)	6 (17.1%)	2 (5.7%)
Asenapine 5 mg	38	31 (81.6%)	7 (18.4%)	0 (0.0%)
Asenapine 15 mg	38	28 (73.7%)	10 (26.3%)	0 (0.0%)
Quetiapine 375 mg	37	22 (59.5%)	14 (37.8%)	1 (2.7%)
Day 11 through Day 16				
Placebo	32	27 (84.4%)	3 (9.4%)	2 (6.3%)
Asenapine 10 mg	28	20 (71.4%)	8 (28.6%)	0 (0.0%)
Asenapine 20 mg	30	23 (76.7%)	7 (23.3%)	0 (0.0%)
Quetiapine 375 mg	29	20 (69.0%)	9 (31.0%)	0 (0.0%)

Source: 11.1.2.01.01.06
[a] Post dose

Sponsor's Table 38, page 95 of CSR for A750-1001

4.2.7.3 Safety Analysis

There were no deaths reported in this trial.

Three subjects experienced serious adverse events- a 51-year-old man, experienced severe atrial fibrillation on Day 1 after receiving a 5 mg dose of asenapine. He required hospitalization and was withdrawn from the trial. A 40-year-old woman, experienced a change in intensity of sinus tachycardia from mild to moderate on Study Day 9, and she was hospitalized. She was receiving quetiapine 375 mg b.i.d.. Study drug was discontinued and she was withdrawn from the trial. A 38-year-old woman experienced the adverse event of severe schizoaffective disorder 1 day after completing screening and starting to taper off her antipsychotic medication.

Nine subjects, including 2 who experienced serious cardiac adverse events, discontinued from the trial due to adverse events. One of these subjects discontinued from the trial due

to laboratory abnormalities (elevated LFT). Five discontinued due to psychiatric adverse events .

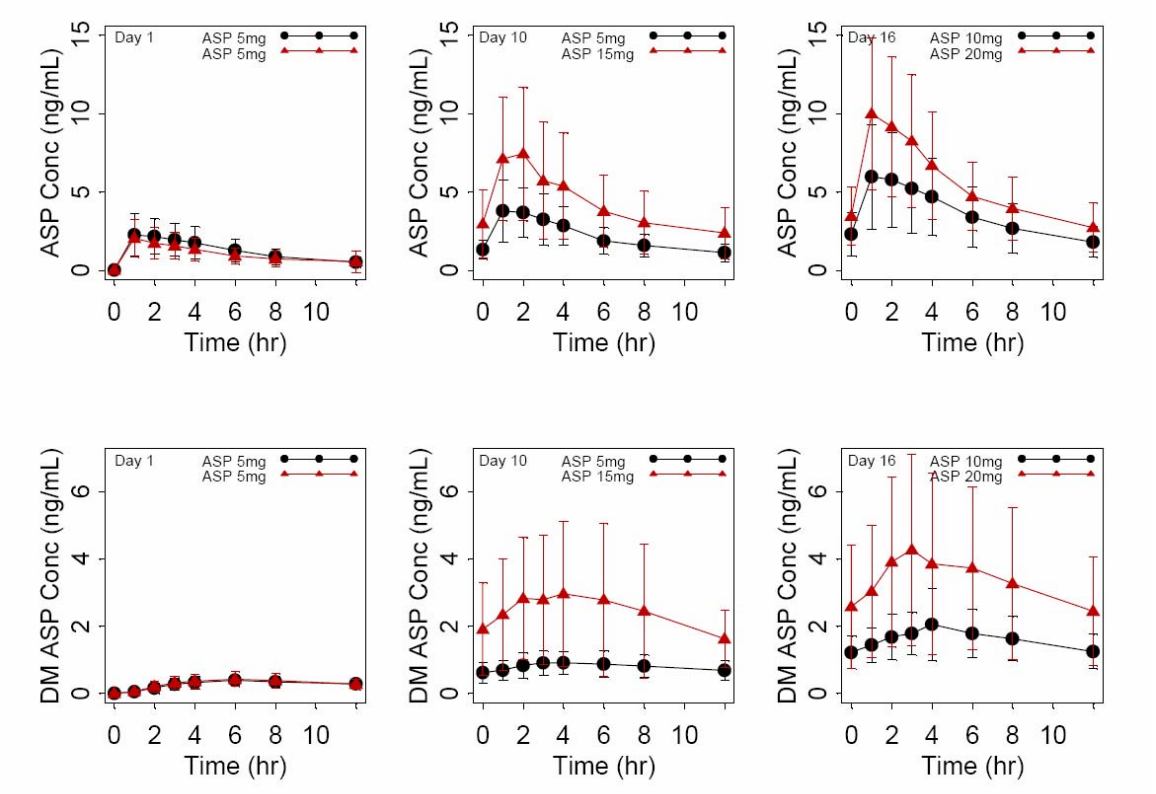
The adverse events, other than oral adverse events (dry mouth, dysgeusia), experienced by 3 or more asenapine-treated subjects and reported for a higher percentage of asenapine-treated subjects than quetiapine- or placebo- treated subjects were somnolence, restlessness, anxiety and dizziness, constipation and fatigue, akathisia, gait disturbance, nasal congestion, loose stools, and dysarthria.

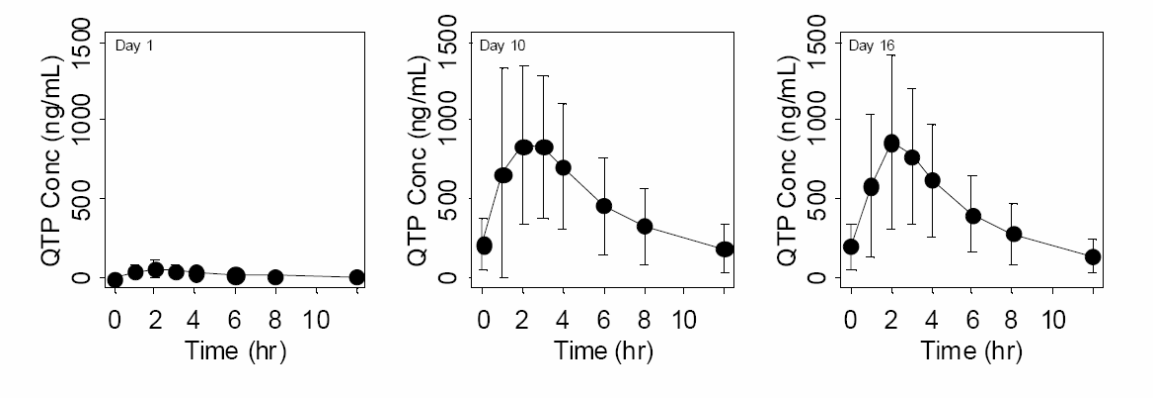
4.2.7.4 Clinical Pharmacology

4.2.7.4.1 Pharmacokinetic Analysis

Mean C_{max} and AUC values were similar between treatment groups on Day 1, when the initial dose was 5 mg for both groups. Differences between groups in mean C_{max} and AUC on Day 10 (5 or 15 mg b.i.d.) and Day 16 (10 or 20 mg b.i.d.) appeared less than proportional to dose for asenapine and asenapine N-oxide, but were proportional to dose for desmethyl asenapine. Mean t½ values on Day 16 were similar between groups for both asenapine and desmethyl asenapine.

Figure 2: Mean (±SD) Plasma Concentration-Time Profiles for Asenapine (ASP), des-Methyl Asenapine (DM ASP) and Quetiapine (QTP)





Sponsor's Figures 5 and 6, pages 106 and 109 of CSR for A750-1001

Table 7: Mean (%CV) PK estimates for Asenapine, des-Methyl Asenapine and N-Oxide Asenapine

Asenapine

Treatment Group = Asenapine 5/10 mg						
	Day = 1, Dose = 5		Day = 10, Dose = 5		Day = 16, Dose = 10	
	N = 35		N = 28		N = 25	
Parameter	n	Mean (%CV)	n	Mean (%CV)	n	Mean (%CV)
Cmax, ng/mL	35	2.61 (50.2)	28	4.23 (45.3)	25	6.56 (50.9)
tmax, hr	34	1.92 (51.5)	28	1.79 (46.9)	25	2.01 (46.0)
$AUC_{(0\text{-}tlqc)}$, ng*hr/mL	35	15.4 (49.1)		NA		NA
$AUC_{(0\text{-}\tau)}$, ng*hr/mL		NA	28	26.6 (38.4)	25	43.4 (53.1)
t½, hr		NA		NA	20	24.1 (41.3)
Treatment Group = Asenapine 15/20 mg						
	Day = 1, Dose = 5		Day = 10, Dose = 15		Day = 16, Dose = 20	
	N = 35		N = 33		N = 29	
Parameter	n	Mean (%CV)	n	Mean (%CV)	n	Mean (%CV)
Cmax, ng/mL	35	2.29 (55.1)	33	8.05 (54.2)	29	10.6 (48.2)
tmax, hr	34	2.48 (109)	33	1.66 (65.8)	29	1.70 (56.1)
$AUC_{(0\text{-}tlqc)}$, ng*hr/mL	35	12.4 (54.7)		NA		NA
$AUC_{(0\text{-}\tau)}$, ng*hr/mL		NA	33	51.2 (56.0)	29	66.1 (46.4)
t½, hr		NA		NA	20	22.4 (23.4)

Source: Appendix B.1 tables 1.2.1 through 1.2.6
N = Number of subjects included in the pharmacokinetic analysis
n = Number of subjects for this parameter
NA = Not applicable

Des-methyl asenapine

Treatment Group = Asenapine 5/10 mg

	Day = 1, Dose = 5 N = 35		Day = 10, Dose = 5 N = 28		Day = 16, Dose = 10 N = 25	
Parameter	n	Mean (%CV)	n	Mean (%CV)	n	Mean (%CV)
Cmax, ng/mL	35	0.410 (37.3)	28	1.02 (38.8)	25	2.21 (48.3)
tmax, hr	34	6.57 (30.9)	28	4.47 (40.1)	25	4.73 (46.7)
$AUC_{(0\text{-}tlqc)}$, ng*hr/mL	35	3.29 (44.9)		NA		NA
$AUC_{(0\text{-}T)}$, ng*hr/mL		NA	28	9.65 (38.9)	25	19.6 (35.7)
t½, hr		NA		NA	24	16.6 (31.8)

Treatment Group = Asenapine 15/20 mg

	Day = 1, Dose = 5 N = 35		Day = 10, Dose = 15 N = 33		Day = 16, Dose = 20 N = 29	
Parameter	n	Mean (%CV)	n	Mean (%CV)	n	Mean (%CV)
Cmax, ng/mL	35	0.457 (52.2)	33	3.21 (70.5)	29	4.52 (63.2)
tmax, hr	33	6.07 (30.2)	32	3.15 (42.7)	29	3.80 (42.1)
$AUC_{(0\text{-}tlqc)}$, ng*hr/mL	35	3.63 (52.7)		NA		NA
$AUC_{(0\text{-}T)}$, ng*hr/mL		NA	33	29.6 (72.5)	29	40.5 (64.9)
t½, hr		NA		NA	27	17.6 (46.3)

Source: Appendix B.2 tables 2.2.1 through 2.2.6
N = Number of subjects included in the pharmacokinetic analysis
n = Number of subjects for this parameter
NA = Not applicable

N-oxide asenapine

Treatment Group = Asenapine 5/10 mg

	Day = 1, Dose = 5 N = 35		Day = 10, Dose = 5 N = 28		Day = 16, Dose = 10 N = 25	
Parameter	n	Mean (%CV)	n	Mean (%CV)	n	Mean (%CV)
Cmax, ng/mL	35	0.0426 (154)	28	0.103 (119)	25	0.180 (48.7)
n>0	11		18		22	

Treatment Group = Asenapine 15/20 mg

	Day = 1, Dose = 5 N = 35		Day = 10, Dose = 15 N = 33		Day = 16, Dose = 20 N = 29	
Parameter	n	Mean (%CV)	n	Mean (%CV)	n	Mean (%CV)
Cmax, ng/mL	35	0.0481 (136)	33	0.221 (93.0)	29	0.303 (68.0)
n>0	13		27		24	

Source: Appendix B.1 tables 3.2.1 through 3.2.2
N = Number of subjects included in the pharmacokinetic analysis
n = Number of subjects for this parameter
n>0 = Number of subjects with Cmax greater than zero

Quetiapine

Treatment Group = Quetiapine 375 mg

	Day = 1, Dose = 25		Day = 10, Dose = 375		Day = 16, Dose = 375	
	N = 34		N = 28		N = 25	
Parameter	n	Mean (%CV)	n	Mean (%CV)	n	Mean (%CV)
Cmax, ng/mL	34	79.7 (60.9)	28	1180 (49.9)	25	1070 (35.9)
tmax, hr	34	1.89 (45.7)	28	2.39 (41.1)	25	2.11 (45.2)
$AUC_{(0\text{-}tlqc)}$, ng*hr/mL	34	312 (54.9)		NA		NA
$AUC_{(0\text{-}\tau)}$, ng*hr/mL		NA	28	6220 (48.9)	25	5610 (47.5)
t½, hr		NA		NA	17	7.15 (17.5)

Source: Appendix B.1 tables 4.2.1 through 4.2.3
N = Number of subjects included in the pharmacokinetic analysis (all-zero profiles excluded)
n = Number of subjects for this parameter
NA = Not applicable

Sponsor's Figures 5 and 6, pages 102-105, of CSR for A750-1001

4.2.7.4.2 Exposure-Response Analysis

The exposure-response relationships of QTcF with asenapine, with its metabolites, des-methyl-asenapine and asenapine N-oxide, and with quetiapine were evaluated using linear mixed effects modeling. The relationship between QTcF and asenapine, des-methyl asenapine, asenapine N-oxide, and quetiapine was simultaneously modeled using a linear model with slope and intercept parameters. The mathematical representation of the final model after model reduction was:

$$INT_i = \theta_1(1+\theta_6 \cdot SEX) + \eta_{BSV1} + \eta_{IOV1} \qquad if\ Day = -1\ or\ 1$$

$$INT_i = \theta_1(1+\theta_6 \cdot SEX) + \theta_7 + \eta_{BSV1} + \eta_{IOV1} \qquad if\ Day = 10\ or\ 16$$

$$SLPasp_i = \theta_2 + \eta_{BSV2} + \eta_{IOV2}$$

$$SLPqtp_i = \theta_5 + \eta_{BSV5}$$

$$QTcF_{ij} = INT_i + SLPasp_i \times Casp_{ij} \times I(asp) + SLPqtp_i \times Cqtp_{ij} \times I(qtp) + \varepsilon_{ij}$$

$$, where \qquad I(asp) = \begin{Bmatrix} 1 & treatment = asp \\ 0 & otherwise \end{Bmatrix} and \qquad I(qtp) = \begin{Bmatrix} 1 & treatment = qtp \\ 0 & otherwise \end{Bmatrix}$$

In these equations, QTcFij was the j^{th} QTcF observation for the i^{th} individual, θ1 represented the population mean estimate of the intercept, θ2 through θ5 represented the population mean estimate of the slopes, θ7 corresponded to mean QTcF prolongation by placebo effect, ηBSV represented the inter-individual variance of the corresponding parameter and was assumed to be a normal, independent, and identically distributed random variable with zero mean and variance ω_{BSV}^2(~NIID(0, ω_{BSV}^2)). The inter-occasion variance of the corresponding parameter was represented by ηIOV and was assumed to be a normal, independent, identically distributed random variable with zero mean and variance ω_{IOV}^2(~NIID(0, ω_{IOV}^2)). C_{asp} and C_{qtp} corresponded to the observed concentration for each compound and ε_{ij} represented the jth residual error for the ith individual and was assumed to be a normal, independent, identically distributed random variable with zero mean and variance σ^2 (~NIID(0, σ^2)).

Asenapine was the best predictor of QTcF for the asenapine treatment groups compared to its two metabolites. Given asenapine and inter-occasion variability for intercept and the asenapine slope in the model, inclusion of metabolites into the model did not significantly improve the model's predictive performance. Parameter estimates from the final model are summarized in the following table.

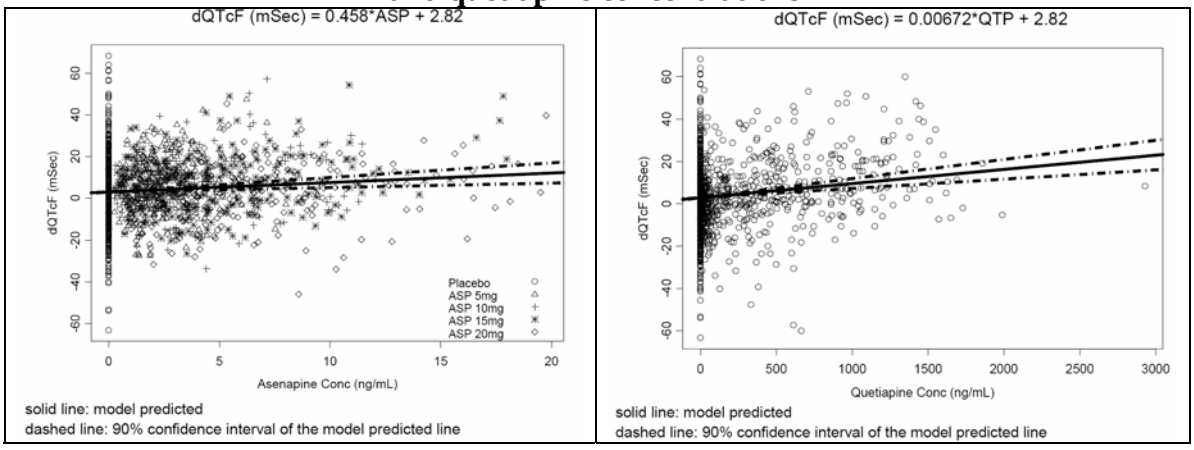
Table 8: Parameter estimates of the population exposure-QTc analysis

Parameter	Parameter Estimate	SE	CV%	90% CI (SE Derived)	90% CI (Bootstrap)
Intercept (ms)	399	2.78	0.697	(394,404)	(395.404)
BSV (ms)	15.3				
IOV (ms)	5.31				
Increase in Intercept by Placebo Effect (ms)	2.82	0.834	29.6	(1.44,4.2)	(1.35.4.14)
Gender Effect (%)	-4.31*	0.0075	-17.4	(-0.0555,-0.0307)	(-0.0552.-0.0302)
Slope for Asenapine (ms/[ng/mL])	0.458	0.147	32.1	(0.215,0.701)	(0.232.0.719)
BSV(ms/[ng/mL])	0.402				
IOV(ms/[ng/mL])	0.567				
Slope for Quetiapine (ms/(ng/mL))	0.00672	0.00141	21	(0.00439,0.00905)	(0.00423.0.00901)
BSV(ms/[ng/mL])	0.00374				
Residual Variability (ms)	9.58	0.344	3.59		

Sponsor's Table 52, page 13 of CSR for A750-1001

Plots of observed ΔQTcF vs. plasma concentrations for asenapine and quetiapine with model prediction are shown in Figure 3.

Figure 3: Plot of time-matched change from baseline in QTcF vs. plasma asenapine and quetiapine concentrations



Sponsor's Figure 7 and 8, pages 111-112 of CSR for A750-1001

The slopes for asenapine and quetiapine were estimated with reasonable precisions (CV 32% and 21% respectively) and their confidence intervals did not contain zero. The asenapine slope estimate indicates that there is a proportional and statistically significant relationship between QTcF and plasma asenapine concentrations, however the magnitude

of the slope is small and suggests an increase of 0.458 ms in QTcF per ng/mL asenapine concentration.

Table 9 reports expected QTcF increase with 90% confidence intervals at mean C_{max} of asenapine and quetiapine. The predicted estimates of mean QTcF prolongation at C_{max} for all doses of asenapine studied (5, 10, 15, and 20 mg b.i.d.) were less than 5 ms and less than those of quetiapine 375 mg b.i.d.. It is notable that the upper limit of the asenapine 90% confidence intervals for the maximum expected increase in QTcF (at C_{max}) for the 5 mg and 10 mg treatment groups was less than the expected maximum increase in QTcF (at C_{max}) for the quetiapine 375 mg treatment group.

Table 9: Expected QTcF Increase at Mean Cmax

Drug/Dose	Mean Cmax (ng/mL)	Expected QTcF Increase at Mean Cmax (ms)	90% CI (SE Derived)	90% CI (Bootstrap)
Asenapine 5mg	4.23	1.9	(0.9,3.0)	(1.0,3.0)
Asenapine 10 mg	6.56	3.0	(1.4,4.6)	(1.5,4.7)
Asenapine 15 mg	8.00	3.7	(1.7,5.6)	(1.9,5.8)
Asenapine 20 mg	10.7	4.9	(2.3,7.5)	(2.5,7.7)
Quetiapine 375 mg (Day 10)	1180	7.9	(5.2,11.0)	(5.0,11.0)
Quetiapine 375 mg (Day 16)	1070	7.2	(4.7,9.7)	(4.5,9.6)

Sponsor's Table 53, pages 113 of CSR for A750-1001

Reviewer's Comment: The reviewer was in general agreement with the sponsor's exposure-QTc modeling. See reviewer's analyses for exposure-ΔΔQTcF modeling, section 5.2.1. The assay sensitivity for this trial was in question in the absence of moxifloxacin arm. However, the effect of quetiapine on QT seemed similar to the data submitted with the paliperidone QT study (NDA 21999). See reviewer's analyses for further details on assay sensitivity.

Additionally, the sponsor also conducted exposure-response (report INT00036960) analyses to assess effect of asenapine administration on the QTc interval in patients with schizophrenia (Phase 3 ACTAMESA study).

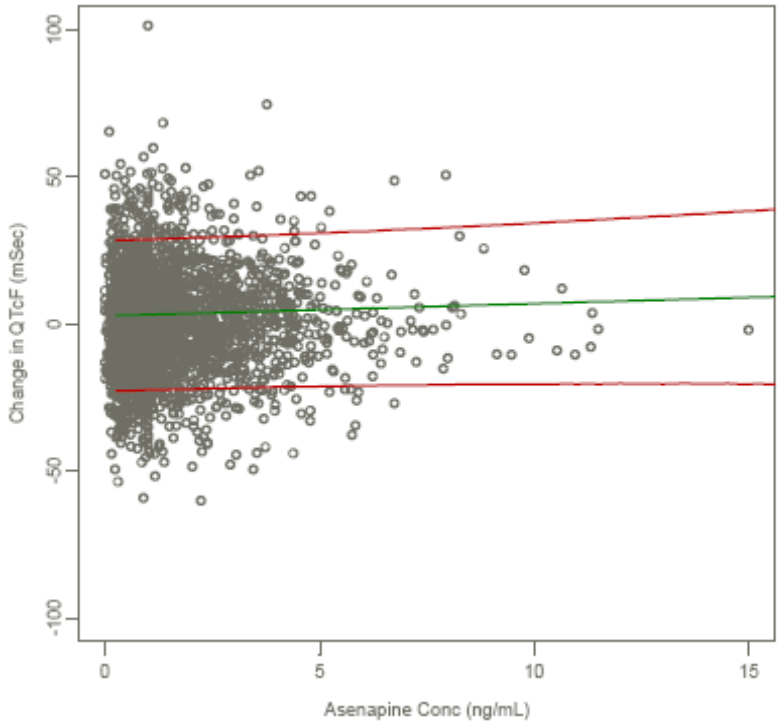
A total of 909 patients were included in the dataset for the asenapine group. All 909 patients included had at least one ECG measurement and 884 patients had at least 1 PK sample collected. Out of 884 patients, 853 patients had at least one PK sample above the quantification limit. Mean ± SD (range) average baseline QTcF (corrected QT according to Fridericia) and average baseline heart rate values were 405 ± 16.8 ms (362.7-470.3) and 74.9 ± 14.0 bpm (43-119), respectively. There were a total of 477 males and 432 females.

All data points prior to study drug administration were used for the assessment of the relationship between QTc and heart rate. Visually, QTcF is apparently dependent on heart rate. The population based correction (QTcP) appeared to correct the baseline QT interval for heart rate appropriately for this dataset, where the correction factor was estimated to be 0.4177. This factor is in between Bazett's (0.5) and Fridericia's (0.33). Nevertheless, all exposure-QTc analyses were performed using QTcF as the dependent

variable, because the thorough QTc exposure-response model was developed using QTcF and the main purpose of this analysis was to compare the Phase 3 exposure-response relationship to that of the thorough QTc trial.

When the Phase 3 ΔQTcF vs. concentrations data were compared to the unconditional prediction interval, they were visually well contained within the prediction intervals for all doses (Figure 4**)**. Overall the observed values show consistency with the prediction interval with a tendency of larger percentage below the median.

Figure 4: Unconditional Prediction Interval Overlaid with Observed ΔΔQTcF vs. Individual Predicted Asenapine Concentrations from Study 25517, A Phase 3 Study



Sponsor's Figure 4, page 20 from Study INT00036960

According to the sponsor, the exposure-QTcF relationship is consistent between the Phase 3 ACTAMESA study and the thorough QTc study (A7501001).

Reviewer's comment: The reviewer did not thoroughly evaluate the simulations conducted by the sponsor. The major evidence towards the effect on QT was available from the QT trial. The value and predictability of establishing such consistency was not immediately clear. However, it was reassuring to see the consistency between trials.

5 REVIEWERS' ASSESSMENT

5.1 STATISTICAL ASSESSMENTS

The statistical reviewer's evaluation was based on the sponsor's data and in accordance with ICH E14 guidance on Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.

This statistical reviewer also performed analysis based on the time-matched difference in QTcF of the drug and placebo after baseline adjustment at each time point (Table 10). The statistical reviewer used one-way ANOVA to calculate the 2-side 90% confidence interval of mean change in QTcF for each day at each time point.

Table 10:Reviewer's Analysis of Difference in Least Square Means from Placebo of Time Matched Change from Baseline in QTcF

Treatment Comparison	Time Post-Dose (hour)	N	Difference (SE)	90% Lower	90% Upper
Day 10					
Asenapine 5 mg b.i.d. vs Placebo	1	30	0.9 (4.2)	-6.0	7.9
	2	30	2.6 (3.4)	-3.0	8.2
	3	30	5.0 (3.9)	-1.5	**11.4**
	4	30	5.8 (3.0)	0.8	**10.8**
	6	30	4.1 (3.0)	-0.8	8.9
	8	29	5.8 (3.4)	0.3	**11.3**
	12	29	0.8 (3.6)	-5.1	6.6
Asenapine 15 mg b.i.d. vs Placebo	1	33	5.6 (3.7)	-0.6	**11.7**
	2	33	6.4 (3.4)	0.9	**12.0**
	3	33	8.7 (3.5)	3.0	**14.4**
	4	33	8.0 (3.4)	2.5	**13.6**
	6	33	5.1 (2.5)	0.9	9.2
	8	33	6.2 (3.2)	0.9	**11.3**
	12	32	1.2 (3.2)	-4.1	6.5
Day 16					
Asenapine 10 mg b.i.d. vs Placebo	1	27	3.4 (3.3)	-2.0	8.8
	2	27	10.5 (3.6)	4.5	**16.5**
	3	27	-0.4 (3.8)	-6.6	5.9
	4	27	9.3 (4.4)	2.0	**16.5**
	6	26	6.0 (3.8)	-0.3	**12.3**
	8	26	5.0 (4.3)	-2.0	**12.1**
	12	26	0.2 (4.9)	-7.8	8.3
Asenapine 20 mg b.i.d. vs Placebo	1	29	2.6 (3.5)	-3.2	8.4
	2	29	5.2 (3.6)	-0.7	**11.2**
	3	29	-1.1 (4.3)	-8.1	5.9
	4	28	4.9 (4.1)	-1.9	**11.6**
	6	29	-1.3 (3.8)	-7.5	4.9
	8	29	-1.8 (4.1)	-8.5	5.0
	12	29	-1.4 (4.6)	-9.0	6.2

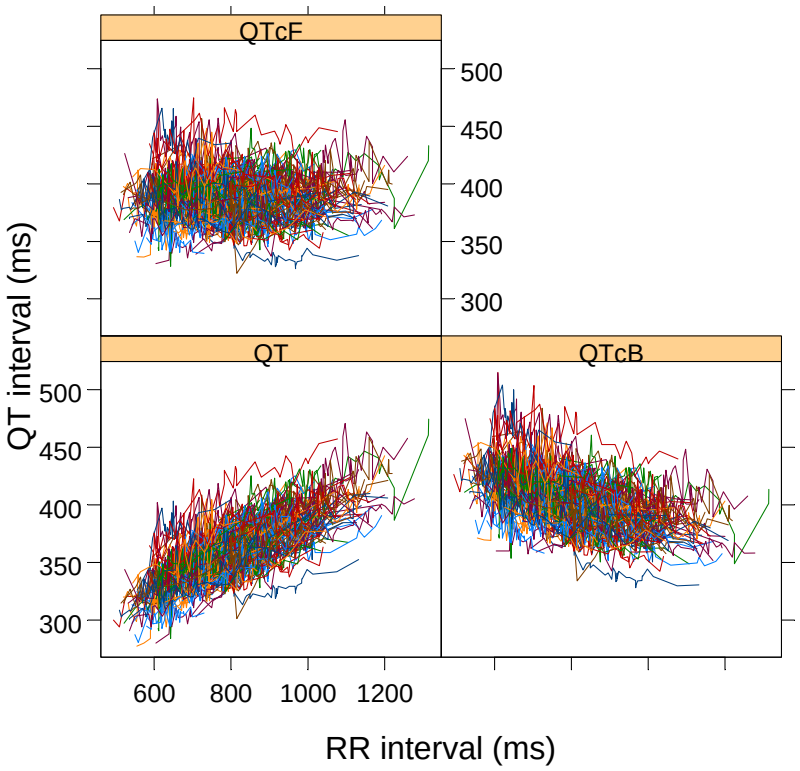
For all dose combinations of asenapine (5/10 mg b.i.d., 15/20 mg b.i.d.), the largest upper bounds of the two-sided 90% confidence interval for asenapine vs. placebo differences after baseline adjustments were above the 10 ms threshold.

Therefore, this statistical reviewer's analysis confirms the sponsor's results that asenapine at the study doses prolongs the QTc interval.

5.2 Clinical Pharmacology Assessments

The observed QT-RR interval relationship is presented in Figure 5 together with the Bazett's (QTcB), Fridericia (QTcF). The QTcF method was reasonable QT correction methods removing the heart rate effect in QT illustrated by a horizontal trend in the QTc vs. RR relationship. The QTcF correction method was used for the reviewer's concentration-QTc analysis.

Figure 5: Baseline day QT, QTcB, QTcF, and QTcLD vs. RR (Each Subject's Data Points are Connected with a Line).

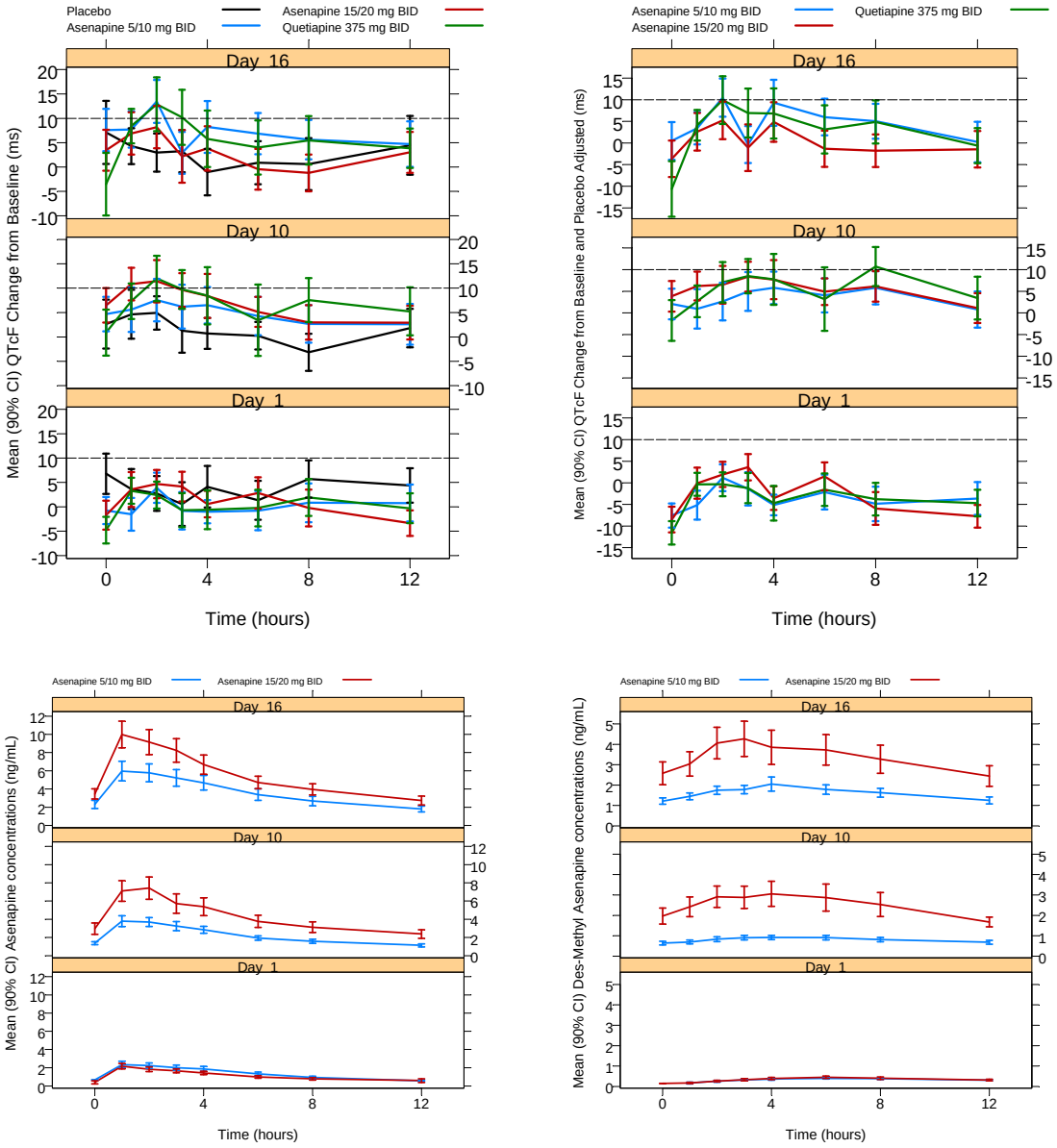


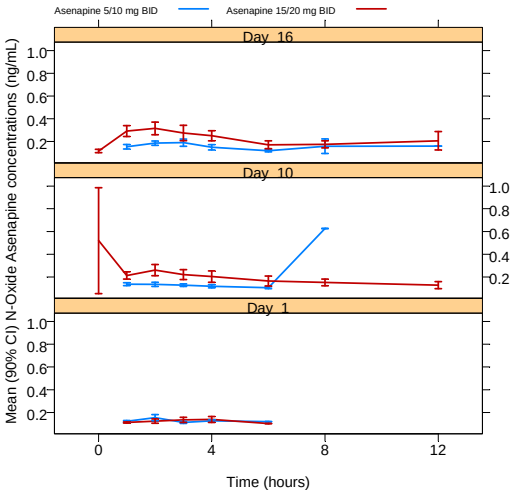
5.2.1 Exposure-Response Analyses

5.2.1.1 ΔΔQTcF and Concentration-Time Profiles

The mean ΔQTcF (change from baseline), ΔΔQTcF (change from baseline and placebo corrected), asenapine, des-methyl asenapine and n-oxide asenapine concentration profiles are shown in Figure 6.

Figure 6: Mean ΔQTcF (Change from Baseline), ΔΔQTcF (top right), and asenapine, des-methyl asenapine, n-oxide asenapine and quetiapine concentration profiles for all treatment groups on days 1, 10 and 16.





The maximum mean ΔΔQTcF of 8-10 ms occurs around 2-4 hours postdose for all treatment arms which closely matches with parent (asenapine or quetiapine) plasma concentration time profile. The graph (not shown) exploring delay in QT effect compared to parent drug concentration profile also supported use of parent drug concentration as a predictor (consistent with the sponsor's results).

5.2.1.2 Concentration-ΔΔQTcF Modeling for Asenapine

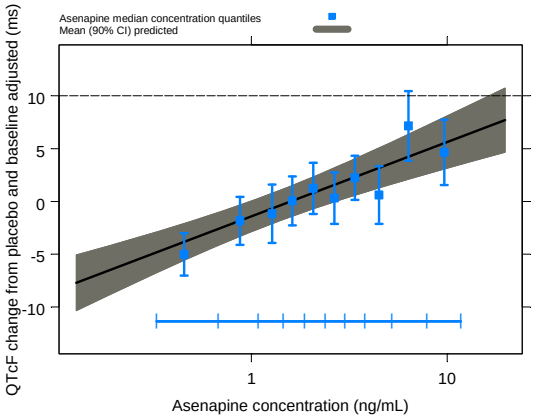
The relationship between asenapine concentrations and QT interval was investigated by using log-linear mixed-effects models. Data collected from the two asenapine dose groups at days 1, 10 and 16 were used for the asenapine concentration-QTcF analysis. Table 11 summarizes the results of the asenapine-QTcF analyses.

Table 11: Exposure-Response Analysis of asenapine associated ΔΔQTcF

ΔΔQTcF=Intercept+slope•log(asenapine concentration)		
Intercept, ms	-1.41 (-2.86; 0.04)	6.23
Slope, ms per log ng/mL	3.05 (2.08; 4.02)	3.27
Residual variability, ms	11.48	

The relationship between quetiapine concentrations and QT prolongation is visualized in Figure 7.

Figure 7: ΔΔQTcF vs. Asenapine Concentration with Observed Median-Quantile Concentrations and Associated Mean ΔΔQT (90% CI) overlaid (blue dots).



The expected QT prolongation at mean asenapine C_{max} (10.6 ng/mL) of suprtherapeutic dose (20mg b.i.d. dose) was 5.8 ms (8.3 ms, 90% upper confidence limit).

5.2.1.3 Concentration-ΔΔQTcF Modeling for Quetiapine

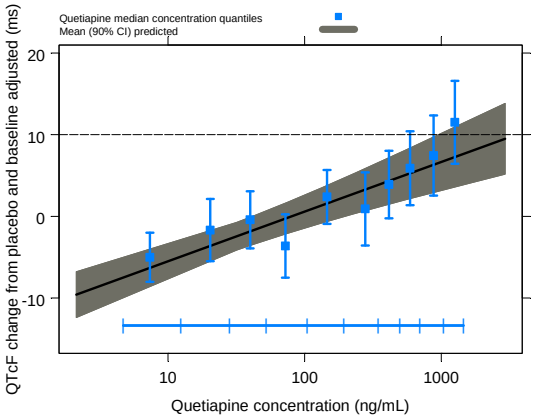
The relationship between quetiapine concentrations and QT interval was investigated by using log-linear mixed-effects models. Data collected from the 375mg b.i.d. quetiapine dose group at days 1, 10 and 16 were used for the quetiapine concentration-QTcF analysis. Table 12 summarizes the results of the quetiapine-QTcF analyses.

Table 12: Exposure-Response Analysis for Quetiapine

ΔΔQTcF=Intercept+slope•log(quetiapine concentration)		
Intercept, ms	-11.59 (-14.93; -8.24)	4.96
Slope, ms per log ng/mL	2.64 (1.78; 3.5)	1.98
Residual variability, ms	13.05	

The relationship between quetiapine concentrations and QT prolongation is visualized in Figure 8.

Figure 8: ΔΔQTcF vs. quetiapine concentration with observed median-quantile concentrations and associated mean QT (90% CI) prolongation overlaid (blue dots).



The expected QT prolongation at mean quetiapine C_{max} (1069.8 ng/mL) of quetiapine dose (375mg b.i.d. dose) was 7 ms (10 ms, 90% upper confidence limit).

5.2.1.4 Assay Sensitivity

Due to absence of moxifloxacin in the QT study, the assay sensitivity was established with the active control, quetiapine. This was performed by comparing the expsoure-response relationship from the current study with the quetiapine data submitted to NDA 21,999 (for paliperidone) as shown in Table 13.

Table 13. Comparison of the Exposure-Response Relationship for Quetiapine

	Study A750-1001 375 mg b.i.d. x 16 days Quetipine	NDA 21,999 Study R096477-SCH-1014 400 mg b.i.d. x 10 days Quetipine
Slope, ms per log ng/ml	2.6 (1.8; 3.5)	3.5 (2.6, 4.5)
Intercept, ms	-11.6 (-14.9; -8.2)	-15 (-21.2, -9.3)
Predicted ΔΔQTc, ms	6.7 ms (3.2, 10.2) for a mean C_{max} of 1000 ng/ml	9.1 ms (7.2, 11.1) for a mean Cmax of 1000 ng/ml

The exposure-response relationship for the two studies was found to be consistent. Therefore, in reviewer's opinion the data from the current study are interpretable.

6 CLINICAL ASSESSMENTS

None of the clinical events identified as of particular importance in the ICH E14 (death, serious ventricular arrhythmia, syncope and seizure) were observed in this study. Two patients had to be discontinued from the study due to atrial fibrillation and sinus tachycardia of moderate severity.

7 APPENDIX

7.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	**Schizophrenia**: The recommended dose range of Sycrest® is 5 mg to 10 mg given twice daily (BID). Sycrest® should be administered at an initial daily dose of 5 mg BID. An increase in dose to 10 mg BID is recommended only after clinical assessment. **Bipolar disorder**: The recommended dose of Sycrest® is 10 mg given twice daily (BID).	
Maximum tolerated dose	Asenapine 20 mg bid is the maximally tolerated dose in the population of subjects with schizophrenia; this dose has been studied in two trials: 041012 and A7501001 (the thorough QT/QTc trial).	
Principal adverse events	The principal adverse events considered associated with Sycrest®, based on the short-term placebo-controlled trials in schizophrenia and bipolar mania, were sedation, somnolence, akathisia, weight increase, and oral hypoesthesia. In the short-term placebo-controlled bipolar mania trials, dizziness generally occurred early in treatment and was of short duration. The incidence of akathisia was dose related. Long-term treatment with Sycrest® did not reveal any clinically relevant differences in the safety profile compared to the short-term trials. Somnolence, sedation and possible extrapyramidal symptoms are dose limiting adverse events.	
Maximum dose tested	Single Dose	5 mg (multiple trials)
	Multiple Dose	20 mg BID for 6 days (A7501001)
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) exposure parameters C_{max} 4.22 (51.2%) ng/mL $AUC_{0-\infty}$ 32.2 (40.1%) ng.h/mL Source: Module 2.7.2.3.2.1 and Module 2.7.2.3.2.5 – pooled analysis across 15 clinical pharmacology trials (N=334 and 331)
	Multiple Dose	Mean (%CV) exposure parameters C_{max} 10.6 (48.2%) ng/mL AUC_{0-12} 66.1 (46.4%) ng.h/mL Source: Module 2.7.2, Table 62, A7501001 (N=29)
Range of linear PK	Up to a dose of 5 mg BID, C_{max} and AUC for asenapine after sublingual administration increase proportional to the dose. Within the therapeutic dose range (5 – 10 mg BID) a deviation from dose-proportionality has been observed, with C_{max} and AUC increasing a factor 1.7 with a two-fold increase in dose. At supratherapeutic doses (> 10 mg BID), this deviation from dose-proportionality is more pronounced. Source: Module 2.7.2.3.2.8	

Accumulation at steady state	Accumulation ratios at 5 mg BID C_{max} – 0.95 AUC – 1.34 Source: Module 5.3.3.1 Clinical Trial Report 25542. Note that ratios are based on between subject comparisons. No within-subject accumulation ratios are available at the therapeutic dose.	
Metabolites	The following 5 metabolites have been detected in plasma in clinical studies: N-desmethylasenapine: Overall more than 10-fold reduction in binding affinity for human receptors examined compared to asenapine. asenapine N^+-glucuronide: No appreciable affinity for human receptors tested. N-desmethylasenapine-N-carbamoylglucuronide: Compound has not been profiled pharmacologically, but no activity is expected due to appreciable reduction (more than 10-fold) in binding affinity for the human receptors for the N-desmethyl metabolite, further loss of binding activity due to the fact that the nitrogen is no longer basic and expected inability to penetrate the brain. asenapine 11-O-sulfate: Receptor binding pattern broadly similar to asenapine, but compound does not penetrate the brain. asenapine N-oxide: 10 to 1000-fold reduction in binding affinity for human receptors compared to asenapine. Source: Module 2.6.2.2.4 and Module 2.4.2.1	
Absorption	Absolute/Relative Bioavailability	Absolute bioavailability (5 mg SL dose) Mean [95% CI]: 34.8 % [31.6 % - 38.7 %] Source: CTD 2.7.1.3.2 – No within-subject assessment of absolute BA has been done, therefore no estimate of between-subject variability in absolute BA is available.
	Tmax	Median (range) at 5 mg single dose • asenapine: 1.0 h (0.33 – 4.0 h) Source: Module 2.7.2.3.2.1, Table 50 – pooled analysis across 15 clinical pharmacology trials (N=334) • N-desmethylasenapine: 6 h (6 – 8 h) • asenapine N^+-glucuronide: 4 h (4 – 8 h) • asenapine 11-O-sulfate: 3.02 h (1.5 – 4.03 h) Source: Module 5.3.3.3 Clinical Trial Report 25546 (N=6, 6, 5) – Asenapine N-oxide concentrations were mostly below LLOQ, therefore no parameters were calculated. Plasma concentration-time profiles of N-desmethylasenapine-N-carbamoylglucuronide have not been assessed.

Distribution	Vd/F or Vd	Mean (%CV) Vd: 1731 L (10.3%) Source: Module 5.3.1.1 Report INT00035825, Table 2 – pooled analysis of IV data (0.5 mg asenapine infusion, N=5)
	% bound	Mean (SD) % protein bound: 95.9 (1.3) % Source: Module 5.3.3.3 Clinical Trial Report A7501017, Table 13 (N=33)
Elimination	Route	• Urine (49 %) • Feces (39 %) Source: Module 5.3.3.1 Clinical Trial Report 25532, Table 11 – Human ADME study (N=4)
	Terminal t½	Mean (%CV) at 5 mg single dose • asenapine 23.1 h (58.4 %) Source: Module 2.7.2.3.2.4, Table 53 – pooled analysis across 13 clinical pharmacology trials with PK sampling for at least 60 h (N=263) • N-desmethylasenapine 17.1 h (42.4 %) • asenapine N^+-glucuronide: 13.4 h (74.3 %) • asenapine 11-O-sulfate: 24.0 h (86.3 %) Source: Module 5.3.3.3 Clinical Trial Report 25546 (N=6, 6, 5) – Asenapine N-oxide concentrations were mostly below LLOQ, therefore no parameters were calculated. Plasma concentration-time profiles of N-desmethylasenapine-N-carbamoylglucuronide have not been assessed.
	CL/F or CL	Mean (%CV) CL: 51.9 L/h (10.3%) Source: Module 5.3.1.1 Report INT00035825, Table 2 – pooled analysis of IV data (N=5)

<table>
<tr><td rowspan="4">Intrinsic Factors</td><td>Age</td><td>Adults
In the age range tested (18 – 57 years) no effect of age on asenapine pharmacokinetics
Source: Module 5.3.3.5 Report INT00036661 - Population pharmacokinetic analysis of Phase 1/2 data
Elderly
The pharmacokinetics of asenapine have not been investigated in the elderly. However, a study (including pharmacokinetic sampling) is currently ongoing in elderly patients with psychosis (A7501021).
Pediatric/Adolescent
The steady-state pharmacokinetics in adolescent subjects (12 to 17 years) were compared with the pharmacokinetics in adult subjects in a clinical pharmacology study (A7501022). Up to and including the 5 mg BID dose level, asenapine pharmacokinetics in the adolescent population are similar to those observed in adults; however, in adolescents, the 10 mg BID dose did not result in higher exposure to asenapine compared to 5 mg BID.
Source: Module 2.7.2.3.3.3</td></tr>
<tr><td>Sex</td><td>No effect of gender on asenapine pharmacokinetics
Source: Module 5.3.3.5 Report INT00036661 - Population pharmacokinetic analysis of Phase 1/2 data</td></tr>
<tr><td>Race</td><td>No effect of race on asenapine pharmacokinetics, except for 13.8 % lower clearance in Black
Source: Module 5.3.3.5 Report INT00036661 - Population pharmacokinetic analysis of Phase 1/2 data</td></tr>
<tr><td>Hepatic & Renal Impairment</td><td>Hepatic impairment: substantial (5-fold) increase in exposure (AUC) only for severe hepatic impairment. For unbound asenapine a 7-fold increase in AUC was observed in this group.
mean % change versus normal
<table>
<tr><td></td><td>Mild</td><td>Moderate</td><td>Severe</td></tr>
<tr><td>C_{max}</td><td>-10 %</td><td>-43 %</td><td>+3 %#</td></tr>
<tr><td>AUC</td><td>+12 %</td><td>+12 %*</td><td>+453 %#</td></tr>
</table>
Source: Module 5.3.3.3 Clinical Trial Report A7501018, Table 7 (N=8, *N=7, #N=6)
Renal impairment: pharmacokinetics are similar for varying degrees of renal function
mean % change versus normal</td></tr>
</table>

<table>
<tr><td></td><td></td><td>
<table>
<tr><td></td><td>Mild</td><td>Moderate</td><td>Severe</td></tr>
<tr><td>C_{max}</td><td>+34 %</td><td>-18 %</td><td>-29 %</td></tr>
<tr><td>AUC</td><td>+31 %*</td><td>+3 %#</td><td>+6 %#</td></tr>
<tr><td colspan="4">Source: Module 5.3.3.3 Clinical Trial Report A7501017, Table 8 (N=8, *N=7, #N=6)</td></tr>
</table>
</td></tr>
<tr><td>Extrinsic Factors</td><td>Drug interactions</td><td>
Effects of concomitantly administered drugs on asenapine pharmacokinetics – mean % change
- Paroxetine (20 mg QD – CYP2D6 inhibition)
C_{max} -13 % / AUC -9 %
Source: Module 5.3.3.4 Clinical Trial Report 25525
- Fluvoxamine (25 mg BID – CYP1A2 inhibition)
C_{max} +13 % / AUC +29 %
Source: Module 5.3.3.4 Clinical Trial Report 041033
- Imipramine (75 mg single dose – CYP1A2/2C19/3A4 inhibition)
C_{max} +17 % / AUC +10 %
Source: Module 5.3.3.4 Clinical Trial Report 25526
- Cimetidine (800 mg BID – CYP 3A4/2D6/1A2 inhibition)
C_{max} -13 % / AUC +1 %
Source: Module 5.3.3.4 Clinical Trial Report 25529
- Carbamazepine (400 mg BID – CYP3A4 induction)
C_{max} -16 % / AUC -16 %
Source: Module 5.3.3.4 Clinical Trial Report 25528
- Valproate (500 mg BID – UGT inhibition)
C_{max} +2 % / AUC -1 %
Source: Module 5.3.3.4 Clinical Trial Report 25527
</td></tr>
<tr><td></td><td>Food Effects</td><td>
Food (high-fat meal prior to or 4 h after administration): small decrease in exposure, probably due to increased liver blood flow
Mean change vs fasted
<table>
<tr><td></td><td>High-fat meal pre-dose</td><td>High-fat meal 4h post dose</td></tr>
<tr><td>C_{max}</td><td>-10 %</td><td>+2 %</td></tr>
<tr><td>AUC</td><td>-21 %</td><td>-13 %</td></tr>
<tr><td colspan="3">Source: Module 5.3.1.1 Clinical Trial Report 041029, Table 5 (N=26)</td></tr>
</table>
</td></tr>
</table>

Expected High Clinical Exposure Scenario	A theoretical worst case scenario would include severe hepatic impairment (7-fold increase in unbound AUC). However, as per ICH E14 guidance, such worst case scenario would be overruled by the limitations in the maximum dose level that can be administered based on safety or tolerability considerations. This dose level is 20 mg BID for asenapine. As a result, a formal calculation of the worst case exposure is considered redundant. In the thorough QT/QTc trial (A7501001) for asenapine the 20 mg BID dose regimen was included. Exposures achieved at 20 mg BID (the maximum dose tested) are included on the first page of this document.

7.2 TABLE OF STUDY ASSESSMENTS

Table 3 Schedule of procedures: screening phase

Test/Study Day	Screening[a]	-11	-10	-9	-8	-7	-6
		Optional					
Informed Consent	X						
Demographics	X						
Medical and Psychiatric History	X						
Physical Exam	X						
Vital Signs	X						
Urine Drug Screen[c]	X						
Thyroid Panel	X						
Clinical Laboratories	X						
Electrocardiogram	X						
Medication Tapering[b,d]		◄	—	—	—	—	►

[a] If no medication tapering was required, Screening and Day –5 could be the same day.
[b] Shorter or longer medication tapering (up to Day -20) was acceptable.
[c] If positive for phencyclidine, cocaine, amphetamines, opiates, or barbiturates, could be repeated 1 week later
[d] Medication tapering was to be done under the supervision of a physician.

Table 4 Schedule of procedures: single-blind placebo run-in phase

Test/Study Day	-5	-4	-3	-2	-1
Clinical Laboratories	X[b]			X	
Urine Drug Screen	X				
Serum Pregnancy Test[c]	X[b]				
Electrocardiogram					X[d]
Vital Signs[e]				X	
Supine/Standing Blood Pressure[e]				X	
PANSS/CGI-S/ESRS-A/TSQM					X
Administer Single-Blind Study Medication BID	X[f]	X	X	X	X

[a] Excluded antipsychotic medication had to be discontinued for at least 5 complete days.
[b] Not required if Screening and Day -5 were the same day.
[c] Women of childbearing potential only. Was not required for women who are post-menopausal and amenorrheic for at least 2 years.
[d] Triplicate ECG measurements taken prior to and 1, 2, 3, 4, 6, 8, and 12 hours following the morning dose.
[e] Taken at 08:00
[f] Cardiographic telemetry monitoring will begin at 0.5 hours prior to a.m. dose and continue throughout the Treatment Phase of the trial.

Table 6 Table of trial procedures: treatment phase (Periods 1 and 2)

Test/Study Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Electrocardiogram (Single Timepoint)[a]			X				X					X				
Electrocardiogram (Multiple Timepoints)[b]	X									X						X
Pharmacokinetics[b]	X									X						X
Supine/Standing Blood Pressure[c]		X				X			X					X		
Vital Signs[d]				X				X				X	X		X	
Vital Signs[e]	X	X				X					X			X		
Clinical Laboratories				X					X						X	
Thyroid Panel																X
PANSS/ESRS-A/CGI-S/CGI-C/TSQM																X
Administer Study Medication BID	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[f]
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] Triplicate ECG measurements at 2 hours following the morning dose.
[b] Triplicate ECG measurements and samples for PK taken prior to and 1, 2, 3, 4, 6, 8, and 12 hours following the morning dose. In addition, samples for PK are taken on Day 16 at 16, 24, 36, and 48 hours following the morning dose.
[c] 1 and 3 hours following the morning dose
[d] 2 hours following the morning dose
[e] Prior to morning dose and 2 and 4 hours after morning dose.
[f] Morning dose only administered on Day 16

Table 7 Schedule of trial procedures: restabilization phase

Test/Study Day	+1	+2	+3	Closeout[a]
Physical Exam				X
Vital Signs				X
Electrocardiogram (Single Timepoint)				X
Clinical Laboratories				X
Thyroid Panel				X
Pregnancy Test				X

[a] Closeout = Discharge. Subjects could be discharged earlier if, in the opinion of the investigator, the subject was stable.

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/s/

Christine Garnett
2/29/2008 01:03:49 PM
BIOPHARMACEUTICS

Pravin Jadhav
2/29/2008 01:15:28 PM
BIOPHARMACEUTICS

Joanne Zhang
2/29/2008 02:19:01 PM
BIOMETRICS

Yunfan Deng
2/29/2008 02:34:37 PM
BIOMETRICS

Suchitra Balakrishnan
2/29/2008 02:41:53 PM
MEDICAL OFFICER

Norman Stockbridge
2/29/2008 05:38:59 PM
MEDICAL OFFICER

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: April 23, 2008

From: Suchitra Balakrishnan, M.D., Ph.D.

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Keith Kiedrow
Regulatory Project Manager
Division of Psychiatry Products

Subject: QT-IRT Consult to NDA 22,117

This memo responds to queries from DPP regarding arrhythmia related issues associated with Asenapine (specifically cases of sinus pause seen with healthy volunteers). The QT-IRT received and reviewed the following materials:

- The Summary of Clinical Safety provided on 8/30/07
- Electronic datasets for the PR and QRS intervals provided by the Sponsor with Study Report A7501001
- QT- IRT review for Study INT 00036960

Background

The QT- IRT recently reviewed Study INT 00036960. In this randomized, placebo-controlled, double-blind, multicenter, parallel-group trial, subjects with schizophrenia or schizoaffective disorder received asenapine 5/10 mg b.i.d., asenapine 15/20 mg b.i.d., placebo, or quetiapine 375 mg b.i.d. for 16 days. Asenapine failed to exclude a 10-ms increase in the QT interval at both doses. With 35 subjects per arm, a dose-response relationship was not observed for asenapine. The review division has requested review of additional information with respect to pro-arrhythmic potential of asenapine, specifically cases of sinus pauses seen in the healthy volunteer studies

1 Previous Clinical Experience

There are 63 trials in the asenapine schizophrenia and bipolar mania clinical development programs that were conducted with the sublingual formulation of asenapine as of the database cut-off of 15 January 2007. The safety information from the completed Phase 2/3 trials was

analyzed in five cohorts.

Table 11 Number of Subjects Treated in the Asenapine Schizophrenia and Bipolar Mania Clinical Programs (continued)

Subject Group	Total Number of Subjects	Number of Subjects 5 or 10 mg BID
Combined Phase 2/3 for Bipolar Mania and Schizophrenia		
asenapine	2251	1953
placebo	706	
comparator	1134	
Ongoing Phase 2/3 Clinical Trials		
asenapine	~ 1045	~1045
placebo	~611	
comparator	~405	

1.1 Deaths:
As of the January 15, 2007 database cutoff date, there were 11 deaths in all asenapine groups, 1 death in the placebo group, and 3 deaths in the olanzapine group. One patient is reported to have died due to cardiac failure in ongoing trials.
Reviewers Comment: There are no deaths in the Clinical Summary reported as sudden cardiac death or due to significant ventricular arrhythmia. One patient died due to aspiration during a seizure 3 months after discontinuing study drug.

1.2 Arrhythmias
In cohort E (combined Phase 2/3 for Bipolar Mania and Schizophrenia), the incidence of tachycardia (17), sinus tachycardia (5) sinus bradycardia (13), ventricular extrasystoles (2) were higher than in the placebo group but comparable to olanzapine.
There was 1 case of atrial fibrillation in the placebo group. There were 2 cases of "cardiac flutter" and 1 case of WPW syndrome with asenapine. The proportion of patients who experienced heart blocks was similar in the asenapine (BBB-1, LBBB-2, and RBBB-3) and olanzapine groups.

Reviewers Comment
The most common arrhythmias seen in all studies were tachycardia and bradycardia and occurred in the subjects dosed between 5-10 mg b.i.d. Narratives for the patients with cardiac flutter and WPW syndrome were not available for review. However, the number of cases of atrial fibrillation/flutter was similar in active and placebo groups in all cohorts.

1.3 Sinus arrests
In cohort F (Clinical pharmacology studies in healthy volunteers) there were 9 episodes of sinus arrest reported in the subjects who received asenapine < 5mg and 4 reports of nodal rhythm. The sponsor attributes these events to neurally mediated reflex bradycardia (NMRB). The sponsor provided the following report in the ISS.

> "Neurally Mediated Reflex Bradycardia (NMRB) is a benign, self-limiting event, and the most common cause of vasovagal syncope. It involves central hypovolemia,

vasodepression, and a degree of bradycardia; the bradycardia may be accompanied by periods of asystole that are due to either sinus pause or heart block. NMRB can occur with or without sinus pause and is typically associated with postural challenge. Healthy, young volunteers with a high resting vagal tone display a higher incidence of NMRB than do psychiatric patients.

"Cardiovascular studies in anesthetized cats, anesthetized dogs, and conscious rabbits indicate that the main hemodynamic effects of intravenous asenapine are a decrease in arterial blood pressure, probably as a result of α1-adrenergic blocking activity, and orthostatic hypotension. The results of these in vivo studies also show that asenapine displays marked anti-histaminergic properties while no effects on cholinergic or ß-adrenergic systems are observed.

"There were no cases of NMRB reported in subjects with schizophrenia or bipolar disease. Four healthy volunteers receiving asenapine and one volunteer receiving placebo had reports of NMRB with sinus pause. These cases are briefly described.

- A 27 year old Caucasian male, and a former competing pentathlon athlete (resting supine heart rate of 52 bpm and blood pressure of 104/60 mm/Hg, standing heart rate of 70 bpm with a blood pressure of 112/82 mm/Hg), received 0.7 mg asenapine intravenously over 30 minutes in study 25506. Forty-five minutes after the start of the infusion, the subject sat up in bed for a blood pressure measurement and complained of dizziness and feeling unwell. He fell back in the bed and the ECG monitor showed asystole of > 8 seconds (recording stopped after 8 seconds). The bed was tilted head down at only a slight angle that allowed the investigator to intervene with brief chest compressions. During this intervention, the subject experienced 3 consecutive episodes of sinus pause of > 8 seconds duration each (recording stopped after 8 seconds). Severe bradycardia with intermittent nodal complexes and AV dissociation persisted until the investigator administered two intravenous injections of 0.6 mg atropine. Normal sinus rhythm was then restored and further recovery was uneventful. The peak asenapine plasma level in this volunteer was 1850 pg/ml. The investigator and a consulting cardiologist concluded this event was causally related to drug administration.
- A 22 year old Caucasian male, endurance athlete (resting heart of 58 bpm), received a 30-mg oral dose of asenapine in study 25501. Approximately 2.5 hours after the dose and 5 minutes after breakfast, the subject sat up in bed and felt dizzy and nauseated. The ECG telemetry strip showed heart rate slowing and an 8.7-second pause. This was followed by heart block with nodal bradycardia, which spontaneously converted to sinus rhythm. He had another episode 2 hours later. Both episodes resolved spontaneously without intervention while the subject remained in the supine position.
- A 33 year old Caucasian male received sublingual asenapine 0.15 mg in study 25511. Approximately 2.5 hours after the dose, he experienced NMRB with syncope 7 minutes after standing which resolved spontaneously without intervention when the subject was in the supine position. The subject's heart rate slowed from 100 bpm to 43 bpm within 19 seconds followed by syncope with an

associated 6.2-second sinus pause.
•A 24 year old Caucasian male received sublingual placebo in study 25511 at baseline and experienced dizziness followed by a 6.4-second sinus pause after 4 minutes of standing. The subject's heart rate slowed from 110 bpm to 40 bpm. The event resolved spontaneously without intervention. The subject continued in the study to received asenapine without any subsequent problem.
•A 52 year old Caucasian male in study 041033 received asenapine 5 mg and fluvoxamine 25 mg BID after having received fluvoxamine for the past 4 days. One hour after his combined dose, he developed sinus pauses. The sinus pauses occurred during 10 minutes while the volunteer was sleeping and lasted for 3 to 12 seconds. The subject recovered the same day and continued in the trial. This event was considered to be due to NMRB.

"In summary, NMRB occurred in four healthy volunteers receiving asenapine and one healthy volunteer receiving placebo. In the asenapine clinical program, NMRB with sinus pause was observed mainly in young and athletic healthy volunteers with high vagal tone and occurred after a postural change following asenapine or placebo. This was not seen in psychiatric patients."

Reviewers Comment: Since these events occurred only in healthy volunteers, the explanation provided by the sponsor appears reasonable.
In conscious dogs, orally administered asenapine induced dose-dependent negative inotropic and positive chronotropic effects accompanied by ECG changes (QTc interval prolongation), orthostatic hypotension on tilt with marked tachycardia. The results of a study in isolated canine Purkinje fibers indicate that asenapine induced mainly decreases in action potential duration, in particular on APD50. These effects were associated with a decrease in the plateau of the action potential reflecting mainly block of calcium channel current. Decreases in action potential duration were dose-dependent and were more pronounced under low stimulation rate (0.33Hz) than under normal stimulation rates (1Hz). N-desmethylasenapine induced comparable effects (decreased action potential duration, particularly APD50, but at approximately 10 times higher concentrations. It is possible that the sinus pauses observed in healthy volunteers could be due to negative inotropic effects of the drug secondary to inhibition of sodium or calcium current. However, NMRB secondary to α-receptor blockade appears to be a more plausible explanation.

1.4 Effects on PR and QRS intervals-Study INT 00036960
The QT-IRT also analyzed the PR and QRS datasets provided by the sponsor for Study INT 00036960. The change from baseline compared to placebo (ΔPR and ΔQRS) and corrected for placebo (ΔΔPR and ΔΔQRS with 2 sided 90% CI) was computed. Compared to placebo both drugs (asenapine and quetiapine) exerted similar effects on the PR and QRS intervals. Slight shortening of both intervals was observed (maximum change ~-9 ms and -3 ms respectively). There is no clinical significance to these findings.

1.5 Other Cardiac AEs
Asenapine may induce orthostatic hypotension associated with dizziness (postural), tachycardia and, in some patients syncope, especially early in treatment, probably reflecting its α1-adrenergic antagonistic properties. It appears that healthy volunteers are more susceptible to the blood

pressure lowering effect of asenapine. In Phase 2/3 studies, the incidence of orthostatic related adverse events was similar in the asenapine group compared to the other comparators. The incidence of syncope was low, 0.5% in the asenapine 5-10 mg BID dose group, which was comparable to the olanzapine group (0.4%) and slightly greater than placebo (0.1%).

QT-IRT COMMENTS:
It appears that the arrhythmia related AEs associated with asenapine are similar to those of olanzapine and consistent with class effects based on our review of the summary of clinical safety, non-clinical summary and additional analysis of ECG intervals in Study INT 0036960

Thank you for requesting our input into the development of this product under NDA 22117. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

Suchitra Balakrishnan
4/23/2008 02:00:08 PM
MEDICAL OFFICER

Norman Stockbridge
4/23/2008 06:06:06 PM
MEDICAL OFFICER

New Drug Application
Clinical Pharmacology Review

NDA:	22-117
Type of Submission:	Original NDA
Submission Date:	August 30, 2007
Associated INDs:	51,641 September 30, 1996 (Treatment of Psychosis) 70,329 August 3, 2004 (Treatment of Acute Mania in Bipolar I)
Generic Name:	Asenapine Maleate
Formulation: **Strengths:**	Sublingual Tablets 5 mg, 10 mg
Route:	Sublingual (N.B. Route is mislabeled in Application Form 356h)
Brand Name:	Sycrest®
Sponsor:	Organon / Schering-Plough
Submission Date(s):	

SN	Date	Code	Descriptor	Contents	OCP
000	8-30-07		Original Submission		X
001	9-28-07	BM / BB	Minor Amendment - Medical / OCP	Highlights of Clinical Pharmacology Requested by Medical Reviewer	X
002	10-24-07	BM	Minor Amendment - Medical	Response to MO request for Regulatory History	X
003	11-20-07	XS	Change in Ownership	Change in ownership	
004	11-30-07	BZ	Minor Amendment – Multiple Disciplines	Response to QT group questions	(x)
005	12-3-07	BS	Minor Amendment – Statistical	Response to statistical reviewer	
006	12-7-07	BB	Minor Amendment – OCP	PK Datasets	X
007	12-10-07	C / BC	Minor Amendment – CMC	Response to CMC Request	
008	12-21-07	BC / BL	Minor Amendment – CMC / Labeling	Update CMC information	
009	12-21-07	BC	Minor Amendment – CMC	Response to CMC Request	
010	12-27-07	SU	Safety Update	4 month Safety Update Exposure Response Analysis and interim report of PK in elderly	
011	12-28-07	BB	Minor Amendment – OCP	PK Datasets and other requested information	X
012	1-11-08	BP	Minor Amendment – Pharm/Tox	Effect on Prolactin in Rats	
013	1-11-08	BM	Minor Amendment Medical	Summary of Clinical Safety - Rhabdomyolysis	
014	1-17-08	BC	Minor Amendment Chemistry	CMC Information - Packaging	
015	1-30-08	BC	Minor Amendment Chemistry	CMC Information – Drug Substance	
016	2-21-08	BP	Minor Amendment – Pharm/Tox	Response to request for information	
017	2-21-07	BC / BL	Minor Amendment – CMC / Labeling	Update CMC Blister labeling	
018	3-11-08	BP	Minor Amendment – Pharm/Tox	Response to request for information	
019	3-27-08	BP	Minor Amendment –	Response to request for information	

				Pharm/Tox		
	020	3-27-08	GC	General Correspondence	Lack of appropriate birth control used in study. Exclusion of data from Bipolar efficacy study.	
	021	4-10-08	BL	Minor Amendment – Labeling	Cartoning and Proposed Tradename	
	022	4-18-08	BC	Minor Amendment – Chemistry	Changes in Manufacturing Process	
	023	4-29-08	BP[a]	Minor Amendment – Pharm/Tox	Response to questions re: carcinogenicity studies.	
	024	4-30-08	BC	Minor Amendment – Chemistry	Response to Comments: Stabilty and Impurity Specifications	
Reviewer:	Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D.					
Team Leader:	Raman Baweja, Ph.D.					

a Mislabeled as BB

1 Table of Contents

1.1 List of Sections

1.2 List of Tables

1.3 List of Figures

2 Executive Summary

2.1 Recommendations

The Office of Clinical Pharmacology / Division of Clinical Pharmacology I (OCP/DCP-1) has reviewed NDA #22-117 with an initial submission date of August 30, 2007.

OCP finds this application unacceptable for the following reasons:

1. Studies examining clinical pharmacology and exposure response were designed, conducted and reported in such a manner that it is not possible to determine how it may or may not be possible to mitigate risks; and in particular in the most vulnerable populations (i.e. children and elderly) who are also expected to be the primary users of this medication.

Major deficiencies include:

1. The vast majority of circulating species in plasma have not been identified.

2. The mass balance data provided only allows the unambiguous assignment of the primary elimination pathways of 1/5 to 1/3 of the dose.

3. Inappropriate design and lack of the appropriate information in drug interaction studies.

Comments may be found under section 2.3 on page 42.

2.2 Summary of Clinical Pharmacology and Biopharmaceutics Findings

2.2.1 Introduction and Background

Chemistry and Mechanism of Action

Asenapine is a heterocyclic dibenzo-oxepino pyrrole antipsychotic, i.e. a tetracyclic D2 antagonist that includes a pyrrole as the fourth ring.

Proposed Indications

Schizophrenia

Acute manic or mixed episodes associated with bipolar I disorder

Proposed Formulation and Strengths

5 mg and 10 mg Fast Dissolving Sublingual Tablets

Proposed Dosage Regimen

Schizophrenia: The recommended dose range of Sycrest® is 5 mg to 10 mg given twice daily (BID). Sycrest® should be administered at an initial daily dose of 5 mg BID. An increase in dose to 10 mg BID is recommended only after clinical assessment. (2.1)

Bipolar disorder: The recommended dose of Sycrest® is 10 mg given twice daily (BID). (2.2)

Administration: Sycrest® Sublingual Tablets should be placed under the tongue and left to dissolve completely; do not swallow tablet. Eating and drinking should be avoided for 10 minutes after administration.

2.2.2 Summary of Major Conclusions

Asenapine appears to be efficacious in the treatment of severe cases of acute mania, with baseline YMRS scores of greater than or equal to approximately 27, although additional studies might be needed prior to an approval.

There appears to be no margin of safety with regards to cardiac toxicity. Various serious cardiac toxicities including asystole, supraventricular arrhythmias and conduction disturbances, and myocardial infarction occurred in healthy volunteers, as did a death due to congestive heart failure in a patient. Many of the cardiac toxicities appear unrelated to effects on QT although there is a positive QT effect that appears more pronounced in women.

Other life threatening toxicites observed include neutropenia, and presumptive agranulocytosis with pancytopenia resulting in death. This appears to be time dependent occurring after approximately 1.2 years of treatment and may be due to a cumulative effect of toxic metabolites. The incidence of death due to agranulocytosis was approximately 1/313 in subjects treated for 1 year and when other suspicious deaths due to respiratory arrests are included the incidence of death due to agranulocytosis may be twice as high (i.e. ~ 1/150). However it should be remembered that this does not include other causes of drug induced death.

Dose and time dependent drug induced liver injury also occurs and appears related to the amount of drug swallowed and is of special concern in children. It may also be worse when used in combination with other psychoactive drugs.

There is evidence of significant pharmacodynamic interactions, including CNS effects, with commonly coadministered drugs (including drugs of abuse and OTC drugs) that result in serious AEs (i.e. coma and psychosis).

Desmethyl-asenapine is a noncompetitive inhibitor of CYP2D6 and drug-drug interactions with other CYP2D6 substrates including OTC allergy and cough and cold medications are likely to occur. As a noncompetitive inhbitor interactions may continue to occur for a substantial period after discontinuing asenapine until enzyme regenerates.

A neonatal death was also reported but no detailed information was submitted so the potential mechanism cannot be determined and any labeling recommendations would likely be insufficient.

Due to differential first pass effect with swallowing, the relative weight normalized dosage in children and frail elderly, and the likely heightened risk with comorbid diseases, these populations may be especially at risk.

The incidence of suicidality in schizophrenics after short term treatment appears similar to olanzapine and placebo however the numbers are likely too small for a definitive conclusion. The peak incidence of suicidality in schizophrenic subjects occurs 1 – 2 weeks after discharge from inpatient care. Based on the available data an examination on whether a longer duration of residence in an inpatient setting or continued residence in a structured environment for several weeks may be more effective in preventing suicides in schizophrenics. For subjects with bipolar disorder there was no suicidality in the placebo group where as there was a 1% incidence of suicidality for both asenapine and olanzapine with a peak incidence of completed suicides (0.3%) for both compounds after 2 weeks of therapy and during inpatient treatment.

The clinical development program appears to be designed and reported in such a manner so as to minimize the detection and acknowledgment of expected and observed toxicities. Consequently, there is insufficient information to allow labeling recommendations that might mitigate risks. In addition quantitative estimates of the relative benefits of asenapine relative to the risks are likely to be unreliable.

2.2.3 Pertinent Clinical Pharmacology and Biopharmaceutic Questions

What formulations were used in the phase I, phase II, and phase III studies and how do these compare to the formulations proposed for marketing?

(b) (4)

The proposed To-Be-Marketed, (TBM), formulation is a (b) (4) sublingual tablet that contains (b) (4) (b) (4) and water which is removed by (b) (4). Four changes have been proposed for the To-Be-Marketed formulation from the Clinical-Trial-Formulation.

- (b) (4)
- Change (b) (4)
- Change in (b) (4)
- (b) (4)

Typically for a (b) (4) sublingual formulation changes to the formulation would generally be considered to be unlikely to be clinically significant however for asenapine faster dissolution means more drug being absorbed sublingually with higher peaks and greater AUCs, and slower *in vivo* dissolution would result in more drug being swallowed with greater first pass effect and more N-desmethyl-asenapine being formed and changes in metabolic profiles and greater changes in time dependent kinetics. In the case of asenapine this might be clinically significant due to the dose and time dependent hepatotoxicity observed with oral administration, metabolite concentration dependent cardiac arrhythmias, as well as significant drug-drug-interactions.

Are the proposed to-be-marketed formulations bioequivalent to the clinical-trial-formulations?

Two pivotal bioequivalence studies were conducted. Study A7501015 examined the effect of changing the (b) (4) and study A7501016 examined the effect of a (b) (4) The sponsor concluded that both changes resulted in bioequivalence.

For the change in (b) (4), geometric mean ratios were high but within the acceptance limits of 0.80 – 1.25 for both Cmax and AUC, with the change in Cmax with the (b) (4) resulting in increased bioavailability, (GMRs for Cmax 1.09 (b) (4) and AUC 1.07 (b) (4) However this required a large sample size (n = 36) due to the large variability. On average a large percent of the AUCinf was extrapolated (7.4%). This is not surprising as sampling was only conducted to 48 hours and there is a long half-life. Unfortunately the datafiles could not be opened to determine whether the results are acceptable or not.

For the change (b) (4) the geometric mean ratios were just barely within the acceptance limits of 0.80 – 1.25 for both Cmax (LL 90%CI: 0.808) and AUC (LL 90%CI: 0.837), even with a large sample size (n = 35), with the change (b) (4) resulting in decreased bioavailability. This is presumably due to (b) (4) On average a large percent of the AUCinf was extrapolated (8.4%). Unfortunately the data files could not be opened to determine whether the results are acceptable or not. With decreased bioavailability and the narrow therapeutic window there is a concern for greater hepatotoxicity and cardiac toxicity. In fact the sponsor conducted telemetry monitoring during the study and reports the following:

"During telemetry monitoring, 10 subjects experienced bradycardia; eight subjects experienced tachycardia; seven subjects experienced sinus pause, 3 subjects experienced junctional rhythm; and 1 Subject experienced bradycardia with junctional rhythm (Appendix B9.3)."

In total 20 of the 35 subjects experienced some form of cardiac arrhythmia.

As this study was conducted in young healthy male and female volunteers with a single low dose this is very concerning.

Does asenapine exhibit linear kinetics over the dosage range?

No. Absorption is nonlinear.

When administered sublingually, linearity over a range of 0.02 mg to 5 mg is apparent from the mean Cmax and AUC data from a number of other studies.

Above a dose of 5 mg, sublingual absorption decreases. This is due to more of the drug being swallowed, and is expected based on the solubility of asenapine in water and pH 4.0 buffer being in the range of 3.7 - 3.8 mg/ml. Consequently, there is greater first pass of the portion of the dose that is swallowed with less exposure to asenapine and a corresponding increased exposure to N-desmethyl-asenapine.

What are the pharmacokinetic characteristics of asenapine?

Asenapine is a high intrinsic clearance drug with an intrinsic clearance that is likely equal to hepatic blood flow. It has an extremely large volume of distribution of roughly 100 - 200 L/kg, and an initial phase half-life of around 5 hours with a terminal phase half-life of around 1 – 1½ days and up to 2½ days in the PET study.

With sufficiently large doses and extended sampling a third compartment can be discerned.

Absorption after sublingual administration is rapid with a median Tmax of 0.5 – 1.0 hours

There were no significant diurnal variation in the overall concentration time profiles however, predose concentrations show clear diurnal variation when dose normalized, however the absolute amount of diurnal variation is small and does not raise any obvious concerns.

What is the metabolic profile of asenapine?

Asenapine appears to be metabolized via four primary metabolic pathways to N-desmethyl-asenapine, 11-hydroxy-asenapine, asenapine N-oxide and asenapine N- glucuronide.

With the exception of the glucuronide the primary metabolites are all further metabolized extensively. For example the 11-hydroxy is also hydroxylated at the 10 position with further O-sulfation, O-glucuronidation and O-methylation by COMT.

As expected the N-glucuronide is formed by UGT1A4 which typically glucuronidates tertiary amines, whereas the enzymes responsible for the 11-hydroxylation, N-oxidation, and N-desmethylation are not as clear. However, it appears that 11-hydroxy is mediated by CYP1A2 and possibly 3A4, N-desmethylation may be mediated by CYP2C9 and possibly other enzymes with secondary N-oxidation by CYP2D6, whereas enzymes responsible for formation of N-oxide asenapine are not clear.

Presently the metabolic profile is only tentative due to limitations in the reporting of the data, (see §6.5 (Requests to Sponsor) on page 477).

What are the pharmacokinetic characteristics of the metabolites?

Desmethyl-asenapine has peak concentrations of 30% of asenapine's at 5 mg BID and below, and around 60% of asenapine's at 10 mg BID. AUCs of desmethyl-asenapine are 3 fold asenapine's at doses of 5 mg BID and below, and 11 fold at 10 mg BID. Desmethyl-asenapine has monoexponential decline during a single dosage interval and although the half-lives reported for desmethyl-asenapine are shorter than asenapine's, this is probably due to assay insensitivity and most likely desmethyl-asenapine has formation rate limited kinetics.

Exposures to asenapine glucuronide are several fold higher than asenapine but are otherwise unnoteworthy and N-oxide concentrations in plasma were frequently barely detectable possibly due to binding to tissues.

Are the metabolites adequately characterized in plasma?

No.

The mass balance study utilited a single 0.3 mg dose of ^{14}C-labeled asenapine administered in addition to asenapine 10 mg SL BID. The sponsor also compared the plasma concentrations of selected species determined by standard bioanalytic methods, (i.e. asenapine, desmethyl-asenapine, and asenapine N-oxide) to total plasma radioactivity as determined by scintillation counting. The plasma concentration profiles for total radioactivity and identified circulating specifies indicated that at least 96.6% of the circulating species have not been identified. In order to compare the exposure to asenapine and the two metabolites to total circulating species the total radioactivity needs to be dose normalized. Examination of the raw data indicates that the sponsor did not do this. Dose normalization would increase the total radioactivity 34.3 fold (i.e. 10.3 mg / 0.3 mg). In addition the AUC_{τ} of these selected species need to be compared to AUC_{∞} for total dose normalized radioactivity.

When this is done, 99.9% of the circulating species have not been identified. In addition, when dose normalized radioactive Cmax is compared to the Cmax of asenapine the total radioactivity is 223 – 552 fold higher, (i.e. 3145/14.1 and 3008/5.44).

When chromatograms of pooled plasma samples over the dosage interval are examined, there are 10 or more unidentified peaks with peak areas apparently greater than 10% of the peak area for asenapine. This means that there are at least this many and possibly more metabolites that may not have been adequately qualified in toxicology studies.

Has the mass balance of asenapine been adequately characterized?

No.

After administration of a radioactive dose on average 88% of the dose was recovered, with approximately 49% recovered in urine and 39% recovered in feces.

Except for direct glucuronidation by UGT1A4 which accounts for 12% - 21% of the dose and elimination of unchanged asenapine which accounts for 5% - 16% of the dose, the relative contribution of the 3 primary oxidative pathways cannot be definitively assigned. This is due to the fact that multiple metabolites were identified for each peak and is also due to lack of identification of other peaks. Consequently the metabolic scheme is uncertain. Consequently the enzymes responsible for each of 3 of the primary pathways and their relative contributions have not been adequately characterized for 64.5% – 82.8% of the dose.

What are the receptor affinities for asenapine and metabolites?

Asenapine has high receptor affinities for all dopamine, serotonin, alpha-adrenergic, and histamine receptors tested, as well as for norephinephrine and dopamine reuptake transporters based upon typical

Cmaxs in the range of 3 - 30 nMol/L (1 - 10 ng/ml) with doses of 5 – 10 mg SL BID, and typical IC_{50}'s in the range of 0.1 – 4 nMol/L..

In addition to the receptors mentioned, the evidence presented by the sponsor suggests that asenapine has effects on potential down-stream intracellular mediators.

Unfortunately the sponsor does not indicate whether binding at the various receptors result in antagonism or agonism, and this would be needed to predict potential pharmacologic effects such as cardiac valvulopathy with agonism of the $5HT_{2B}$ receptor.

Effects on other potential receptors, e.g. ion channels, were not found during this review, however the QT review mentions effects on canine calcium channels that are consistent with certain cardiac toxicities that have been seen in humans.

Until more information is available on the unidentified circulating species and receptor affinities are available for them the clinical significance of metabolites cannot be assessed.

What transporters are involved in asenapine's disposition?

Asenapine itself is not a substrate for pGP, however the sulfate and glucuronide conjugates probably are although active transport of metabolites was not studied.

What is asenapine's protein binding and the effects of changes in protein binding?

Protein binding of asenapine was 95% and is primarily to low molecular weight non-albumin plasma proteins.

What is the effect of pharmacogenetic polymorphisms on asenapine pharmacokinetics and pharmacodynamics?

This was not studied however as a CYP 2D6 and 2C9 substrate these might be clinically significant.

What are pharmacokinetic characteristics of the enantiomers of asenapine?

The plasma concentrations of the (S,S) - and (R,R) - enantiomers of asenapine are similar after simultaneous single sublingual doses of 2.5 mg of the (S,S) - enantiomer and 2.5 mg of the (R,R) - enantiomer of asenapine. Formation of the N - desmethyl metabolite seems to be enantioselective, i.e. the (S,S)-enantiomer is converted to more than two - fold higher N - desmethyl - asenapine concentrations than the (R,R)-enantiomer The difference in exposure to the two N-desmethyl metabolites might indicate either a difference in volume of distribution due to differences in tissue penetration or binding or more likely a difference in clearance with increased exposures to other metabolites and potentially different in risk : benefit ratios for the different enantiomers if administered separately. In addition this makes the interpretation of drug-drug interactions more difficult as binding to both on- and off-target receptors are frequently different between enantiomers.

Are there any indications of time dependent kinetics based on the *in vitro* data, i.e. enzyme activated inhibition?

Yes. N-desmethyl-asenapine is potentially a time-dependent inhibitor of CYP2D6 as it is a suicide substrate inhibitor. Consequently, the effect of inhibition might be small with a single dose but would increase upon multiple dosing due to the cumulative inhibition due to multiple doses. In addition, the effect of inhibition could be quite long lived based on the time needed to regenerate enzyme. This could be significant even with a single dose if the amount of enzyme inhibited with a single dose is sufficiently large.

Does asenapine exhibit time invariant kinetics *in vivo*?

There was no *in vitro* evidence of induction by asenapine on CYPs 1A2 or 3A4.

With regards to inhibition, N-desmethyl-asenapine is a suicide substrate inhibitor of CYP2D6. Although was not expected to affect the kinetics of asenapine it was expected to result in time dependent kinetics for N-desmethyl-asenapine. However nonlinear kinetics for both asenapine and desmethyl-asenapine were observed in the elderly PK study with maximal exposures several fold greater than in healthy volunteers. (See the question on food effect on the following page for further discussion.)

What is the absolute bioavailability of asenapine?

The absolute bioavailability after an oral dose is approximately 2% - 3%, whereas after sublingual administration the average absolute bioavailability for a single 5 mg dose is approximately 35%. This decreases with higher dosages (i.e. 10 mg) although quantitative values are not available and the variability and range are needed to be able to thoroughly assess safety.

The lower bioavailability with higher doses is likely due to solubility issues and as decreased bioavailability and differences in metabolism have safety implications this is especially important for smaller children who may have lower bioavailability with similar doses.

What is the relative buccal and supralingual bioavailability?

Both the supralingual and buccal routes had lower Cmaxs, AUCs and delayed Tmaxs as compared to the sublingual route, with absorption via the supralingual route being less than the buccal route. The supralingual route was not bioequivalent to sublingual administration and although the buccal route met the criteria for bioequivalence, it barely did so. The formulation used is different than the to-be-marketed formulation and has a 20% lower bioavailability, and the dose used is in the range where bioavailability is greater than with clinical dosages, which would minimize the chance of seeing toxicities in this study. Thus buccal and supralingual bioavailability is expected to be much less than after sublingual administration and is a safety concern with clinical dosages.

What is the effect of drinking water in close proximity to taking asenapine?

When water is taken less than 10 minutes after asenapine administration the exposure to asenapine decreases, presumably due to transfer of unabsorbed asenapine from the oral cavity to the stomach and increased first pass effect by way of GI absorption as compared to sublingual administration.

Since, taking asenapine orally appears to be related to acute hepatotoxicity and since there appears to be a very narrow therapeutic index, water should not be taken for at least 10 minutes after the administration of asenapine.

There is little to no difference in mean exposures to asenapine and desmethyl-asenapine when water is administered 10 or 30 minutes after dose administration.

What is the effect of food on the bioavailability of asenapine?

Food decreases exposure to asenapine by about 20% when administered concurrently. In addition when food is administered 4 hours after asenapine dosing it decreases asenapine exposures by about 10% (but not peak concentrations), apparently due to slowed hepatic and splanchic blood flow.

This food effect study was not conducted under true fasted conditions as the ‘fasted’ individuals were administered a ‘liquid breakfast’ and an ‘isotonic sports drink’ 1 hour prior to taking asenapine. Thus the magnitude of the decrease in bioavailability especially when taken with a meal may actually be larger. As asenapine has a narrow therapeutic window with regards to hepatotoxicity even small changes and metabolic shunting could be clinically significant.

What is the effect of activated charcoal?

Charcoal administration effects oral absorption more than sublingual absorption. When administered with charcoal there is a decrease in asenapine exposure after oral administration of approximately 50% compared to a decrease in asenapine exposure of approximately 25% after sublingual administration. In addition the effect of charcoal administration on desmethyl-asenapine exposure is even greater than the effect on asenapine, and this is especially true with oral administration.

Does asenapine exhibit route dependent pharmacokinetics?

Quantitatively the relative bioavailability of asenapine after oral administration compared to sublingual administration is approximately 7% with an estimated absolute oral bioavailability of around 3%.

In addition, the exposure to desmethyl-asenapine is only 4.6% lower after oral administration, however the rapid delivery results in a 60% higher peak desmethyl concentration after oral administration.

These results indicate that the first pass effect is not due to metabolism to desmethyl-asenapine but rather to a different elimination pathway. Data indicates it is not due to biliary excretion of asenapine and it is unlikely due to glucuronidation because this tends to be a low affinity pathway. The most likely pathways responsible for the first pass effect are either N-oxidation or 11-hydroxylation. Depending upon which pathway it is, the clinical ramifications regarding labeling may vary greatly, as an N-oxide is likely much more toxic. In drug interaction studies virtually no information was included on formation by 11-hydroxylation. Consequently, the true effects of drug interactions and shunting cannot be determined.

Are there pharmacokinetics differences by Race or Ethnicity?

As asenapine is a CYP2D6 substrate and CYP2D6 activity is trimodally distributed with different frequencies by race and ethnicity, race and ethnicity would be expected to result in differences in metabolism. Specifically 7%- 10% of Caucasians are expected to be poor metabolizers and 17% of Ethiopians are expected to be extensive metabolizers.

Single and multiple dose pharmacokinetics for asenapine, desmethyl-asenapine, asenapine glucuronide and asenapine 11-O-sulfate in Japanese and Caucasians did not show any clear differences between the groups. However, due to the small sample size (n = 8 / group) no firm conclusions can be drawn from this study. In addition, this reviewer noticed only 1 Ethiopian reported as being enrolled in other studies.

Are there pharmacokinetics differences by gender?

No specific gender study was performed. Since asenapine is a CYP1A2 substrate and drugs that are substrates of CYP1A2 tend to have higher exposures in women and the elderly the effect of gender and age need to be examined.

This is omission should be noted as agranulocytosis with structurally similar compounds may be greater in women.

Does asenapine's pharmacokinetics change with increasing age?

It was thought that no study in the elderly had been performed. However, on April 11, 2008 an abbreviated study report in the elderly was found. It had been submitted in Amendment 010 the 120 safety update report, under Reports of Efficacy and Safety / Schizophrenia / Other Study Reports / Study A7501021 a phase III efficacy and safety study in the elderly under the legacy study report under an entirely different study number with no description.

This abbreviated study only provides interim pharmacokinetic summary statistics with no raw data or safety information. On average Cmax and AUCs in the elderly (65 – 85 years of age) were 30% - 40%

higher for asenapine compared to younger adults and for desmethyl-asenapine they were double. When the range of exposures in the elderly are examined the highest exposure for asenapine is 3 fold higher than the highest exposures in younger subjects and for desmethyl-asenapine it is 11 fold higher. However, the relatively high amount of N-desmethyl-asenapine indicates that there is likely some type of metabolic shunting occurring that will either increase inhibition of CYP2D6 or cause shunting to desmethyl-asenapine and /or toxic metabolites such as the N-oxide. Thus without adequate information on the metabolic scheme risks cannot be mitigated. In fact we don't even have safety data from this study to help identify the incidence of side effects. In addition without individual data the effect of predictive factors such as age and gender on the exposures cannot be determined.

As asenapine is a sublingual formulation the degree of dementia might have an impact on the amount of drug swallowed and this should be examined as use in this elderly population is expected to be especially high. Unfortunately significant cardiac safety signals have been observed that are not typically observed with other classes of antipsychotics, although they are seen to varying degrees with structurally similar compounds, and that are generally considered to be of particular clinical importance in the elderly.

In addition, the risk of agranulocytosis with structurally similar compounds is increased in the elderly, possibly due in part to lower baseline WBCs, so lack of information in the elderly is an important omission in the clinical development program.

What are the pharmacokinetic characteristics in children?

No raw pharmacokinetic data or metrics in children were supplied. As with the pharmacokinetic study in the elderly only an abbreviated report was provided with summary statistics for pharmacokinetic metrics. It appears that many of the subjects were on Adderal® for ADHD and were also diagnosed with bipolar disorder or psychosis. There were a high percentage of blacks enrolled in this study. This raises the question whether this is simply due the recruiting area or to more black children being placed on antipsychotics for ADHD due to their socioeconomic circumstances, or whether it an intentional attempt to minimize Caucasians due the higher likelihood that they would be CYP2D6 poor metabolizers. In addition, since African American children are more likely to be at the upper end of the height and weight spectrum they would thus be more likely to have exposures that are more similar to adults and less likely to experience adverse effects.

Examination of patient demographics revealed that 0 / 17 females and only 5 / 23 males had body weights of $\leq$ 45 kg. This is significant as 45 kg is the median population weight in adolescents between 12 – 17 years of age. Thus the pharmacokinetic data from this population likely underestimates the true exposure measured by AUC that would be expected in the actual treated population.

Thus unless further information is obtained, studies in adolescents are likely to result in excessively high concentrations in normal weight adolescents at the lower end of the age range. This is concerning since, there appears to be a very narrow safety margin for hepatotoxicity if dosage is not adjusted. This is especially worrisome with off label use in even younger children as a sublingual formulation would be a natural choice for prescribers to use off label, and the lack of appropriate dosage strengths might mean an even greater proportion of the dose would be swallowed as compared with adults and thereby significantly increase the risk of hepatotoxicity.

Another concern with adolescents is the greater propensity for ingestion of high fat meals and the alterations in hepatic blood flow and increase in potentially hepatotoxic metabolites this might entail.

What is the effect of renal insufficiency on asenapine?

Two "full" studies were conducted on the effects of renal impairment on the pharmacokinetics of asenapine and desmethyl-asenapine. One study was conducted at a low dose 0.3 mg, possibly for safety reasons and this was followed by a second study with a single 5 mg dose (n = 8 / group).[1] The findings

[1] 9 for normal renal function in the 5 mg study

were mixed however it appears that desmethyl-asenapine exposures are lower in moderate and severe renal insufficiency (GMRs 0.82 and 0.73 respectively), possibly indicating a decreased formation of desmethyl-asenapine. It is known that CYP2D6 activity is decreased in end stage renal failure however this doesn't adequately explain the findings regarding desmethylasenapine.

Other metabolites such as the derivatives of the 11-hydroxy-asenapine and N-glucuronides were not assessed so the alterations in other quantitatively major active metabolites cannot be assessed.

What is the effect of hepatic insufficiency on asenapine?

Two "full" studies were conducted on the effects of hepatic impairment on the pharmacokinetics of asenapine and desmethyl-asenapine. One study was conducted at a low dose 0.3 mg, possibly for safety reasons and this was followed by a second study with a single 5 mg dose (n = 8 / group).[1] Average exposures to asenapine are over 5 fold higher in subjects with severe hepatic impairment, although some individual patients with mild hepatic impairment (n = 2) also had higher exposures to asenapine and N-desmethyl-asenapine. In addition the increased exposure to free drug was much higher, (3 fold the UL of exposures in normal volunteers making the average increase similar to the average increase of nearly 2 fold in moderately impaired subjects).

Since only slightly higher than the likely clinical dosage appears to be associated with hepatotoxicity, the presence of even 1 or 2 individuals in the mild hepatic impairment groups with much higher total exposures and others with normal total exposures and much higher free exposures leaves no margin of safety. Thus even if the risk : benefit ratio turns out to be acceptable for patients with normal hepatic function; it is unlikely to be acceptable for patients with even mild degrees of hepatic function.

What is the effect of smoking on asenapine pharmacokinetics?

Asenapine is a CYP1A2 substrate which forms 11-hydroxy-asenapine -sulfate. As tobacco use induces CYP1A2 a decreased exposure to asenapine due to induction is expected. In addition there is a possibility of decreased absorption secondary to vasoconstriction due to nicotine.

When examined no effect of smoking was seen on the pharmacokinetics of asenapine or desmethyl-asenapine. Although neither the effect on 11-hydroxy-asenapine or downstream metabolites such as sulfate conjugates were studied. However the study was conducted in chronic smokers and during the smoking phase of the study the subjects smoked from 5 minutes before to 10 minutes after asenapine administration. Thus the true effect of smoking on asenapine is unknown, as chronic smokers would not be expected to have any induction secondary to a single cigarette. In spite of this the low peak concentrations and AUCs seen in this study as compared with other studies may be indirect evidence of induction or slowed absorption.

As schizophrenics tend to be heavy smokers the effect of smoking is more likely to be evident in patients with bipolar illness where intermittent smoking may be more relevant, or if the drug is used off label for schizoaffective disorder. However since the clinical importance of metabolism by 11-hydroxylation is still unknown the true effects of smoking in schizophrenics are also unknown.

What is the potential for asenapine to inhibit CYP2D6?

The effect of asenapine to inhibit CYP2D6 was examined with 3 cosubstrates under varying conditions:

- Asenapine 5 mg BID administered for 11 days on a single dose of paroxetine 20 mg
- Asenapine 5 mg BID administered for 9 days on a single dose of dextromethorphan
- A single dose of asenapine 5 mg followed by a 4 day washout on the multiple dosing of paroxetine 20 mg qd for 1 week and the effect on dextromethorphan 9 days after the single dose of asenapine.

[1] 6 for severe hepatic impairment in the 5 mg study

- Effect of a single dose asenapine 5 mg on a single dose of imipramine 75 mg

Effect of multiple doses of asenapine on a single dose of paroxetine

A low dose of asenapine 5 mg BID resulted in a doubling of paroxetine. The mechanism for this interaction, e.g. effect on CYP3A4 or another enzyme, is unknown.

Effect of a single dose of asenapine on multiple doses of paroxetine

Even after 7 days of dosing paroxetine 20 mg qd, trough concentrations were still increasing. Although paroxetine does exhibit nonlinear kinetics, even at a higher dose of 30 mg mean half-life is 15 -22 hours with maximal half-lives of 65 hours. Consequently, steady-state should have already been reached). Instead it's possible that irreversible inhibition from the initial single dose of asenapine 7 days before was still inhibiting the elimination of paroxetine. This has clear implications for switching from asenapine to other antipsychotics or adding other drugs that are CYP2D6 substrates, e.g. antidepressants or narcotics.

Consequently, the degree of accumulation of desmethyl-asenapine and paroxetine when both are given in combination could be quite high under clinical dosing conditions and could result in an increased incidence of hepatic or other toxicities. Thus the present study clearly does not provide sufficient assurances of safety under clinical use.

Comparative Effect of Asenapine and Paroxetine on Exposure to Dextromethorphan

The DX/DM ratio after paroxetine 20 mg po qd is about 7.5% of the DX/DM ratio after asenapine 5 mg SL BID demonstrating that paroxetine is a more potent inhibitor. Based upon these DX/DM ratios it appears that paroxetine is 13.4 fold more potent. However the degree of effect on the DX/DM ratio is due to a combination of changes in both dextrorphan and dextromethorphan. A better indicator of the degree of inhibition of CYP2D6 is by examination of the relative change in exposures to dextromethorphan in the presence of each compound. Although not examined, this can be determined indirectly by comparing the amounts of dextromethorphan recovered in urine in the presence and absence of each inhibitor.

For paroxetine the post-dosing to pre-dosing GMR for dextromethorphan for an 8 hour timed urine collection is 13.1 compared to 1.55 for asenapine. Consequently paroxetine causes on average an 8.45 greater increase in dextromethorphan than asenapine, athough it should be noted that a low dose of asenapine was used and the effect of asenapine on dextromethorphan with a 10 mg dose is likely greater. When individual values are compared some subjects in the paroxetine group have exposures of nearly 45 times higher than baseline, whereas no one receiving asenapine had an increase of even 10 fold. Although with the 10 mg dose the effect is likely greater and may approach the degree of inhibition with paroxetine. The primarily concerns are if children receive the 10 mg dose, greater effects with swallowing, inhibiton for several days after stopping, and severe AEs due to dextromethorphan or other CYP2D6 substrates such as antidepressants, cough and cold remedies, or narcotics should they be given in combination, particularly in children and the elderly.

Imipramine

No effect of a single dose of asenapine 5 mg SL was seen on a single dose of imipramine 75 mg in 24 subjects, although there was trend for higher asenapine concentrations (~10%) in the presence of imipramine. However this was a single dose study and asenapine is a mechanism based inhibitor. Consequently when the drugs are administered simultaneously there may not be time for inactivation of CYP2D6 by asenapine to occur. Although the rationale for dosing imipramine prior to asenapine is so that ingestion of water will not send asenapine to the stomach this is also likely to minimize inhibition because

a) Imipramine is administered first
b) Inhibition is more likely to occur with oral administration both due to the higher asenapine concentrations in the liver during first pass as well as the presentation of asenapine first if it were to be administered first.

Consequently, the results of this study cannot be considered representative of what is expected during clinical use and the studies with paroxetine and especially dextromethorphan are thus more informative.

Based on the study numbers it appears that this study (25525) was designed after the multiple dose paroxetine interaction study (25526).

What is the effect of CYP2D6 inhibition on asenapine?

There was a slightly lower exposure to asenapine in the presence of steady-state dosing of paroxetine 20 mg qd in 26 subjects but this was within acceptable limits with a GMR of 0.87 for Cmax, (90% CI 0.80 - 0.96), and 0.91 for AUC, (90% CI 0.85 - 0.97).

In contrast, there was a 26% increase in exposure (AUC) to desmethyl-asenapine, (90% CI 1.11 – 1.42), presumably due to inhibition of CYP2D6 N-oxidation.

Thus addition of asenapine to a potent CYP2D6 inhibitor could result in metabolic shunting with unknown clinical consequences.

How do other drugs effect the metabolism of asenapine by glucuronidation?

Valproate

The effect of valproic acid 500 mg PO BID on the pharmacokinetics of asenapine, N-desmethyl asenapine, and asenapine N-glucuronide following a single 5 mg dose of asenapine was assesed in 24 healthy male subjects.

There was clearly no effect of valproate on total asenapine Cmax or AUC.

In contrast the extent of exposure for desmethyl - asenapine as expressed by GMR of AUC∞ was on average 30% lower in the presence of valproate (90% CI: 0.64 – 0.77) whereas no effect was seen on Cmax. This may indicate decreased formation of desmethyl–asenapine by inhibition of CYP2C9, which is polymorphic.

The effect of valproate on the pharmacokinetics of asenapine–glucuronide was to decrease both AUC∞ and Cmax on average by 85%, meaning exposure in the presence of valproate was 1/7 the exposure in the absence of valproate. This appears to indicate that valproate competes with glucuronidation by UGT1A4 with not much effect on active secretion.

The lack of effect on asenapine kinetics and the decreases in both asenapine glucuronide and desmethyl asenapine indicates that coadministration with valproate likely results in shunting to 11-hydroxylaton. This is likely primarily mediated by CYP1A2, consequently coadministration of asenapine with valproate and a 1A2 inhibitor such as fluvoxamine could be quite dangerous. This is expected to occur occasionally in practice and might be predicted to occur most frequently in patients with bipolar spectrum disorder.

Regarding side effects there were more side effects for asenapine when given in combination with valproate as compared to when given alone. The greater values are as follows:

Fatigue	6 (25%) vs. 2 (8%)
Headache	6 (25%) vs. 1 (4%)

Unfortunately the effect of asenapine on valproate was not examined. In addition, there still exists the possibility of a pharmacodynamic interaction via mitochondrial metabolism that this study was not designed to detect.

What is the effect of likely co-administered inducers on asenapine, e.g. Carbamazepine?

The effect of a low dose of carbamazepine, (200 mg PO BID), on the pharmacokinetics of asenapine, N-desmethyl asenapine, asenapine N-glucuronide, and asenapine N-oxide following a single 5 mg dose of asenapine was assessed in 24 healthy male subjects.

Carbamazepine induces the elimination of asenapine resulting in a secondary decrease in glucuronidation. Lower concentrations early on in both of their concentration vs. time profiles with more similar concentration vs. time curves later on indicates that elimination is driving the earlier phase of the declining profile while redistribution may be driving the later phase.

There is a much greater percentage decrease in N-desmethyl-asenapine exposure (30%) compared with the decreases in asenapine and asenapine glucuronide exposures (i.e. 15% for each). This may indicate that elimination of N-desmethyl-asenapine is also mediated by oxidation to 11-OH-desmethyl-asenapine by CYP3A4. Consequently formation of 11-OH-asenapine by CYP3A4 may also be increased and shunting to metabolites of 11-hydroxylation may be behind the apparent increase in severe fatigue when the drugs are taken in combination. N-oxide concentrations were largely below the limit of quantitation and were more frequently measured following asenapine alone as compared with in the presence of carbamazepine.

What is the effect of the nonspecific CYP450 inhibitor cimetidine on asenapine?

The effect of cimetidine, (800 mg PO BID), on the pharmacokinetics of asenapine, N-desmethyl asenapine, asenapine N-glucuronide, and asenapine N-oxide following a single 5 mg dose of asenapine was assessed in 12 healthy male subjects.

Cimetidine is an imidazole that binds directly to the heme of certain P450s accounting for its ability to inhibit multiple isozymes.

It's interesting that cimetidine was studied and only 12 subjects were evaluated as compared to other studies that enrolled more subjects. In addition to the potential for drug interactions cimetidine causes agranulocytosis at a rate of approximately 1 in 100,000 and there have been reports that coadministration of cimetidine with compounds that are structurally related to asenapine might increase the risk of agranulocytosis.

In the presence of cimetidine exposure to asenapine doesn't change although Cmax is lower (GMR 0.87 90% CI 0.77 – 0.98) and although the exposure to asenapine glucuronide increases slightly, (GMR 1.22 90% CI 1.11 – 1.34 on average); the exposure to desmethyl-asenapine approximately doubles (GMR 2.22 90% CI: 1.91 – 2.58).

Although the sponsor claimed that asenapine N-oxide metrics weren't reported as it was largely undetectable, this reviewer was still able to calculate AUCs and compare them between treatments. Due to the low concentrations descriptive statistics of pharmacokinetic metrics were not helpful however comparative histograms were plotted and show that there may be a slight trend for slightly higher N-oxide AUCs in the presence of cimetidine.

As only a single dose of asenapine was examined the full implications of the increase in desmethyl-asenapine exposure was not examined. It is expected that there may be a quicker onset of time dependent irreversible metabolism. In the cimetidine arm there were more subjects who experienced hypotension and dizziness. In addition it's also possible that the slightly higher N-oxide exposures might translate into an increase in toxicity, which for an N-oxide would expect to include hematologic toxicities.

What is the effect of the CYP1A2 inhibitor fluvoxamine on asenapine?

The effect of a low dose of fluvoxamine 25 mg bid on the kinetics of asenapine, D-desmethyl-asenapine, and asenapine 11-O-sulfate following a single 5 mg SL dose of asenapine was examined in 26 healthy nonsmoking males.

Fluvoxamine increased the exposure to asenapine by 30%, (90% CI 1.14 – 1.46), decreased exposure to asenapine 11-O-sulfate by at least 30%, (90% CI 0.52 – 0.98 for AUCtlast), and increased exposure to desmethyl-asenapine by 2 fold, (90% CI 1.82 – 2.43).

Since the clinical dose of fluvoxamine is up to 300 mg daily the effects that are likely to be seen in clinical practice are much larger. In addition it should be noted that this study was conducted in nonsmokers, whereas most schizophrenics are smokers who will have CYP1A2 induced. Thus blocking 1A2 by fluvoxamine will result in an even greater effect in smokers, and will likely result in a much different risk profile compared to what was seen in the safety database.

The increase in exposure to desmethyl-asenapine is likely due to inhibition of 11-hydroxylation of desmethyl-asenapine. This will result in shunting to N-oxidation, although increased formylation is also a possibility. The shunting to N-oxidation will result in greater inhibition of CYP2D6 and as a suicide substrate result in even greater inhibition and thus result in nonlinear accumulation of desmethyl-asenapine upon multiple dosing. It's also possible that the increased inhibition of CYP2D6 will result in increased hepatotoxicity.

What is the effect of CYP1A2 inducers on asenapine?

This was not studied, however as this is expected to increase the formation of the catechol there may be increased interactions with COMT and the possibility of increased cardiotoxicity.

What is the effect of CYP2C9 inhibitors on asenapine?

This was not studied and the incomplete information on mass balance and the metabolic scheme makes the clinical consequences difficult to predict.

Are there any potential pharmacodynamic interactions that may be of concern with asenapine?

Yes. It is becoming more apparent that many toxicities and even the efficacy of many psychoactive drugs are mediated via effects on mitochondria. Thus even in the absence of pharmacokinetic interactions pharmacodynamic interactions are expected to be present. Any antipsychotic used for bipolar disorder is likely to be used as an add on therapy to other drugs such as carbamazepine, valproic acid and lithium thus the increase in AEs seen in the pharmacokinetic interaction studies is worrisome and the side effect profiles in larger combination studies should be examined prior to any marketing.

Are there any concerns with asenapine with other drug metabolizing enzymes?

The most obvious enzyme of potential concern is COMT, however the effect of asenapine on COMT has not been studied. In addition, prescribing information from the sponsor on a structurally similar compound, mirtazapine, indicate that mirtazapine should not be used within 14 days of the use of an MAOI because of the risk of serious effects such as hypertentive crisis and hyperthermia. Similar advice is probably appropriate for asenapine.

Is there any need for clinical pharmacology and biopharmaceutic review of the dissolution method and specifications?

This cannot be determined without actually performing such a review, however the clinical data suggests that changes in dissolution *in vivo* is clinical significant, whether an *in vitro* method could be developed that is sufficiently sensitive to detect such changes is presently unknown.

Are there any issues with switching antipsychotic medications?

Asenapine appears to be a suicide substrate inhibitor for CYP2D6. As a suicide substrate, inhibition of CYP2D6 would be due to a decrease in the total amount of enzyme and would result in inhibition in CYP2D6 poor metabolizers as well as in extensive metabolizers and would not be overcome with increasing substrate concentrations. In addition, recovery might take several weeks until the enzyme has had time to regenerate, thus there would be issues with administering other CYP2D6 substrates even after asenapine could no longer be detected in plasma. As most psychiatric medications are CYP2D6 substrates, this would make switching from asenapine to most other psychiatric medications or addition of other psychoactive drugs problematic and would likely result in overdosing.

What was the effect of asenapine on hormones?

This was not reviewed. However increases in prolactin are expected.

What was the effect of asenapine on sleep?

This was not studied however antipsychotics typically have variable effects on sleep patterns. Although a number of cases of nightmares and other sleep disturbances were noted and are also included in the labeling for structurally similar compounds.

* **What was the effect of asenapine on QTc?**

Asenapine clearly prolonged QTc. However the effect was greater at the proposed clinical dose of 10 mg BID than at 20 mg BID with an UL of the 90% CI of the peak mean effect on ΔΔQTcF at 10 mg of 17.1 mSec. This paradoxical inverse U may be due to a dose dependent effect on calcium channels resulting in an increase in the PR segment and a shortening of QTc, or could be due to the effects of metabolites on other receptors such as 5HT receptors. An effect on calcium channels is worrisome as this can be associated with AV block and junctional rhythms which are particularly dangerous in the elderly and which have been observed in a number of healthy young subjects receiving asenapine.

* **Are there any other important clinical pharmacology / safety issues?**

Yes. Cardiac asystole and sinus pause have been observed with asenapine as well as a number of other cardiac arrhythmias and an apparent myocardial infarction and death due to cardiac failure.

Cardiac asystole was seen after a 30 minute 0.7 mg IV infusuion. Although attributed by the sponsor to a vasovagal response cardiac massage stimulated nodal bradycardia, however the patient reverted to asystole and again responded to cardiac massage but with bradycardia and with intermittent nodal complexes and AV dissociation until two doses of atropine and Haemaccel was administered. Even though this occurred with IV dosing the exposures to asenapine with this regimen is similar to what is seen with clinical sublingual dosing.

In the multiple rising oral dose study one subject had asystole for 8.7 seconds with a junctional escape rhythm following a single 30 mg oral dose. The asenapine exposures in this study are low compared with sublingual dosing however the desmethyl-asenapine exposures are similar.

In the paroxetine interaction study a black male experienced atrial fibrillation approximately 2 hours after paroxetine 20 mg and 1.5 hours after a single dose of asenapine 5 mg SL. It appears that the Afib may have lasted nearly 24 hours as it required cardioversion with sotalol the following day. In the multiple dose asenapine arm one subject had pain between the scapulae and SOB along with a negative T wave in leads II, III and AVF on the second day of dosing with asenapine.

In the pivotal BE study comparing single 5 mg sublingual doses of (b) (4) formulations 20 of 35 subjects had cardiac effects observed on telemetry, 10 subjects experienced bradycardia, 8 tachycardia, 7 sinus pause, 3 junctional escape rhthyms, and 1 bradycardia with junctional rhythm.

In another study a subject experienced bradycardia following a single 5 mg SL dose with the (b) (b) (4) tablet. Although this was explained by the sponsor as being neurally mediated it occurred while the subject was supine.

In an ongoing study, (246021), there was also a death due to cardiac failure 2 months after maprotiline was added. Based on labeling from structurally similar compounds and the information in this submission, it appears this could be a pharmacokinetic interaction with asenapine and / or a pharmacodynamic interaction.

Many of the other cardiac toxicites seen are known AEs with multiple structurally similar drugs. In fact MI fitting the description of the case in the paroxetine interaction study is a labeled AE with the structurally similar drug clozapine.

The most common cardiac AEs were bradycardia (3.6%) and tachycardia (2.8%). The thorough QT review as well as a number of the phase I studies reported numerous changes in ECG morphology and more detailed review would be needed to assess their significance. The concern with asenapine is that so many of these serious AEs are being seen in healthy volunteers without cardiac problems at low doses and short treatment durations. Thus this is much greater concern compared with other drugs in the class as these AES are known to occur at anytime during treatment without prior warning and the intended patient population which has a high prevalence of comorbid cardiovascular disease.

“Dose and time dependent” liver injury was seen in 9 of 20 subject and in 7 subjects the increases were greater than 2x ULN. In these 7 subjects the increases occurred between days 2 and 10 with oral doses of 3 mg – 30 mg BID. In two of the seven, increases in LFTs were approximately 5 and 10 time the upper limits of normal. The increases in LFTs in this study are associated with desmethyl-asenapine and asenapine exposures seen with clinical dosing i.e. 5 mg – 10 mg SL.

There was one case of increased total bilirubin at day 2 and 10 with a 20 mg oral dose in this study, (85136) and is listed among the 7 cases of suspected drug induced liver injury. This needs to be looked in further as to whether it’s hepatic in origin or has another cause, e.g. hematologic.

There were also 3 cases of increased LFTs (> 3 x ULN) in two BE studies with formulations that are expected to dissolve slower and have more drug swallowed. Study 41009 comparing polymorphic forms had two cases and study 41026 had one case after adminsitration of a direct compression sublingual tablet. This is 5% of the subjects in these studies. In study 41009 one case might have been an exascerbation of an underlying condition and detailed information was not provided on the second case. However the third case in study 41026 occurred after only a single 5 mg dose.

There were also 4 cases of elevated LFTs in the paroxetine interaction study out of 24 subjects, only one of which was > 3x ULN. However all cases were in the asenapine treatment arm. Two cases occurred after co-adminstration of asenapine. One subject exhibited mildly increased ALATs beginning on day 7 (3 days after beginning dosing; ALAT 119), and this apparently remained stable until day 26 (10 days after discontinuing asenapine) and finally decreased to 59 U/L 7 days later. This subject also had a mildly elevated GGT (60 U/L) and bilirubin (18 μM/L) prior to beginning asenapine. The fourth subjects’ ALAT began to increase after 6 days of treatment reached a maximal increase with an ALAT of nearly 10x ULN a few days after coadministration of the single dose of paroxetine and finally declined to 78 U/L 2 weeks after discontinuation. These cases suggest that coadministration of even a single dose of paroxetine may induce hepatic injury and it is worse in the subjects who already may be more sensitive to the hepatic injury with asenapine.

There were also a number of increases in bilirubin that were associated with the thorough QT study mentioned in the pop PK analysis. The TQT study employed higher doses than would be used clinically

15 mg - 20 mg BID and the medical reviewer was informed of the possible increased bilirubins. However it appears that the sponsor has only submitted the summary statistics for laboratory values prior to and after treatment with asenapine and not during treatment.

Many antipsychotics commonly cause drug induced liver injury, both cholestatic and non-cholestatic in origin. However fatal cases are not unknown and the risk appears to vary with the drug. In particular elevations in liver enzymes are especially common with the structurally related drug olanzapine. For asenapine it appears that dose and swallowing the drug are risk factors. Thus this may be an especially important risk in children or frail demented elderly who may be smaller and swallow more asenapine.

Also in study 41009 a subject had a "schizophrenic reaction" to asenapine, however it appears that the subject may have also taken 'robitussin', and pseudoephedrine for seasonal allergies at the same time. There is the possibility that the 'robitussin' may have contained dextromethorphan.

Hematologic toxicity was not systematically looked into however, due to the structural and metabolic similarity to clozapine and other compounds in the class, virtually all of which are known to cause to agranulocytosis to varying degrees it was expected that it might occur. Due to the lower molar dose of asenapine as compared to clozapine the incidence would also be expected to be lower even though this effect might be immunologically mediated. In addition the relative risk of agranulocytosis or alternatively aplastic anemia appears to be genetically linked. In addition to the one case of neutropenia that the sponsor notes in the integrated summary of safety this reviewer found a probable death due to aplastic anemia from August 2005 in one of the 'ongoing' clinical trials that would not have been included in the safety database. The death occurred in a 44 yo F who was just listed as having died with no explanation provided. The lab reports showed clear evidence of progression toward pancytopenia over an 8 month period prior to the death with a differential leukocyte pattern (i.e. relative lymphocytopenia) which is what is described for clozapine. In addition the lab reports indicated an alert for sponsor notification 2 months prior to the death. In addition, the lab reports for the woman who died from Quincke's edema are also suspicious for a similar downward trend in hematologic parameters after year on asenapine.

Other serious AEs seen in ongoing studies include acute MI, several cases of chest pain, Afib, Right Bundle Branch Block, 145 cases of psychosis, neonatal death, a toxic skin reaction, acute respiratory failure resulting in death including a death due to an allergic reaction with Quincke's angioedema, a number of injuries some due to falls, renal failure and urolithiasis.

What were the results of PK/ PD modeling and simulation of the PET study data?

The modeling and simulation did not result in a better dose estimate than simply fitting an Emax model to the D2 receptor binding PET data and eyeballing the doses needed to achieve these concentrations. However, the quantitative estimations of having a positive or failed study under various scenarios would be quite useful for business decisions, although additional model refinement is clearly needed as shown by the poor predictability of the current model.

Fits of the asenapine D2 occupancy data from studies 25510 and 25516 to an Emax model indicates that a peak concentration of 3 – 9 ng/ml is needed to achieve 90% occupancy and that extrapolation of the data available at the time of the study indicated that a daily dosage of 5 - 10 mg is necessary to achieve this assuming dose linearity.

In retrospect it appears that the early low dosages used in clinical trials were due to toxicity concerns with the exposures achieved with asenapine.

W**hat conclusions can be drawn from exposure response analysis of acute schizophrenia trials?**

For study 41004 all treatments result in the same final value of total PANSS score. The difference from placebo for the asenapine group in change in total PANSS score is due to a higher initial baseline score in the asenapine group. In addition the active comparator risperidone did not show an effect, which is

quite unusual for risperidone. Thus this is a 'failed' study and the major problems noted in this review have already been described in the financial press [1].

For study 41023 the active treatments did result in final values different from placebo but the decrease in PANSS scores were only about 5 units greater than with placebo and the higher 10 mg dose failed to differentiate from placebo.

The sponsor claims a dose response based on modeling, however, close examination of the sponsor's plots indicate that the true values plateau and there is no increased response to a 10 mg dose over a 5 mg dose.

What were the results of the use of mixed models of repeated measures?

The reason for dropping out especially by treatment and duration on treatment was poorly explained and therefore modeling dropouts while possible may not be especially accurate in the present ER analysis. Specifically the large proportion of drop-outs categorized as lost to follow-up, other, and especially withdrew consent is troubling. In addition, that only one subject was assigned to worsening of schizophrenia is not believable as this appears to be inconsistent with spaghetti plots of response vs. time

Other possibilities that need to be considered is whether subjects on drug may be more likely to remain in the study in spite of a lack of efficacy due to subconscious bias, or placebo subjects being more likely to remain on treatment if adverse effects are evident, as well as other possibilities. The only way to control for this may be to have a separate blinded individuals assess efficacy and tolerability and have no other communication with the subjects or each other so they can't influence drop out rate. Then have a third individual assessing the reason why a subject wants to drop out.

What are the results of the exposure response analysis in acute mania?

According to the sponsor theses studies were performed in subjects with 'moderate' or 'severe' mania and mixed mania with baseline YMRS scores $\geq$ 20. Based upon clinical practice until the a few years ago, this reviewer performed an exploratory assessment of response by baseline disease severity.

Examination of the YMRS score over time by quintile reveals that for placebo the final score at 3 weeks is correlated with the initial baseline score, indicating that initial disease severity is a good predictor of placebo response. When the plots for asenapine and for the active control olanzapine are examined the mean final score at the end of 3 weeks of treatment is approximately 10 – 13 regardless of the initial baseline score. Scores of 11 – 12 are consistent with hypomania. Comparison of the responses with active treatments to placebo by quintile of severity reveals that the responses to the lowest two quintiles are virtually identical between active treatment and placebo and only differentiate with the 3 more severe quintiles. In addition, there appears to be a greater difference from placebo as severity increases.

Although this suggests that the drug might be approved in more severe cases, since these results are only achieved by combining the data from two studies we do not have the robustness of repeated study results. Consequently this may be insufficient for approval.

This raises two important points. First until about 2000 practice treatment guidelines for the use of antipsychotics in mania were limited to subjects essentially who were hypermanic. Thus by inclusion of all subjects with full blown mania in drug trials we may have driven the mean results by the more severely ill subjects. Secondly, it indicates that promotion of off-label use and current 'expert opinion' practice treatment guidelines for the off-label use of antipsychotics in hypomania and especially in bipolar spectrum disorder such as promoted by NIMH in a May 5th, 2007 press release are inappropriate. This is especially true for the use in children since the YMRS scores in children for whom mania might be diagnosed in practice, based on certain recommendations, are on the order of 4 for a few hours at a time.

[1] http://www.glgroup.com/News/Does-The-FDA-Acceptance-of-The-NDA-for-Asenapine-Signal-A-Good-Outlook-for-Schering-Plough-(NYSE--SGP)--19717.html

Whereas in this study efficacy only appears to occur with YMRS scores equal to or greater than 27 and the drugs barely bring the YMRS scores to 5 after 3 months.

The patterns seen in this study was also confirmed by analysis of data from studies with other antipsychotics from other NDAs and there are even hints in some of the statistics reviews for other NDAs.

Based on these analyses and the severe side effects associated with antipsychotics, including death, and the increasingly common practice and recommendations for using antipsychotics in children with ADHD there is a major public health concern and these concerns should be communicated to the public as soon as possible regardless of whether further review of asenapine is warranted and before a final decision on this drug is made.

A preliminary examination of subscale data by combined symptoms indicative of psychotic features was performed but was insufficient to even result in clear differentiation by psychotic features or not. Thus without much larger studies with sufficient power we cannot presently determine whether asenapine or other drugs work on the psychotic features of mania, and whether this is driving the efficacy in more severely ill subjects or not, or if the efficacy is independent of psychotic features but only a function of severity alone. If the latter is true and the drug does not work well in schizophrenia but does work in mania due to a differential response by indication, then there may be a different mechanistic reason for differential responses by indication and even by the antipsychotic employed unrelated to D2 receptor blockade.

Discussion of the differential response by severity with the statistician revealed that the statistician had found differing degrees of efficacy by race, with Asians driving the statistical significance of the study. As this reviewer had previously found an increased pharmacodynamic sensitivity to olanzapine in healthy Chinese to psychometric testing that was not explainable by pharmacokinetic differences this reviewer decided to examine whether the distribution of subjects by race was similar across quintiles. However analysis indicates that disease severity and not race is the driving factor.

What are the results of the exposure response analysis for maintenance effect for mania?

After 3 weeks of treatment during the acute treatment phase with asenapine mean YMRS falls to approximately 10 - 12 regardless of initial severity. This is in contrast to placebo treated subjects in whom YMRS falls to 10 - 12 in the lowest two quintiles but not in the more severely ill subjects.

Regardless of severity (i.e. quintile) the mean YMRS in asenapine treated patients continues to decrease slowly so that by 2.5 – 3 months of treatment the mean score is below 5 which is on the order of severity with 'bipolar spectrum disorder' for which these drugs are being recommended for by NIMH. However, it's clear that even by 3 months most subjects have dropped out with only 85 of 213 subjects (40%) still enrolled. This raises the question whether long term maintenance treatment is truly appropriate or if it's simply a function of who had a response at 3 or 4 weeks regardless of any continuing effect. This is especially concerning as there is no placebo control and other approved treatments have shown minimal advantages over placebo, and as this is only a single study and not two separate studies.

A better design would be a controlled withdrawal trial that is placebo controlled. Consequently, there appears to be insufficient information for a maintenance effect claim.

What is the exposure response for EPS?

In Amendment 010, the 4 month Safety Update, submitted Dec 27, 2007 the sponsor included study report INT00065682, Exploratory exposure response analyses of extrapyramidal symptoms (EPS) based on Phase 2 and Phase 3 trials for asenapine.

There was insufficient time for the reviewer to perform a detailed critique of the study report and data submitted however examination of the sponsor's graphical analysis indicates a dose response relationship with symptoms of EPS over a period of six weeks. However, this was only an analysis of

SARS scores which measures Parkinsonian symptoms. Although the frank SARS scores decrease over 6 weeks, over a longer period of time we might see a dose response with tardive dyskinesia. Although haloperidol had higher SARs scores observations, consistent with what has been seen with other atypicals this could also be due to the nonlinear bioavailability with asenapine. In contrast study 25517 in spite of comparable dosing of asenapine and Olanzapine showed nearly twice the incidence of total EPS with asenapine. In addition there has been a high incidence of restless legs syndrome with asenapine in many of the phase I studies with incidences of over 75% in some of the larger , which conceivably might actually be symptoms of akathisia. Thus comparative risks of various types of EPS cannot be determined from the current analyses with respect to tardive or with respect to other atypical antipsychotics, and further analysis is needed.

What is the exposure response analysis for suicidality?

During one of the early meetings with the clinical meeting, (probably the scoping meeting) the issue of suicidality was raised by the clinical reviewer. It was stated that the number of cases of suicidality was high compared to placebo, but that it was lower than placebo when corrected for duration of exposure. Since no placebo was employed in the maintenance trials this reviewer performed a preliminary evaluation of exposure response for suicidality and found that when suicidality was appropriately compared for treatments of similar duration that there were similar rates between the drug treatments and placebo. In addition, suicidality was highest in the 1 – 2 weeks after discharge for acute treatment of schizophrenia, with a delay for the drug groups (presumably due to allowing any effect to wear off due to noncompliance). This is noteworthy for two additional reasons. The timing is similar to what is generally considered the period of highest risk and occurred in spite of subjects being evaluated prior to discharge as to risk of suicide. Consequently, the ability to assess risk of suicide is questionable and studies should be performed to determine if a longer duration of inpatient stay or transfer to another supervised living situation will decrease the risk of suicidality.

Are there any broader implications of the exposure response analyses?

The lack of differentiation in the time course of response for asenapine from placebo along with improvements in the drug effect with baseline YMRS of less than 27 suggests that response in mildly and moderately ill patients may be due to simply environmental factors and not drug.

What was the quality of this submission, and how did it affect the quality and reliability of this review?

Please refer to §6.9 Submission Quality in the appendices.

What feedback is there for the Good Review Management Practice pilot program?

Please refer to §6.10 Good Review Management Practice – Pilot Program - Critique in the appendices.

2.3 Comments

2.3.1 Comments to the Medical Division

2.3.1.1 Comments Previously Provided to the Medical Review Team

On Friday May 1, 2008 this reviewer went to the medical division to discuss a death in the ongoing studies. Due to workload the medical review team requested followup midweek the following week. On Thursday May 8th, 2008 a followup e-mail was sent to the medical review team informing them of a possible case of aplastic anemia.

2.3.1.2 Comments to be Provided to the Medical Review Team

Plasma metabolic exposure profiles, the metabolic scheme, mass balance, and enzymes responsible for various elimination pathways need to be clarified. This will likely require additional studies.

Many issues in the clinical pharmacology development program remain unanswered. These include the effects of age, gender, smoking, race/ethnicity and pharmacogenetics, as well as pharmacokinetic and pharmacodynamic drug-drug interaction studies. Design of the future studies including assess of effects on various metabolic pathways should be based upon more complete metabolism information. A follow-up meeting between OCP and the sponsor to discuss details of any future development is recommended.

Data suggests that there may be pharmacodynamic interactions with other psychotropic medications that increase cardiac, hepatic, and hematologic toxicities in addition to any pharmacokinetic interactions.

Psychometric testing indicates that asenapine has an adverse effect on both short term and long term memory. This may be significant on historicity in schizophrenics as well as elderly patients with dementia. Whether this is particular to asenapine or a class effect cannot be determined from the information in the submission. Consideration should be given to following up on this with other antipsychotics.

The exposure response analysis in bipolar disorder I disorder that indicates that efficacy is limited to only those patients with the most severe mania and that this is a class effect it is recommended that an adequately powered confirmation study be conducted prior to any approval.

Based upon the suicides and suicidality seen in the acute mania trials in both the asenapine and active control arms and the lack of any suicides or suicidality seen in the placebo arm, in addition to other adverse effects and the lack of response in subjects with YMRS scores less than approximately 27, it is recommended that a public health warning for a class effect be considered at the earliest possible time even before any final decision is made regarding whether asenapine is deemed approvable. Alternatively, at the very least it is recommended that a public advisory committee hearing be held as soon as possible.

Additional analyses will need to be performed including comparison of suicidality / suicides in dropouts and by drop out type, and for subjects remaining on treatment how they were responding to treatment. However these should be able to be completed in 1 day and almost certainly in less than a week. In addition even if other antipsychotics are examined the required analyses should not take greater than a few weeks. Consequently it is recommended that data analysis begin as soon as possible so that risk communication is not delayed.

It is recommended that full sets of case report forms be obtained for subjects who have died (including full autopsy reports). Submission of full case reports for cases of serious adverse events observed during development might also be considered. Specifically the cases of particular interest include the

schizophrenic reaction in the pivotal bioequivalence study and possible signs of cardiovascular abnormalities. In addition, the medical division is referred to previous comments from OCP.

If asenapine is eventually approved it is recommended that the Risk Mitigation Plan include surveillance and possibly other strategies for cardiac, hepatic, and hematologic toxicities particularly in the most vulnerable populations. For hematologic toxicities this may need to include monitoring of laboratory values and possibly pharmacogenomic assessments when available.

Please also see the comments to the other review disciplines and to the sponsor.

2.3.2 Comments to the Pharm/Tox Team

2.3.2.1 Comments Previously Provided to the Pharm/Tox Reviewer

At the mid-cycle review meeting held Friday, February 1, 2008 the Pharm/Tox team made a request to the OCP team leader whether there were any new human metabolites of interest. On Wednesday, February 6th, 2008 OCP met with the Pharm/Tox and Pharm/Tox was informed verbally that there were at least 10 metabolites in humans that likely had exposures greater than 10% of asenapine and thus may not have been adequately qualified. Pharm/tox asked the identities of these metabolites and was told by OCP that the sponsor did not identify them and it was not known.

At a later date (~ 1 month later) the OCP review team discussed the possibility of a followup communication and a second verbal followup was provided.

2.3.2.2 Comments to be Provided to the Pharm/Tox Review Team

Please remember to request appropriate pharmacology / toxicology studies when and if appropriate human and preclinical studies are conducted to identify and quantify human metabolites.

To assess potential clinical safety issues agonism and antagonism at the various receptors is needed by the clinical pharmacology team. We were unable to find this information in the submission and if it is available we request assistance in finding it in any future review cycle.

Information on screening at other receptors and in particular effects on ion channels also is needed and may need to be requested if not already provided.

2.3.3 Comments to the Statistical Review Team

2.3.3.1 Comments Previously Provided to the Statistical Reviewers

Several discussions were held with the statistical review team.

With regard to the bipolar efficacy studies, OCP pointed out the difference in efficacy observed based on initial disease severity, and statistics pointed out findings regarding Asians having a greater response to drug. Based upon this information from statistics further analyses were performed by OCP that showed that Asians were overrepresented among the most severely ill patients and underrepresented among less severely ill subjects. This distribution by race was presented at the OCP briefing.

Multiple attempts were made to informally discuss the schizophrenia studies with the statistical review team however in spite of attempts due to schedule conflicts no discussions were able to be held.

2.3.3.2 Comments to be Provided to the Statistical Review Team

The use of Mixed Models of Repeated Measures (MMRM) in the efficacy analysis for schizophrenia was intriguing and research in this area should be continued with better documentation regarding why subjects dropped out.

Factors that should be assessed include, initial disease severity, duration of illness, duration of current episode, subtype, and prior response to different structural classes of compounds.

2.3.4 Comments to the Chemistry Review Team

2.3.4.1 Comments Previously Provided to the Chemistry Reviewer

This reviewer met with the Chemistry reviewer to find out about drug particle sizes in clinical and developmental study batches due to the potential for hepatotoxicity and other toxicities with swallowing.

2.3.4.2 Comments to-be Provided to the Chemistry Review Team

Due to the low solubility of asenapine small delays in dissolution of particles post disintegration are likely to result in more drug being swallowed. Due to the potential increased risk of hepatotoxicity, cardiac, and hematologic toxicity with even small increases in the amount of drug absorbed any changes in manufacturing may have clinical implications and the post-marketing chemistry reviewer team needs to be aware of this.

2.3.5 Comments to the Sponsor

2.3.5.1 Comments Previously Provided to the Sponsor

Please refer to comments previously provided in §6.5 (Requests to Sponsor) on page 477.

2.3.5.2 Comments to be Provided to the Sponsor

1) The mass balance data provided only allows the unambiguous assignment of the primary elimination pathways of 1/5 to 1/3 of the dose.

2) The plasma concentration profiles for total radioactivity and identified circulating specifies indicated that at least 96.6% of the circulating species have not been identified, and when the total radioactivity is dose normalized it indicates that potentially 99.9% of the circulating species have not been identified. In addition chromatograms of pooled plasma samples from over a dosage interval indicate at least 10 unidentified species with exposures greater than 10% of asenapine.

3) Based upon incomplete information mentioned in items 1 and 2 we are unable to determine the appropriateness of metabolite assessments in the drug-drug interaction studies.

4) OCP is available for a follow-up meeting with the sponsor to discuss details of the NDA review to assist them in any future development of this or other compounds.

2.3.5.2.1 Commitments to be Performed Prior to Approval (Prior Approval Commitments)

To be discussed with medical division.

2.3.5.2.2 Labeling Comments

Labeling comments will be included in an amendment to the review.

2.3.5.2.3 Commitments to be Performed Post-Approval (Phase IV Commitments)

None presently.

2.4 Signatures

Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D. **Date**

Senior Reviewer
Division of Clinical Pharmacology I

Ramen Baweja, Ph.D. **Date**

Team Leader
Division of Clinical Pharmacology I

OCP Briefing Meeting:

Date:	Monday, May 12th, 2008	
Time:	1:00 PM – 2:30 PM	
Location:	Building 51 Room 1211	
Level:	Required Office Level CPB Briefing	
Attendees:	***Psychiatry***	LevinRo, ZornbergG, MathisM, LaughrenT
	Pharmacology	Chalenka-FranaszekE, FossomL, AtrakchiA
	Statistics	TBD
	Chemistry	
	Office of Clinical Pharmacology	
	KavanghR, BawejaR, MehtaM, UppoorR, HuangS, LeskoL, RamanA, LazorJ, Urs Meyers, IyerG	
	Others	StrongJ

cc: **DFS** NDA 22-117 (DFS)
HFD-130 (LevinRo, ZornbergG, MathisM, LaughrenT, Chalenka-FranaszekE, RosloffB, OliverT, ChenYF, KordzakhiaG, YangP, HungJ, TeleC, OliverT, UpdegraffK, KiedrowK)
HFD-860 (KavanaghR, BawejaR, UppoorR, MehtaM)

3 Labeling

(b) (4)


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(b) (4)

4 Signatures

Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D. **Date**

Senior Reviewer
Division of Clinical Pharmacology I

Ramen Baweja, Ph.D. **Date**

Team Leader
Division of Clinical Pharmacology I

OCP Briefing Meeting:

Date: Monday, May 12th, 2008

T**ime:** 1:00 PM – 2:30 PM

Location: Building 51 Room 1211

Level: Required Office Level CPB Briefing

Attendees:

Psychiatry

LevinRo, ZornbergG, MathisM, LaughrenT

Pharmacology

Chalenka-FranaszekE, AtrakchiA, FossomL

Office of Clinical Pharmacology

KavanaghR, BawejaR, UppoorR, MehtaM, RahmanA, LazorJ, HuangSM, LeskoL, IyerG, Urs Meyers

Others

StrongJ

cc: **DFS** NDA 22-117 (DFS)

HFD-120 (ZornbergG, MathisM, LaughrenT, Chalenka-FranaszekE, RosloffB, TeleC, OliverT, ChenYF, KordzakhiaG, YangP, HungJ, KeidrowK, UpdegraffK)

HFD-860 (KavanaghR, BawejaR, UppoorR, MehtaM)

5 Review

5.1 Chemistry

The following chemistry information is as reported by the sponsor.

5.1.1 Drug Substance

5.1.1.1 Nomenclature

Recommended Modified International Nonproprietary Name (rINNM)

asenapine maleate

Recommended International Nonproprietary Name (rINN)

asenapine (for Org 5222 active entity)

US Adopted Name (USAN)

asenapine maleate

Systematic chemical name(s)

CA Index Name

(3aR,12bR)-rel-5-chloro-2,3,3a,12b-tetrahydro-2-methyl-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole (2Z)-2-butenedioate (1:1)

Other names

trans-5-chloro-2,3,3a,12b-tetrahydro-2-methyl- 1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole (Z)-2-butenedioate (1:1)

CAS Registry Number *85650-56-2*

Company or Laboratory Code *Org 5222*

5.1.1.2 Molecular formula

Asenapine base: *$C_{17}H_{16}ClNO$*

Asenapine maleate: *$C_{17}H_{16}ClNO.C_4H_4O_4$*

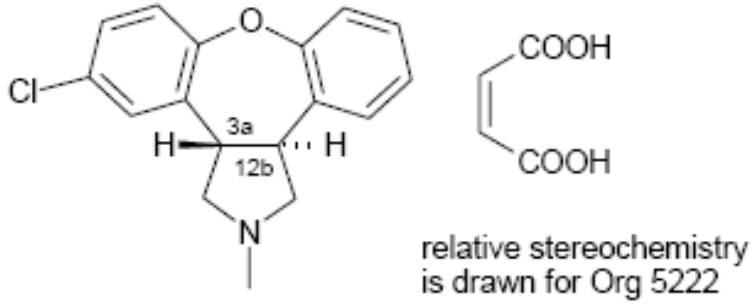
5.1.1.3 Relative Molecular Mass

Asenapine base: *MW = 285.77*

Asenapine maleate: *MW = 401.84*

5.1.1.4 Structure

Figure 1 Asenapine Maleate Structure



5.1.1.5 Physico-Chemical Properties

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[redacted]

5.1.1.5.2 Physical Form and Appearance

White to off-white powder.

5.1.1.5.3 Melting Point

The melting point has an average onset temperature of 139.9°C.

5.1.1.5.4 Hygroscopicity

Org 5222 polymorphic form L displays almost no affinity for water as was studied by Dynamic Vapor Sorption (DVS).

5.1.1.5.5 Partition coefficient

The logarithm of the n-octanol/water coefficient (log P) is 4.9 (neutral species) and 1.4 (cationic species) at 21.5 - 23.8 °C.

5.1.1.5.6 pH in Solution

At 23.5 °C, the pH in a 0.1% m/v solution of Org 5222 in water is 4.6 and the pH in a saturated solution in water is 4.2.

5.1.1.5.7 pKa in Solution

The pKa value of the protonated free base of Org 5222 (extrapolated from various methanol/water ratios to water) is 8.6 at 21.5-23.8 °C.

5.1.1.5.8 Solubility

Table 1 Solubility of Asenapine Base

Solvent	***Temperature °C (at which solubility was determined)***	***Solubility (mg/mL)***
DMSO	*Ambient***	*≥71*
*0.1 M Phosphate buffer pH 7.4**	*Ambient*	*2.7*
Dichloromethane	*Ambient*	*≥17*
Ethanol	*Ambient*	*14*
Methanol	*Ambient*	*≥17*
Acetone	*Ambient*	*≥18*
Iso-octane	*Ambient*	*0.005*
Heptane	*Ambient*	*0.003*
Ethyl acetate	*Ambient*	*4.0*
Water	*Ambient*	*3.7*
0.1 M Hydrochloric acid	*Ambient*	*13*
*0.2 M Phosphate buffer pH 4.0**	*Ambient*	*3.8*
*0.1 M Phosphate buffer pH 7.0**	*Ambient*	*3.0*
*Ammonia-ammonium chloride buffer pH=10.0**	*Ambient*	*0.010*
(b) (4) *(0.5 %/5 %)*	*Ambient*	*4.1*
(b) (4) *in 0.1 M hydrochloric acid (0.5 %/5 %)*	*Ambient*	*12*
(b) (4) *in 0.2 M phosphate buffer pH 4.0* (0.5 %/5 %)*	*Ambient*	*4.3*
(b) (4) *0.1 M phosphate buffer pH 7.0* (0.5 %/5 %)*	*Ambient*	*3.4*
Water 5.4 0.01 M Hydrochloric acid	*37*	*6.0*
*Acetate buffer pH 4.5**	*37*	*5.5*
*0.2 M Phosphate buffer pH 6.8**	*37*	*4.5*

** Type of Buffer*
Buffer pH 4.0: 0.1 M Citric Acid + 0.2 M Na2HPO4
Buffer pH 4.5: 0.028 M Acetic Acid + 0.022 M sodium acetate + 0.0009 M aqueous sodium hydroxide solution
Buffer pH 6.8: 0.2 M KH2PO4 + 0.2 M aqueous sodium hydroxide solution
Buffer pH 7.0: 0.1 M NaH2PO4 + 0.2 M Na2HPO4
Buffer pH 7.4: 0.1 M NaH2PO4 + 0.2 M Na2HPO4
Buffer pH 10.0: 1.31 M NH4Cl + 1.34 M NH3-solution
*** At ambient temperature, the temperature was not controlled.*

5.1.2 Drug Product

(b) (4)

5.1.2.4 Physical Chemical Stability

Asenapine maleate salt was selected for use in asenapine tablet drug product based on chemical *stability, melting point, good purification upon crystallization, and acceptable solubility in water.*

Asenapine maleate drug substance is not readily susceptible to heat, pH, light, or oxidative agents. During long term and accelerated stability studies asenapine maleate drug substance has been shown to be chemically stable for at least 18 months when stored at 25 °C/60% RH and at least 6 months when stored at 40 °C/75% RH.

5.1.2.5 Method of Manufacture

Asenapine tablets are freeze-dried sublingual tablets formed via lyophilization in their aluminum blisters.

5.1.2.6 Qualitative – Quantitative Composition

Table 2 Qualitative-Quantitative Composition of Asenapine Tablets

Component	Reference Standard	Function(s)	5 mg Tablet		10 mg Tablet	
			Mass (mg)	% (wt/wt)	Mass (mg)	% (wt/wt)
asenapine maleate[1]	In-house standard	active ingredient	7.03	28.7	14.06	46.1
Gelatin	Ph. Eur. / NF / JP	structure forming agent	(b) (4)			
Mannitol	Ph. Eur. / USP / JP	structure forming agent	(b) (4)			
Purified water[2]	Ph. Eur. / USP / JP	suspension vehicle	(b) (4)			–
Total			(b) (4)			

1 1.40617 g of asenapine maleate salt is equivalent to 1.0 g of asenapine (active entity).
2 Essentially removed during processing

5.1.2.7 Container Closure System

Asenapine tablets of both 5 mg and 10 mg strengths are filled into all-aluminum blister packs which may be also referred to as cold form aluminum blister packs.

One blister pack contains 10 tablets

(b) (4)

5.2 Overview of Clinical Development Program

To be filled in post briefing.

5.3 In Vitro Pharmacology

5.3.1 Receptor Binding

pKis and IC_{50}s for various receptors from humans and other species are shown in Table 4, Table 5, and Figure 2 on the following pages.

Asenapine has high receptor affinities for all dopamine, serotonin, alpha-adrenergic, and histamine receptors tested, as well as for norephinephrine and dopamine reuptake transporters based upon typical Cmaxs in the range of 3 - 30 nMol/L (1 - 10 ng/ml) with doses of 5 – 10 mg SL BID, (see Table 53, Table 55 and Figure 51) and typical IC_{50}'s in the range of 0.1 – 4 nMol/L, (see Table 4 and Table 5). Although this estimate does not take into account free concentrations which are around 5% of total it's likely that the receptor binding experiments were conducted in the presence of albumin and so a correction is not needed. In addition, the results of PET studies also suggest that corrections for protein binding are unnecessary, (see Table 155).

In addition to the receptors mentioned, above Figure 2 also shows that asenapine has effects on potential down-stream intracellular mediators.

Unfortunately the sponsor does not indicate whether binding at the various receptors result in antagonism or agonism, and this would be needed to predict potential pharmacologic effects such as cardiac valvulopathy with agonism of $5HT_{2B}$ receptors.

Table 4 Reported pKis for Human Receptor Binding and Transporters

	R&DRR INT00002643					Study 00003223				
Receptor	**Asenapine**	**(-)asenapine**	**(+)asenapine**	**N-desmethyl**	**N-oxide**	**Org 191634-0 N-sulfated-N-Desmethyl**	**Org 213772-0 11-OH**	**Org 214025-0 11-O-sulfate**	**Org 216761-0 N-Gluc**	**Org 220473-0 7-OH**
5-HT1A	8.60 ± 0.04	8.04 ± 0.03	8.57 ± 0.02	8.21 ± 0.09	5.97 ± 0.01	8.0	8.4	7.5	<5	7.6
5-HT1B	8.40 ± 0.08	8.77 ± 0.11	8.60 ± 0.02	6.70 ± 0.01	7.45 ± 0.02					
5-HT2A	**10.15 ± 0.09**	**10.21 ± 0.08**	**10.40 ± 0.11**	8.62 ± 0.04	8.22 ± 0.14	7.6	10.0	**9.9**	<6	**9.9**
5-HT2B	**9.75 ± 0.03**	**9.42 ± 0.29**	**9.04 ± 0.40**	8.61 ± 0.27	7.42 ± 0.09	8.0	10.0	**9.4**	<6	**9.5**
5-HT2C	**10.46 ± 0.15**	10.00 ± 0.13	10.38 ± 0.28	8.73 ± 0.25	8.22 ± 0.04	7.7	9.9	**9.4**	<6	**9.9**
5-HT5A	**8.84 ± 0.21**									
5-HT6	**9.60 ± 0.04**	9.58 ± 0.11	9.90 ± 0.08	7.86 ± 0.07	7.07 ± 0.02	7.7	**10.0**	**9.7**	<6	**9.1**
5-HT7	**9.94 ± 0.04**	**10.04 ± 0.05**	9.67 ± 0.13	7.98 ± 0.05	7.24 ± 0.08	7.5	9.8	9.6	<6	8.8
D1	**8.85 ± 0.04**	**8.80a**	**8.82 a**	6.92 a	6.69 a					
D2L	**8.90 ± 0.08**	**8.69 ± 0.13**	**8.72 ± 0.14**	7.26 ± 0.04	6.20 ± 0.14					
D2S	**8.84 ± 0.05**	**8.86 ± 0.13**	**8.96 ± 0.16**	7.32 ± 0.09	6.32 ± 0.15	7.0	8.4	7.8	<6	8.4
D3	**9.38 ± 0.06**	**9.37 ± 0.29**	**9.32 ± 0.07**	7.72 ± 0.05	6.69 ± 0.03	7.4	8.4	8.1	<6	**9.1**
D4	**8.95 ± 0.07**	8.98 ± 0.08	8.61 ± 0.07	7.01 ± 0.11	6.35 ± 0.08					
D4.7						6.9	9.0	8.4	<5	8.6
α1A	**8.93 ± 0.04**	**8.84 ± 0.04**	**8.99 ± 0.06**	7.56 ± 0.07	6.50 ± 0.04	7.8	9.0	8.3	<6	8.4
α2A	**8.94 ± 0.05**	**9.07 ± 0.07**	8.62 ± 0.05	7.76 ± 0.02	6.26 ± 0.03	7.1	8.2	7.7	<6	8.2
α2B	**9.49 ± 0.02**	**9.66 ± 0.03**	**9.40 ± 0.11**	8.64 ± 0.10	6.89 ± 0.05					
α2C	**8.91 ± 0.12**	**8.96 ± 0.09**	8.31 ± 0.02	7.43 ± 0.02	6.21 ± 0.05	7.2	8.0	7.8	<6	8.0
H1	**9.00 ± 0.13**	8.48 a	8.92a	7.20 a	6.48 a	7.7	8.9	8.8	<6	**9.9**
H2	8.21 ± 0.10	7.92 a	7.25 a	5.39 a	5.48 a					
M1	5.09 ± 0.03	5.14 ± 0.01	4.99 ± 0.12	5.08 ± 0.04	4.22 ± 0.04					
M2	4.50 ± 0.09	4.41 ± 0.09	4.48 ± 0.08	4.44 ± 0.08	4.19 ± 0.01					
M3	4.67 ± 0.03	4.81 ± 0.06	4.66 ± 0.27	4.59 ± 0.05	4.17 ± 0.01					
M4	5.04 ± 0.10	5.14 ± 0.07	5.21 ± 0.05	5.03 ± 0.08	4.43 ± 0.01					
M5	<5					<5	<5	<5	<5	<5
SERT	<5					<5	<5	<5	<5	<5
NET	<5.5					<5.5	<5	<5	<5	<5
DAT	<5					<5	<5	<5	<5	<5

Table 5 Estimated IC_{50}s (nMol/L) for Human Receptor Binding and Transporters Based on Reported pK_is

	R&DRR INT00002643					Study 00003223				
Receptor	Asenapine	(-)asenapine	(+)asenapine	N-desmethyl	N-oxide	Org 191634-0 N-sulfated- N-Desmethyl	Org 213772-0 11-OH	Org 214025-0 11-O-sulfate	Org 216761-0 N-Gluc	Org 220473-0 7-OH
5-HT1A	2.5	9.1	2.7	6.2	1,071.5	10.0	4.0	31.6		25.1
5-HT1B	4.0	1.7	2.5	199.5	35.5					
5-HT2A	0.1	0.1	0.0	2.4	6.0	25.1	0.10	0.13		0.13
5-HT2B	0.2	0.4	0.9	2.5	38.0	10.0	0.10	0.40		0.32
5-HT2C	0.03	0.1	0.0	1.9	6.0	20.0	0.13	0.40		0.13
5-HT5A	1.4									
5-HT6	0.3	0.3	0.1	13.8	85.1	20.0	0.1	0.2		0.8
5-HT7	0.1	0.1	0.2	10.5	57.5	31.6	0.2	0.3		1.6
D1	1.4									
D2L	1.3	2.0	1.9	55.0	631.0					
D2S	1.4	1.4	1.1	47.9	478.6	100.0	4.0	15.8		4.0
D3	0.4	0.4	0.5	19.1	204.2	39.8	4.0	7.9		0.8
D4	1.1	1.0	2.5	97.7	446.7					
D4.7										
α1A	1.2	1.4	1.0	27.5	316.2	15.8	1.0	5.0		4.0
α2A	1.1	0.9	2.4	17.4	549.5	79.4	6.3	20.0		6.3
α2B	0.3	0.2	0.4	2.3	128.8					
α2C	1.2	1.1	4.9	37.2	616.6	63.1	10.0	15.8		10.0
H1	1.0					20.0	1.3	1.6		0.1
H2	6.17									
M1	8,128	7,244	10,233	8,318	60,256					
M2	31,623	38,905	33,113	36,308	64,565					
M3	21,380	15,488	21,878	25,704	67,608					
M4	9,120	7,244	6,166	9,333	37,154					
M5	2.5	9.1	2.7	6.2	1,071.5	10.0	4.0	31.6		25.1
SERT	4.0	1.7	2.5	199.5	35.5					
NET	0.1	0.1	0.0	2.4	6.0	25.1	0.10	0.13		0.13
DAT	0.2	0.4	0.9	2.5	38.0	10.0	0.10	0.40		0.32

Figure 2 Asenapine Enantiomer Binding to Various Receptors by Species – Report SDGRR 4393

Table 1. Pharmacology of Org 5222 and enantiomers *in vitro*

Test	Receptor	Parameter	Org 5222	Org 10968 (-)	Org 10969 (+)
Serotonin					
5-HT binding (human receptor clone)	5-HT_{1A}	pK_i	7.1		
8-OH-DPAT binding (rat hippocampus)	5-HT_{1A}	pK_i	7.6		
8-OH-DPAT binding (human receptor clone)	5-HT_{1A}	pK_i	8.1	7.7	8.1
GTPγS binding (human receptor clone)	5-HT_{1A}	pIC_{50}	*	7.0	*
		α	0.3	0	0.5
cAMP turnover (human receptor clone)	5-HT_{1A}	pIC_{50}	7.1	7.0	7.2
		α	0.5	0	0.5
5-HT binding (pig striatum)	5-HT_{1D}	pK_i	7.1	7.1	7.3
5-HT release (guinea pig cortex)	5-HT_{1D}	%increase	50% at 10^{-7}mol/L		
Ketanserin binding (rat cortex)	5-HT_{2A}	pK_i	10		
Ketanserin binding (human receptor clone)	5-HT_{2A}	pK_i	10.4	10.3	10.3
PI turnover (human receptor clone)	5-HT_{2A}	pIC_{50}	10.6	10.3	10.4
5-HT binding (pig choroid plexus)	5-HT_{2C}	pK_i	10.1	10.0	10.1
5-HT binding (human receptor clone)	5-HT_{2C}	pK_i	9.1	9.6	9.8
Mesulergine binding (human receptor clone)	5-HT_{2C}	pK_i	10.1	10.0	10.5
PI turnover (human receptor clone)	5-HT_{2C}	pIC_{50}	8.9	8.6	8.5
Dopamine					
Spiperone binding (human receptor clone)	D_{2S}	pK_i	8.8		
Spiperone binding (human receptor clone)	D_{2L}	pK_i	8.8		
Spiperone binding (human receptor clone)	D_3	pK_i	9.1		
Spiperone binding (human receptor clone)	D_4	pK_i	8.9		
Antagonism of quinpirole adenyl cyclase inhibition (human receptor clone) control	D_{2L}	pIC_{50}	6.3		
+Org 5222	D_{2L}	pIC_{50}	4.1		
	agonist/antagonist shift		138		
Acetylcholine					
Oxotremorine M binding (rat cortex)	$M_{1,2}$	pK_i	5.2		
Pirenzepine binding (rat brain)	M_1	pK_i	4.4		
QNB binding (rat brainstem)	$M_{1,2}$	pK_i	6.0		

* Accurate IC_{50} value could not be calculated due to a biphasic effect

Effects of acute and chronic (21 days, b.i.d.) s.c. treatment of rats with Org 5222 on the levels of dopamine (DA) and serotonin (5-HT) and their major metabolites [3,4-dihydroxyphenylacetic acid (DOPAC), 3-methoxy-4-hydroxyphenylacetic acid (HVA) and 5-hydroxy indoleacetic acid (5-HIAA) in the nucleus accumbens with olfactory tubercles and the caudate nucleus.

		DA	DOPAC	HVA	5-HT	5-HIAA
Acute[1]	60 min	NC	increase	increase	NC	NC
	12 h	NC	increase	NC	NC	NC
Chronic[2]	21 days(A)	NC	NC	NC	NC	NC
	21 days(B)	NC	increase	increase	NC	NC

NC = no significant change

1) Single doses were administered 60 min or 12 h before decapitation and the subsequent determination of DA, 5-HT and their major metabolite levels in the brain areas.

2) The last injection was given 12 h (A) or 30 min (B) before decapitation and the subsequent determination of DA, 5-HT and their major metabolite levels in the brain area.

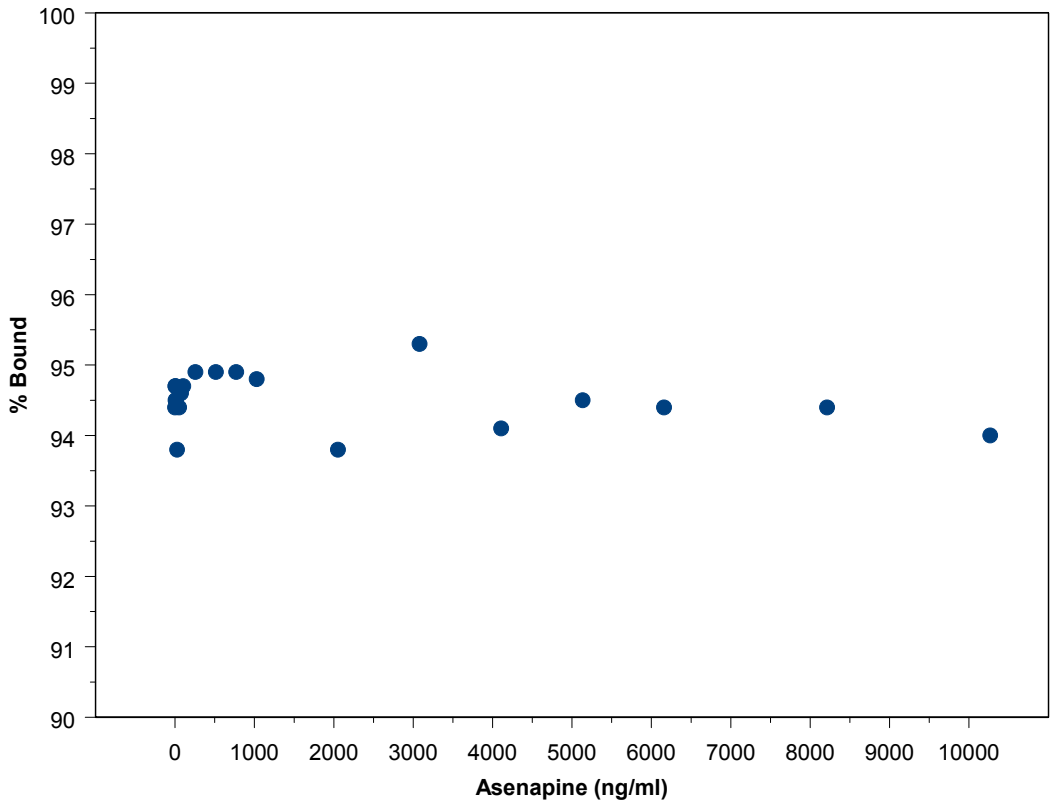
5.3.2 Protein Binding

Asenapine binding to human plasma proteins assessed by equilibrium dialysis was non-saturable over a concentration range of 1.4 to 10,268 ng/ml, with a mean free fraction of 5.5%, (see Table 6 and Figure 3).

Table 6 Asenapine Plasma Protein Binding over a Concentration Range of 1.4 to 10,268 ng/ml – Study SDGRR 2972

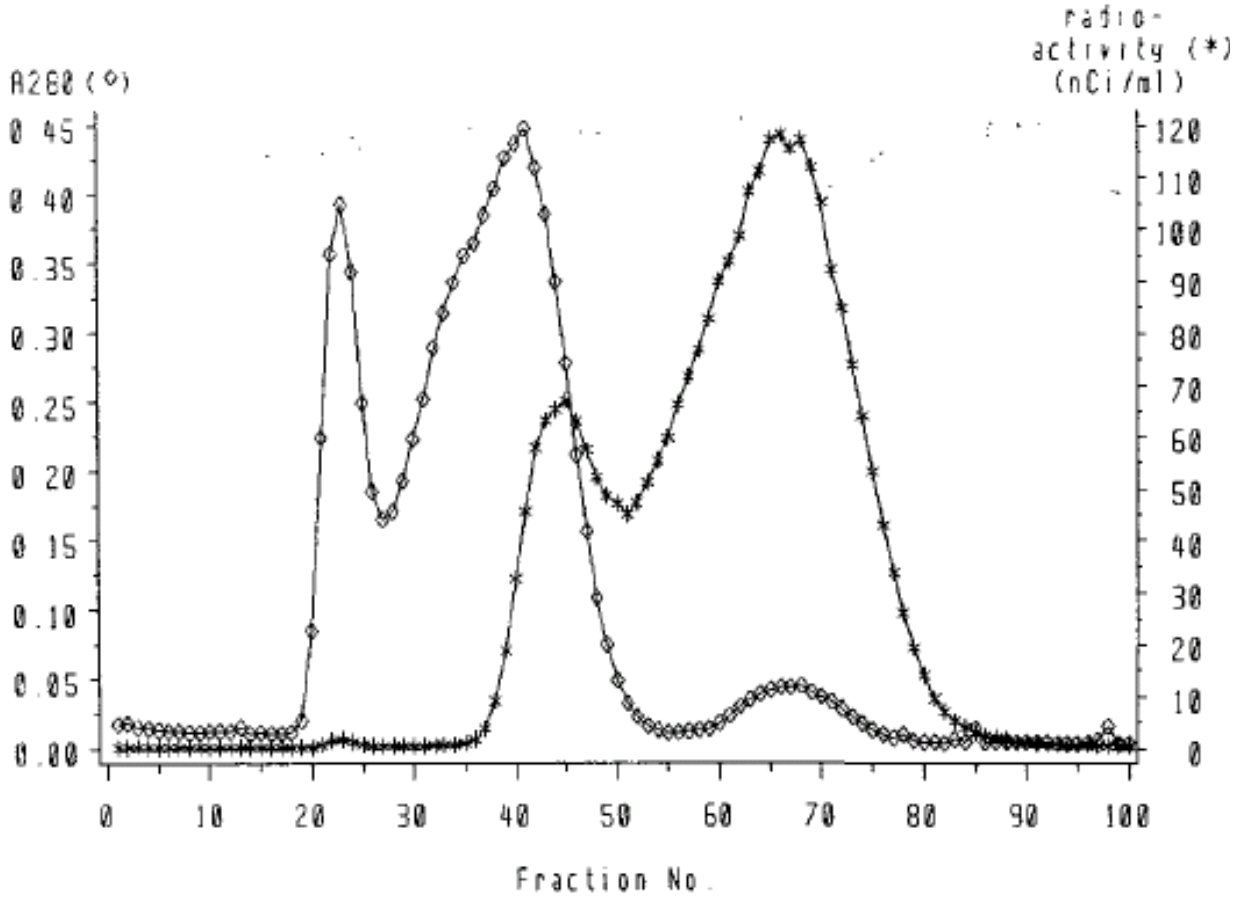
Fraction Bound f_{Bnd} (%)	Fraction Unbound fu (%)
94.5 + 0.4 (0.4) 93.8 – 95.3	5.5 + 0.4 (7.0) 4.7 – 6.2

Figure 3 Asenapine Plasma Protein Binding over a Concentration Range of 1.4 to 10,268 ng/ml – Study SDGRR 2972



The elution profile of radiolabeled [^{3}H]-asenapine from a Sephadex G-200 column indicates that the majority of radioactivity comes off the column as unbound radioactivity whereas a small fraction comes off with a retention time similar to that of low molecular weight proteins. This indicates that asenapine is likely primarily bound to albumin, (see Figure 4).

Figure 4 Elution Profiles of Plasma Proteins (A_{280}) and Radiolabeled [^{3}H]-Asenapine 80 ng/ml from a Sephadex G-200 Column — Study SDGRR 2972



In two other studies, high binding (>95%) to plasma proteins was shown for asenapine, desmethyl-asenapine and asenapine 11-O-sulfate. For asenapine and desmethyl-asenapine total binding was higher in women than in men. However the binding to albumin and to AAG is much lower and these should only account for binding of around 81.5% and 53.2% of asenapine and desmethyl-asenapine respectively. Consequently, a significant fraction of the binding of these species is due to some other unidentified plasma protein, (see Table 7 - Table 9).

Thus it's unclear what changes in plasma proteins might result in changes in free fraction. Since asenapine is a high intrinsic clearance compound, changes in protein binding might result in differences in kinetics.

Table 7 Asenapine and Desmethyl-Asenapine Binding in Human Plasma by Equilibrium Dialysis over 4 hours – Study DM2005-005222-007

Conc. (ng/ml)	Fu (%)			
	Asenapine		Desmethyl-Asenapine	
	Males	Females	Males	Females
1	4.01 ± 2.01	1.66 ± 0.23	3.97 ± 2.30	2.45 ± 0.46
25	2.81 ± 1.03	1.72 ± 0.38	0.872 ± 0.111	1.84 ± 0.48
500	3.10 ± 1.30	2.07 ± 0.55	3.24 ±4.10	1.86 ± 0.90
Average	3.28 ± 1.47	1.81 ± 0.40	2.86 ± 2.89	2.08 ± 0.65

N = 3 - 7

Table 8 Equilibrium Dialysis Plasma Protein Binding of 11-Hydroxy- Asenapine Sulfate (ORG-214025) 200 ng/mL – Study DM2006-005222-015

Species	% Free	% Bound
Human	2.88 ± 0.12 (4.05) 1.75 - 3.03	97.1± 0.12 (0.12) 97.0 - 97.2
Rat	0.98± 0.05	99.0± 0.05
Rabbit	0.23± 0.02	99.8± 0.02

Table 9 Asenapine and Desmethyl-Asenapine Binding to Human Serum Albumin and α1-Acid Glycoprotein by Equilibrium Dialysis over 4 hours – Study DM2005-005222-007

Conc. (ng/ml)	Fu (%)			
	Human Serum Albumin		α1-Acid Glycoprotein	
	Asenapine	Desmethyl-Asenapine	Asenapine	Desmethyl-Asenapine
1	47.1 ± 1.9	38.3	25.4 ± 4.6	45.8 ± 5.1
25	45.8 ± 3.0	36.9 ± 3.1	18.9 ± 3.5	58.0 ± 16.2
500	45.4 ± 1.4	37.2 ± 2.9	25.2 ± 2.1	68.7 ± 14.1
Average	46.1 ± 2.1	37.3 ± 2.5	23.0 ± 4.6	57.5 ± 15.1

Table 10 Reviewer's Estimated Total Asenapine and Desmethyl-Asenapine Binding to Plasma Proteins based on Binding to HSA and AAG in Study DM2005-005222-007

Substrate	Asenapine		Desmethyl - Asenapine	
Protein	HSA	AAG	HSA	AAG
f_{Bnd} (%)	46.1 ± 2.1	37.3 ± 2.5	23.0 ± 4.6	57.5 ± 15.1
Additional % Bound due to AAG	(100 – 46.1) * 37.3 = 20.1%		(100 – 23.0) * 57.5 = 44.1%	
Estimated Total % Bound	46.1 ± 20.1 = 60.2%		23.0 ± 44.1 = 67.1%	
Estimated Total % Free	39.8%		32.9%	

5.3.3 Binding to Red Blood Cells

Asenapine and or a metabolite binds to and sequesters in red blood cells such that the radioactivity measured in RBCs is higher than expected concentration based on passive diffusion alone. Table 11 shows the sponsor's value for the extent of binding, whereas Table 12 shows the reviewer's calculations.

Even though they differ slightly there is probably minimal to any pharmacokinetic significance, although pharmacodynamic significant is unknown.

N.B. These calculations do not account for free concentrations consequently the fraction bound is approximately 20 fold higher.

Table 11 Sponsor's Calculated *In Vitro* Binding of [^{3}H]-Asenapine to male human erythrocytes Study R&DRR NL0029630

[^{3}H]-Org 5222[a] (ng/mL)	Time (min)	Hcrit	Whole blood Radioactivity (Bq/mL)	Plasma Radioactivity (Bq/mL)	R	E
0	60	0.395	3772	5185	0.73	0.18
5		0.395	3855	5280	0.73	0.18
25		0.405	3766	5123	0.73	0.18
200		0.400	3905	5471	0.72	0.17
1000		0.400	3941	5304	0.74	0.19
10000		0.410	3814	5001	0.76	0.22
Mean ± SD (%CV)					73.5 ± 1.4 (1.9%)	18.7 ± 1.75 (9.4%)

[a] Blood samples were spiked with 0, 5, 25, 200, 1000 and 10000 ng/mL unlabeled Org 5222 and 3.66 kBq/mL [^{3}H]-Org 5222 (equivalent to 2.1 ng·mL^{-1})
E = fraction bound to erythrocytes
R = whole blood to plasma radioactivity ratio

Table 12 Reviewer's Calculated *In Vitro* Binding of [^{3}H]-Asenapine to male human erythrocytes Study R&DRR NL0029630

[^{3}H]-Org 5222[a] (ng/mL)	Time (min)	Hcrit	1- Hcrit	Plasma Radioactivity (Bq/mL)	Expected Whole Blood Radioactivity with Passive Diffusion [Plasma Radioactivity/(1-Hcrit)]*Hcrit	Measured Whole blood Radioactivity (Bq/mL)	RBC:Plasma Ratio
0	60	0.395	0.605	5185	3137	3772	1.114
5		0.395	0.605	5280	3194	3855	1.118
25		0.405	0.595	5123	3048	3766	1.080
200		0.400	0.600	5471	3283	3905	1.071
1000		0.400	0.600	5304	3182	3941	1.114
10000		0.410	0.59	5001	2951	3814	1.097
Mean ± SD (%CV)							1.099 ± 0.02 (1.8%)

[a] Blood samples were spiked with 0, 5, 25, 200, 1000 and 10000 ng/mL unlabeled Org 5222 and 3.66 kBq/mL [^{3}H]-Org 5222 (equivalent to 2.1 ng·mL^{-1})
E = fraction bound to erythrocytes
R = RBC to plasma radioactivity ratio

5.3.4 Cell Transport - Pgp

The sponsor reported the following results for cell transport studies with asenapine and N-desmethyl-asenapine:

'Bi-directional transport studies were performed in MDCK and MDR1-MDCK (MDR1) cells to determine the extent of P-glycoprotein (P-gp) mediated transport of [^{3}H]- asenapine and [^{3}H]-N-desmethyl asenapine. The bi-directional transport studies were carried out at 31.6, 100 and 316 nM of asenapine and N-desmethyl asenapine. In addition, [3H]-diazepam (1 µM), [^{3}H]-prazosin (2 µM) and [^{3}H]-quinidine (2 µM) were included as negative, weak positive, and moderate positive P-gp controls, respectively.

The apical to basolateral (A→B) transport of asenapine across the MDCK and MDR1 cell monolayers was characterized by mean effective permeability (Pe, ×106 cm/s) values of 3.12 – 3.51, and 1.90 – 2.43, respectively, over the concentration range studied (31.6 – 316 nM). The corresponding values for N-desmethyl asenapine are 2.24 – 2.94, and 1.82 – 2.25, respectively. The efflux ratios of asenapine in MDCK and MDR1 cells ranged from 0.862 – 1.02, and 0.914 – 1.29, respectively, and the corresponding values for N-desmethyl asenapine were 0.677– 0.836, and 0.596 – 0.720, respectively.

The MDCK normalized efflux ratio of asenapine and N-desmethyl asenapine in MDR1 cells ranged from 1.02 – 1.34 and 0.767 – 1.06, respectively. The corresponding values for P-gp control substrates were 0.903, 0.982, and 2.49 for diazepam, prazosin and quinidine, respectively.' (See Table 13 and Figure 5).

These results suggest that asenapine and N-desmethyl asenapine have low to moderate effective permeability under our experimental conditions and at best are weak substrates of the human P-gp transporter. Thus, it is unlikely P-gp will have a significant impact on the in vivo disposition of asenapine and N-desmethyl asenapine.'

Due to the high binding to the cell membranes effective permeability coefficients, (*Pe*), are reported for asenapine and desmethyl-asenapine, whereas apparent permeability coefficients, (*Papp*), are reported for the control substrates.

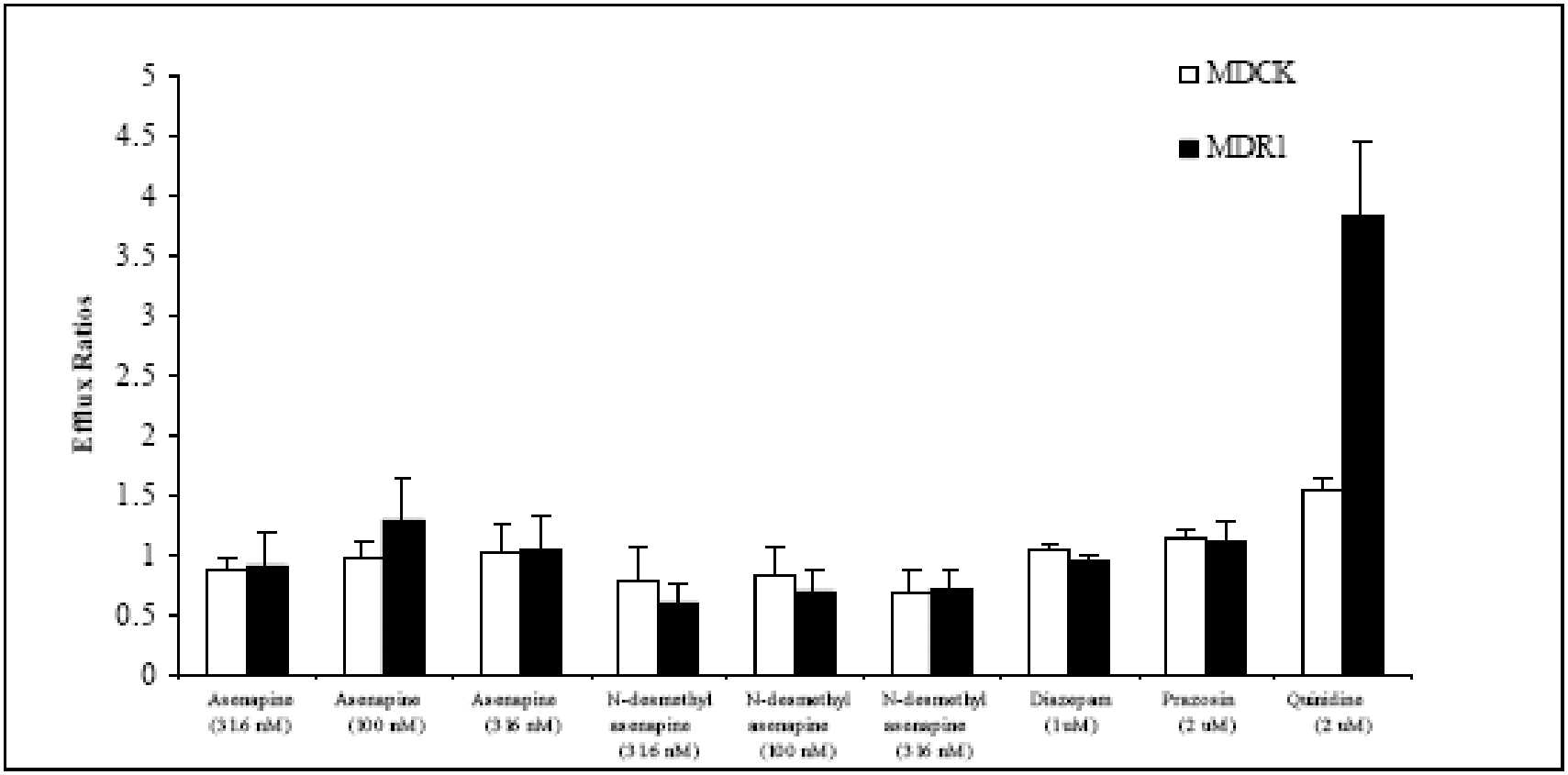
As a highly lipophilic substances these results are expected, however different results might be found for the 7- and 11- Hydroxy metabolites and especially for the sulfate and glucuronide conjugates. Also, other transporters in addition to P-gp may be involved and these other potential substrates and transporters have not been examined.

Table 13 P-gp Cell Transport of [^{3}H] Asenapine and [^{3}H] N-Desmethyl-Asenapine – Study DM2005-005222-008

	Substrate	Type of Control	Concentration	A → B Pe or Papp (cm/sec x 10^6 cells)	B → A Pe or Papp (cm/sec x 10^6 cells)	P-gp Efflux Ratios $\frac{B \to A P_i}{A \to B P_i}$
				MDCK	MDR1	MDR1/MDCK
Controls	Diazepam	Negative	1.0 µM	1.04 ± 0.04	0.939 ± 0.047	0.903
	Prazosin	Weak positive	2.0 µM	1.14 ± 0.08	1.12 ± 0.18	0.982
	Quinidine	Strong positive	2.0 µM	1.54 ± 0.11	3.83 ± 0.63	2.49
Test Substrates	Asenapine		31.6 nM	0.862 ± 0.101	0.914 ± 0.256	1.06
			100.0 nM	0.960 ± 0.152	1.29 ± 0.35	1.34
			316.0 nM	1.02 ± 0.23	1.04 ± 0.29	1.02
	N-Desmethyl asenapine		31.6 nM	0.777 ± 0.291	0.596 ± 0.160	0.767
			100.0 nM	0.836 ± 0.226	0.698 ± 0.185	0.835
			316.0 nM	0.677 ± 0.186	0.720 ± 0.158	1.06

a Mean ± SD, n = 4

Figure 5 Efflux Ratios of [^{3}H]-Asenapine, [^{3}H]-N-desmethyl asenapine, and [^{3}H]-P-gp Control Substrates for MDCK and MDR1 Cells – Study DM2005-005222-008



*: Efflux ratios for asenapine and N-desmethyl asenapine were calculated using Pe due to extensive membrane retention, while Papp was used for calculating efflux ratios of diazepam, prazosin, and quinidine.

5.4 Drug Metabolism

5.4.1 Overview of Human Drug Metabolism

Come back to post briefing.

5.4.2 *In Vivo* Drug Metabolism

5.4.2.1 Location of Information

In vivo drug metabolism and mass balance was formally examined at steady-state in study 25532. Results were reported in the clinical trial report for study 25532, (including sub-reports) as well as the reports INT00008145 (AKA 040105) and INT00003211 (AKA 40218). The additional reports were not always cross referenced appropriately and were found by accident. The manner of reporting the information from the mass balance study was confusing as it required extensive cross checking of documents that were labeled with different report codes on the page headers. For future reference these are included in Table 14.

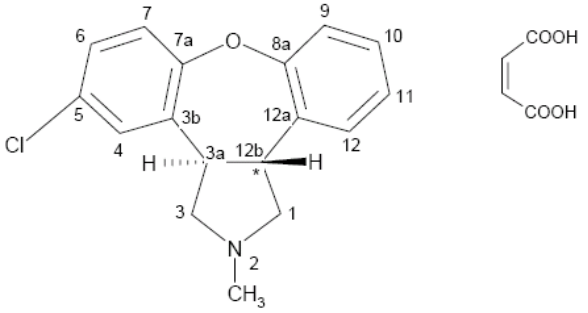
Table 14 Cross References of Reports of Differing Aspects of Mass Balance Study 25532

Study Report Code	Additional Coding inside Main Report	Report Title
25532		Open, non-randomized, single center trial to determine the excretion balance, metabolic profile and pharmacokinetics of asenapine after a sub-lingual dose of [14C]-labeled asenapine.
	NL0057152	Bioanalysis of Asenapine, Org 30526 and Org 31437 in human plasma samples from Clinical Trial 25532
	PBR-041201	The Determination of [14C]-Asenapine in Human Plasma, Urine and Faeces Samples Originating From a Human ADME Study With Liquid Scintillation Counting
INT00003211	040218	Profiling of a Metabolism Study with [14C]-Labeled Asenapine in Healthy Volunteers (Additional to Clinical Trial Protocol 25532)
INT00008145	040105	Isolation and Identification of Metabolites of Asenapine (ORG 5222) in Various Types of Samples

5.4.2.2 Study Design

Study 25532 utilized a single 0.3 mg dose of ^{14}C-Asenapine [56 μCi] administered on day 10 of asenapine administration by placing an ethanolic solution containing the radioactive dose on a 10 mg tablet of unlabeled asenapine and administering it sublingually. This resulted in a total dose of 10.3 mg in six healthy male volunteers that included three smokers and three nonsmokers. Figure 6 shows the numbering of asenapine and location of the ^{14}C label.

Figure 6 Asenapine Numbering and Location of ^{14}C Label



* is the place of the [^{14}C]- label in [^{14}C]-asenapine maleate.

Plasma was sampled through 72 hours post dose. In addition feces and urine were to be collected until >90% of the total radioactivity was recovered; although this was not done, possibly due to partial loss of the collected sample, a technical issue, or inaccurate dosing.

Subjects were also phenotyped for CYP1A2, 2C19, 2D6, and 3A4 using the cocktail shown in Table 15.

Table 15 Phenotyping Cocktail – Study 25532

CYP P450	Substrate	Dose (mg)	Measurement	Matrix
1A2	Caffeine	100	Paraxanthine / caffeine ratio at 6 h	Plasma
2C19	Mephenytoin	100	4-OH S-Mephenytoin / S-Mephenytoin excreted over 8 h	Urine
2D6	Dextromethorphan	30	Dextrorphan / dextromethorphan at 4 h	Plasma
3A4	Cortisol	Endogenous	6 β-OH Cortisol / Cortisol excreted over 8 h	Urine

Results for phenotyping are stated as being reported in report INT00003211, however this reviewer was unable to find any data on phenotype.

Subject Demographics

Table 16 shows the demographics of the enrolled subjects, Subjects 5 and 6 were withdrawn from the study due to opisthotonus on day 5. It's noteworthy that these two subjects had the lower weights and thus possibly higher concentrations. Although there were supposed to be 3 smokers and 3 non-smokers, the smoker who dropped out had nicotine metabolite exposures that were inconsistent with smoking.

Table 16 Demographics of Subjects in Mass Balance Study – Study 25532

Subject	Age	Gender	Race	Height (cm)	Weight (kg)	BMI (kg/m^2)	Smoker (Yes/No)	Serum Nicotine Metabolites (ng/mL)
1	40	Male	White	177	87.6	28.0	Yes	724.0
2	23	Male	White	179	90.1	28.1	No	<10.0
3	54	Male	White	176	82.1	26.5	No	<10.0
4	33	Male	White	180	80.1	24.7	Yes	424.0
5[a]	23	Male	White	184	69.5	20.5	No	<10.0
6[a]	21	Male	Asian	167	62.3	22.3	Yes	<10.0
N = 4[a]	**38 ± 13**			**178 ± 1.8**	**85.0 ± 4.7**	**26.8 ± 1.6**		

a Dropped out due to severe opisthotonus on day 5

b Mean ± SD of study completers

5.4.2.3 Analytic Methodology

Initially a µ-Bondapak phenyl column was used (HPLC system 1) however the metabolite profile was not reproducible on a replacement column. Consequently, a new HPLC system was developed on a µ-Bondapak C18 column (HPLC system 2). This necessitated a change in the mobile phase gradient. The two HPLC systems used are shown in Table 17.

Table 17 Comparison of HPLC Systems Used for Metabolic Profiling of Mass Balance Study 25532

System	*HPLC System 1*	*HPLC System 2*
Guard-column	µ-Bondapak phenyl	µ-Bondapak C18
Column	µ-Bondapak phenyl (internal length: 300 mm; internal diameter: 7.8 mm)	µ-Bondapak C18 (internal length: 300 mm; internal diameter: 7.8 mm; particle size: 10 µm)
Solvents	A. 0.1 mol·L^{-1} Ammonium acetate buffer, adjusted to pH=4.2 with acetic acid	A. 0.1 mol·L^{-1} Ammonium acetate buffer, adjusted to pH=4.2 with acetic acid
	B. Methanol/ Acetonitrile (1/3 v/v %)	B. Methanol/ Acetonitrile (1/3 v/v %)
Gradient	5% B isocratic during 5 minutes	10% B isocratic during 3 minutes
	5 to 35% B in 30 minutes (linear)	10 to 40% B in 17 minutes (linear)
	35 to 90% B in 20 minutes (linear)	40 to 90% B in 30 minutes (linear)
	90 to 100% B in 1 minutes (linear)	90 to 95% B in 1 minute (linear)
	100% B isocratic during 9 minutes	95% B isocratic during 8 minutes
	100% to 5% B in 5 minutes (linear)	95 to 10% B in 1 minute (linear)
Flow	2.0 mL/min	2.0 mL/min
Temperature	50°C	50°C
LS-Flow	3.5 mL/min	3.5 mL/min
LS Cell-volume	0.5 mL	0.5 mL

System 1 and system 2 employed different HPLC numbering systems.

Metabolite numbering, except for human metabolites, was generally performed based on the retention time for each separate matrix. For human metabolites numbering for HPLC system 2 for all matrices were based on the retention times for peaks from chromatograms from all matrices. Thus the retention time of metabolite U10 is comparable with the retention time of metabolite F10. In contrast HPLC System 1 utilized a different peak numbering system.

Multiple metabolites have been identified and associated with a single or even two overlapping peaks from HPLC system 2. The identification of multiple metabolites associated with these peaks was based on further characterizations of the pooled urine and feces peak components. To do this the sponsor subjected the effluent of the initial radiochromatography (HPLC system 2) to a second HPLC-UV chromatographic process (HPLC system 3) and collected fractions of the effluent of this second chromatographic process. Fractions of effluent representing separate peaks were recombined and the metabolite(s) contained in them were identified. Although it might be possible to further identify amounts associated with these individual fractions, time constraints prevent this. See Figure 7 for an example of the HPLC fraction chromatogram of urine peak 35 (aka PC2) showing two subpeaks, U35A and U35B.

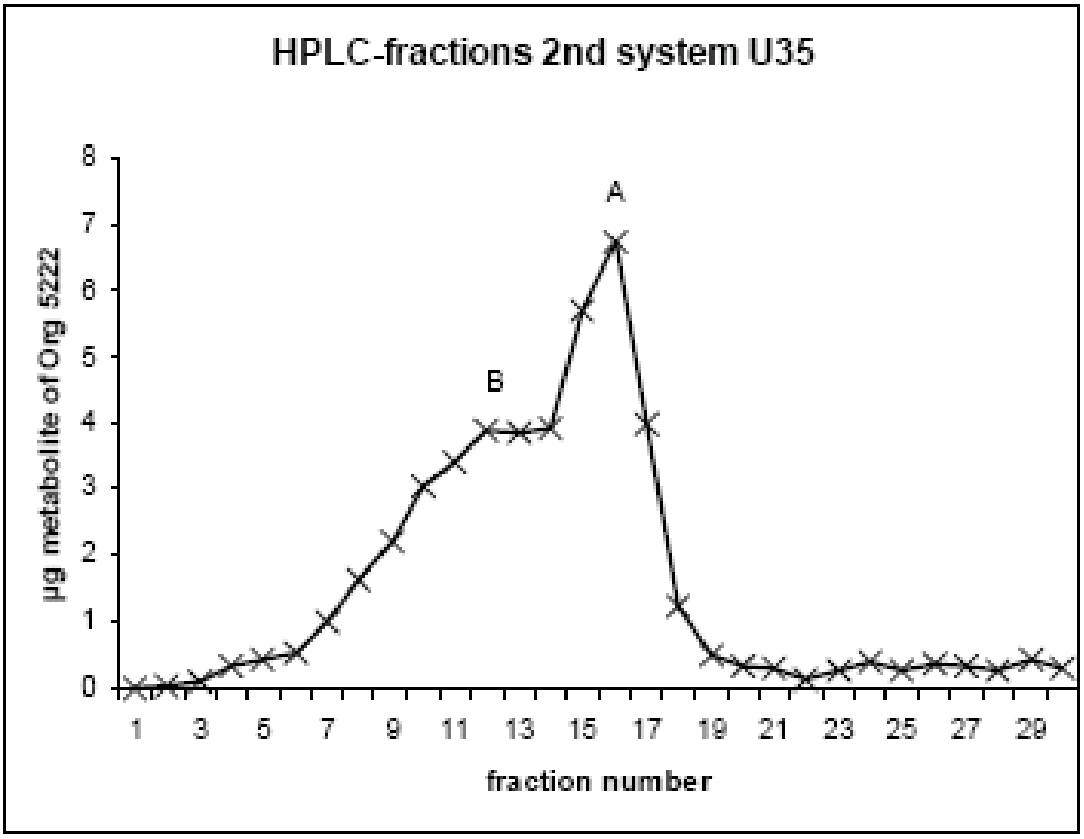
In addition, a fourth HPLC system was also utilized for radio-chromatograms, that included purification and identification of the subpeaks of HPLC system 2 but the description is confusing and will not be discussed further.

Retention times, numbering and identified metabolites associated with various peaks and HPLC systems are shown in Table 18.

Table 18 Peak Numbering Found in HPLC Chromatograms from Plasma, Urine and Feces Samples Collected after Sublingual Administration of [^{14}C]-Asenapine – Study 25532

Nominal Description	HPLC System 2										HPLC System 1	
	Combined Peak #	Urine			Feces			Secondary Isolation (HPLC Systems 3 and 4)			Peak no.	Mean RT (minutes)
		Peak no.	Mean RT (minutes)	Relative RT	Peak no.	Mean RT (minutes)	Relative RT	Combined Peak #	Isolation codes	Mean RT (minutes)		
	PC1	U1	15.2	0.45								
N(2)-des-methyl asenapine 10-Methoxy 11-O-Glucuronide & N(2)-des-methyl asenapine 10-O-Glucuronide 11-Methoxy	PC2	**U2**	**16.6**	**0.49**				PC2	U35	16.6	1	24.5
	PC3	U3	17.6	0.52								
	PC4	U4	18.5	0.55								
	PC5	U5	19.3	0.57								
N(2)-des-methyl asenapine 10-methoxy 11-O-Sulfate & N(2)-des-methyl asenapine 10-O-Sulfate 11-Methoxy N-des-methyl asenapine 11-O glucuronide Asenapine-11-O-glucuronide Plus some other sulphates and glucuronides	PC6	**U6**	**22.0**	**0.65**				PC6	U80	22.0	4	32.1
	PC7	U7	22.7	0.68								
U8/9 contained some conjugated metabolites (sulphates and glucuronides)	PC8	U8	23.3	0.69								
	PC9	**U9**	**23.6**	**0.70**				PC8/9	U87	23.3/23.6	6/7	35.1/36.2
U10/11 Asenapine 11-O-Sulfate N-oxide asenapine sulphates and glucuronides F10/11 is identified as the 10, 11-dihydroxy-des-methyl asenapine and 10, 11-dihydroxy-asenapine.	PC10	**U10**	**25.1**	**0.74**	**F10**	**25.1**	**0.75**	PC10/11	U108	25.2/25.5	10	38.9
	PC11	**U11**	**25.6**	**0.76**	**F11**	**25.6**	**0.76**		P72	22.4		
U12/13 asenapine glucuronide	PC12	**U12**	**26.8**	**0.80**				PC12/13	F71b	24.9/25.6		
	PC13	**U13**	**27.2**	**0.81**	F13	27.2	0.81		U117	26.8/27.3	11	40.8
									P84 and P88	24.6/25.1/25.3		
	PC14				**F14**	**28.4**	**0.85**					
	PC15	U15	29.0	0.86	**F15**	**29.0**	**0.86**					
U16- N(2)-des-methyl asenapine glucuronide	PC16	**U16**	**30.7**	**0.91**	F16	30.7	0.91	PC16	U151	30.7	13	44.6
									P107 & P110	28.4/28.9		
	PC17				F17	31.4	0.93					
	PC18				F18	32.1	0.96					
F19 co-elutes with the N(2)-des-methyl of asenapine	PC19				F19	32.6	0.97	PC19	P116	29.7		
asenapine	PC20				**F20**	**33.6**	**1.00**	PC20	F127	33.6	15	47.5
									P115 & P120	29.7/30.6		
	PC21				F21	34.6	1.03					
11-hydroxy N-formyl asenapine	PC22				**F22**	**35.1**	**1.04**	PC22	F151c	35.1		
X-hydroxy N-formyl asenapine (the position of the hydroxyl group could not be assigned)	PC23				**F23**	**36.2**	**1.08**	PC23	F159c	36.2		

Figure 7 HPLC Fractions from HPLC System 3 associated with Urine Peak 35 (AKA PC2) from HPLC System 2 – Report 040218



5.4.2.4 Extent of Recovery of Radioactivity

Cumulative radioactivity recovery was >85% in 3 of the 4 subjects with approximately 40% of the dose recovered in feces and 50 – 60% of the dose recovered in urine. The low recovery of radioactivity in subject 3 was attributed by the sponsor as likely due to inadvertent loss of part of the urine sample. This is a reasonable possibility. Total individual and mean recoveries by route are show in Table 19, Figure 8, and Figure 9.

Table 19 Cumulative Radioactivity Recovery in Urine and Feces after Sublingual Administration of Asenapine 10 mg plus [^{14}C]-Asenapine 0.3 mg – Study 25532

	Excreted Radioactivity (% of the Radioactive Dose)					
	Subject 1	Subject 2	Subject 3	Subject 4	Mean ± SD	Mean ± SD (excluding subject 3)
Urine	50.7	58.8	37.0	49.0	48.9 ± 9.0 37 - 59	52.8 ± 5.3
Feces	36.2	37.1	34.8	47.0	38.8 ± 5.6 35 - 47	40.1 ± 6.0
Total	86.9	95.9	71.8	96.0	87.7 ± 11.4 (72 – 96)	93.0 ± 5.2

Figure 8 Cumulative Radioactive Excretion Profile by Subject after Sublingual Administration of Asenapine 10 mg plus [^{14}C]-Asenapine 0.3 mg – Study 25532

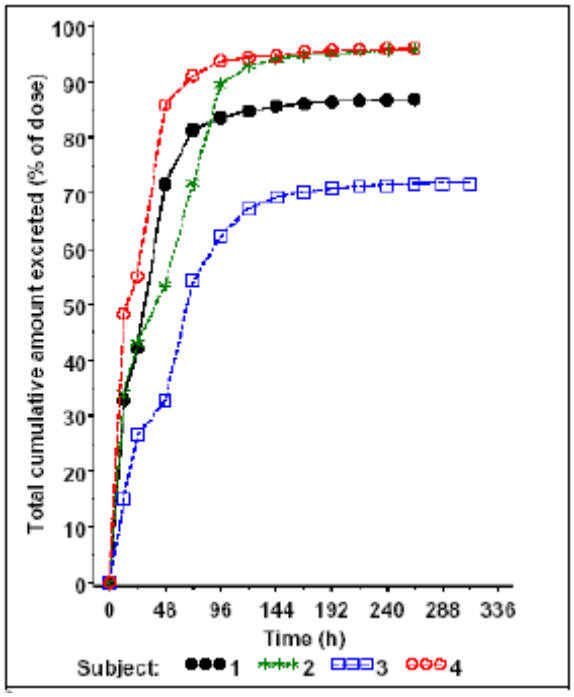
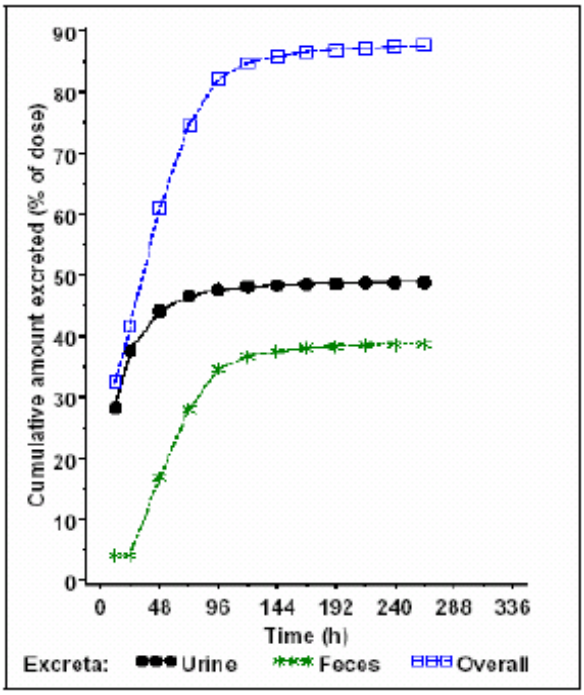


Figure 9 Cumulative Radioactive Excretion in Urine and Feces after Sublingual Administration of Asenapine 10 mg plus [^{14}C]-Asenapine 0.3 mg – Study 25532



5.4.2.5 Plasma Metabolic Profiles

5.4.2.5.1 HPLC System 1

At first plasma samples at selected time points between 1.5 – 12 hours were analyzed per subject on HPLC system 1. These data were used to give quantitative data. Representative radiochromatograms and quantitative data are shown in Figure 10 and Table 20 respectively.

Figure 10 Radio-Chromatograms at 1.5 and 4 hours from Subjects 1 & 4 – Study 25532 / Report 040218

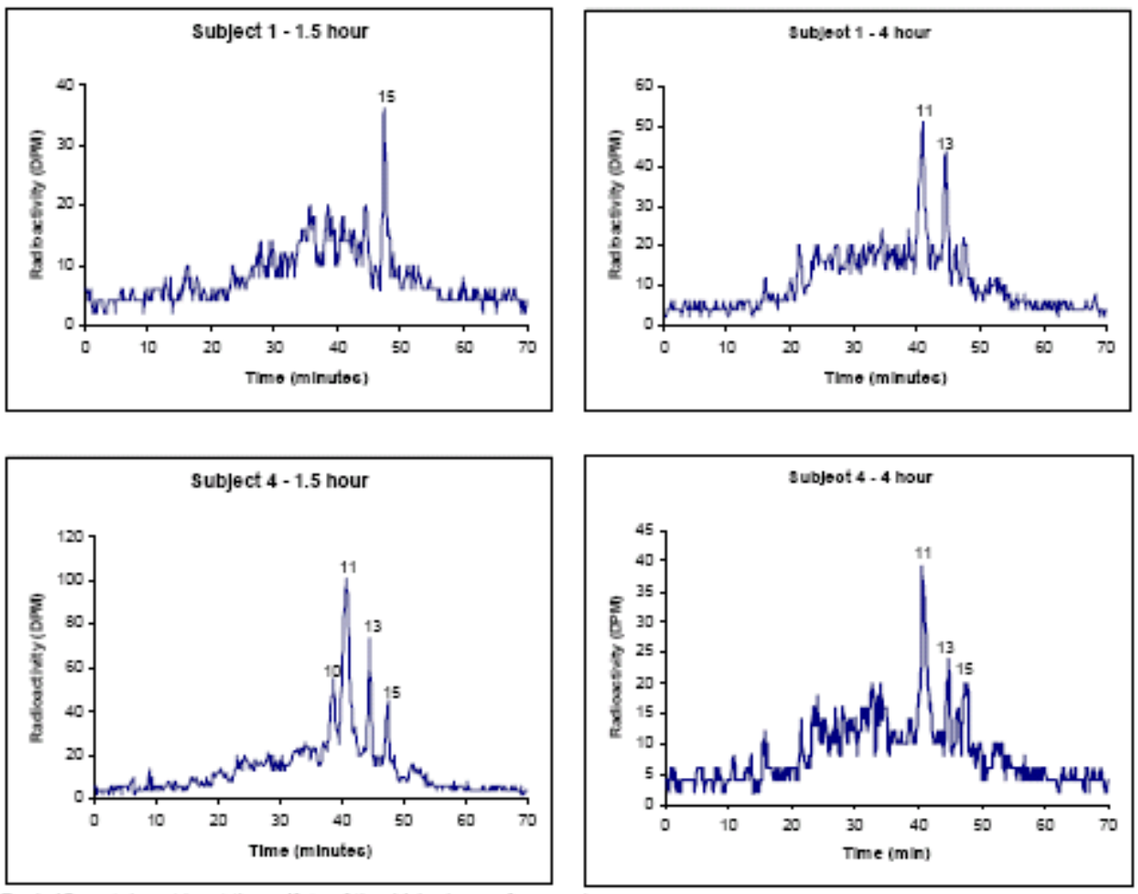


Table 20 Individual Plasma Concentrations by Time Point Detected by HPLC System 1 after Sublingual Administration of ^{14}C-Asenapine – Study 25532 / Report 040218

Subject	Peak	Analyte Identity	RT	1.5 h	2.0 h	4.0 h	8.0 h	12.0 h
1	10	11-OH-Asenapine	38.7	—	—	—	—	—
	11	Asenapine-Glucuronide	40.8	—	—	6.3	3.5	—
	13	N-Desmethyl-Glucuronide	44.6	—	—	2.6	2.9	—
	15	Asenapine	47.5	2.2	2.2	—	—	—
2	10	11-OH-Asenapine	38.7	2.0	—	—	—	—
	11	Asenapine-Glucuronide	40.8	13.2	12.5	10.1	—	—
	13	N-Desmethyl-Glucuronide	44.6	1.9	—	—	—	—
	15	Asenapine	47.5	2.8	3.1	—	—	—
3	10	11-OH-Asenapine	38.7	—	—	—	—	—
	11	Asenapine-Glucuronide	40.8	7.6	10.7	15.9	10.5	3.4
	13	N-Desmethyl-Glucuronide	44.6	—	—	—	—	—
	15	Asenapine	47.5	3.8	—	—	—	—
4	10	11-OH-Asenapine	38.7	4.5	2.3	—	—	—
	11	Asenapine-Glucuronide	40.8	12.0	11.8	9.3	6.7	—
	13	N-Desmethyl-Glucuronide	44.6	3.8	3.0	3.3	—	—
	15	Asenapine	47.5	2.1	1.4	3.0	—	—

Figure 10 and Table 20 only show the three metabolites that the sponsor also measured by standard analytic methodologies, yet in the study reports the sponsor states that at least 9 different peaks could be identified using system 1. The sponsor then further explains that the resolution of the obtained metabolite signals of urine and feces samples obtained on HPLC system 1 was sub-optimal (see Figure 10), and the integration of the metabolite profiles was inconclusive (see Table 20).

5.4.2.5.2 LSC and Bioanalysis of Selected Metabolites

In addition to comparing radioactivity via HPLC system 1, the sponsor also compared the plasma concentrations of selected species determined by standard bioanalytic methods, (i.e. asenapine, desmethyl-asenapine, and asenapine N-oxide) to total plasma radioactivity as determined by scintillation counting.

Figure 11 shows the mean plasma concentration vs. time profile for asenapine, desmethyl-asenapine, asenapine-N-oxide, and total ^{14}C in asenapine, ng-eq/mL. Since this study was conducted at steady-state the total radioactivity reflects the radioactivity for a single dose, whereas the concentrations of asenapine and the two metabolites can readily be seen to be superimposed on concentrations from prior dosing. Thus even though the relative exposures to asenapine and the metabolites are at best only a few % of the exposure to all species just based on the relative concentrations, if corrected for superpositioning the relative exposures would be even lower and the amount of unidentified species would account for nearly all of the circulating radioactivity. In addition, asenapine was administered at a dose of 10 mg, whereas the radioactive dose was less than 0.3 mg, yet the peak asenapine concentration is around 10 ng/mL, which is what we expect from a 10 mg dose. Thus it appears that the relative exposures for asenapine the metabolites and the radioactivity were not corrected for the disparate doses.

Figure 11 Mean Plasma concentration-versus-time curves – Study 25532

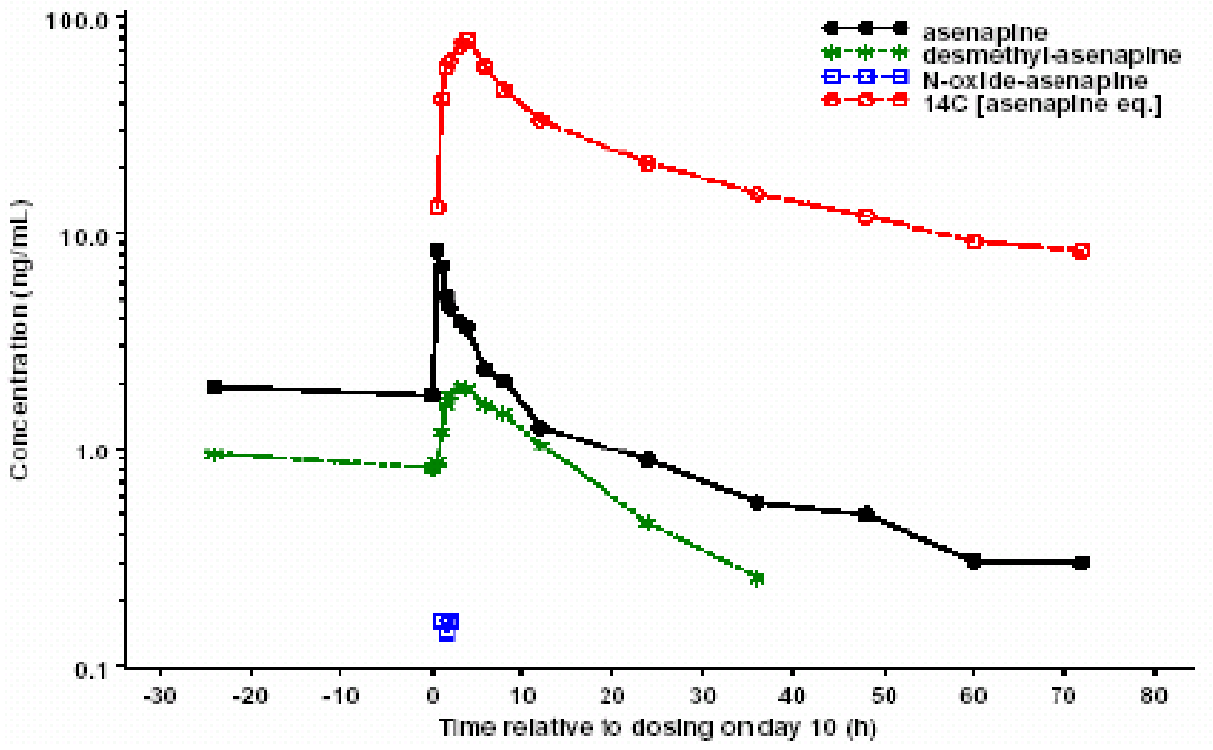


Table 21 shows the concentration vs. time data for total radioactivity both in terms of raw data and dose normalized, and the raw data for asenapine, desmethyl-asenapine, and asenapine N-oxide. When dose normalized radioactive Cmax is compared to the Cmax of asenapine the total radioactivity is 223 – 552 fold higher, (i.e. 3145/14.1 and 3008/5.44).

In addition when appropriate dose normalized AUCs are compared the unidentified radioactivity is clearly even larger with 99.9% of the circulating radioactivity unidentified. The pharm/tox reviewer was advised of this a few days after the midcycle meeting held at the end of Janurary 2008.

Table 21 Plasma Concentration vs. Time Data for Total Radioactivity, Asenapine, Desmethyl-Asenapine, and Asenapine N-Oxide – Study 25532

Day	Normalized Dose	Subject	10										11		12		13
Time (h)			0	0.5	1	1.5	2	3	4	6	8	12	24	36	48	60	72
^{14}C [asenapine equivalents] (ng/mL)*	(0.3 mg)	1	0	6.67	13.7	23.6	39.8	65.7	69.7	60.7	46.9	36.1	22.9	16.2	10.9	9.01	7.02
		2	0	19.6	53.8	64.7	64.2	61.7	64.7	43.7	31	27	16.2	13	10.2	7.27	8.36
		3	0	15.1	45.2	75.2	77.7	84.6	91.6	77.2	62.2	40.9	24.6	18.1	16.2	13.5	11.3
		4	0	11.7	55.7	69.2	68.7	77.2	87.6	55.3	44.9	30.5	20	13.3	10.7	7.02	6.67
Dose Normalized ^{14}C [asenapine equivalents] (ng/mL)* (DN to 10.3 mg)		1	0	229	470	810	1366	2256	2393	2084	1610	1239	786	556	374	309	241
		2	0	673	1847	2221	2204	2118	2221	1500	1064	927	556	446	350	250	287
		3	0	518	1552	2582	2668	2905	3145	2651	2136	1404	845	621	556	464	388
		4	0	402	1912	2376	2359	2651	3008	1899	1542	1047	687	457	367	241	229
Asenapine (ng/mL) 10.3 mg		1	1.29	7.16	7.24	4.49	4.35	3.48	3.37	2.14	1.77	1.09	0.629	0.398	0.365	0.173	0.246
		2	1.24	6.82	6.07	4.5	3.55	2.99	2.67	1.61	1.39	0.881	0.657	0.374	0.348	0.234	0.187
		3	2.55	14.1	9.5	6.92	5.39	4.77	4.49	3.15	3.01	1.9	1.33	1.06	0.853	0.617	0.524
		4	2.06	5.23	5.44	4.71	4.54	4.3	4	2.48	2.14	1.21	0.922	0.425	0.424	0.197	0.246
Desmethyl−asenapine (ng/mL)		1	0.435	0.459	0.567	0.639	0.859	1.37	1.58	1.24	1.14	0.787	0.304	0.144	0	0	0
		2	0.363	0.412	1.01	1.43	1.51	1.34	1.28	1.39	1.08	0.811	0.305	0.207	0	0	0
		3	1.66	1.75	1.97	2.65	3.05	3.15	2.75	2.31	2.26	1.58	0.784	0.398	0.287	0.204	0.122
		4	0.782	0.842	1.3	1.71	1.72	1.95	2.05	1.49	1.42	1.01	0.434	0.27	0	0	0
Asenapine N−oxide (ng/mL)		1	0	0	0.137	0	0.135	0	0	0	0	0	0	0	0	0	0
		2	0	0.247	0.217	0.12	0.171	0.133	0	0	0.117	0	0	0	0	0	0
		3	0	0.256	0.233	0.189	0.191	0	0.174	0	0	0	0	0	0	0	0
		4	0	0	0	0.205	0.129	0.175	0.174	0	0	0	0	0	0	0	0

Table 22 Plasma Exposures to Asenapine and Selected Metabolites Relative to Total ^{14}C Radioactivity after Asenapine 10 mg and 0.3 mg 14-C-Asenapine at Steady-State - Study 25532

Dose		10.3 mg			0.3 mg	10.3 mg	
Metric	Subject	Asenapine	Desmethyl − Asenapine	Asenapine N−oxide	^{14}C [asenapine equivalents]	Dose Normalized ^{14}C [asenapine equivalents]	% extrap
AUCτ [a] (ng/mL x hr^{-1})	1	33.3	12.8	0.2	1523.2	52297	11.5
	2	27.8	13.6	0.9	1282.6	44036	25.6
	3	50.6	27.7	0.7	1952.8	67046	16.5
	4	35.7	17.7	0.6	1470.0	50470	8.5
Fraction of ^{14}C (%)	1	2.2	0.8	0.01	—	—	—
	2	2.2	1.1	0.07	—	—	—
	3	2.6	1.4	0.04	—	—	—
	4	2.4	1.2	0.04	—	—	—
	Mean[b]	2.3	1.1	0.04	—	—	—
Fraction of Dose Normalized ^{14}C (%)	1	0.06	0.02	0.000	—	—	—
	2	0.06	0.03	0.002	—	—	—
	3	0.08	0.04	0.001	—	—	—
	4	0.07	0.04	0.001	—	—	—
	Mean[c]	0.067	0.032	0.001	—	—	—

a AUC∞ for ^{14}C. N.B. AUC∞ used because it's a single dose.
b Mean = 3.44 (i.e. minimum without dose normalization 96.6% unidentified)
c Mean = 0.102 (i.e. 99.9% unidentified)

Pharmacokinetic metrics as reported by the sponsor are shown in Table 23. Total ^{14}C is elimination rate limited however what's most interesting is that the elimination of desmethyl-asenapine appears to be more rapid than asenapine which should not be. The reason for this is unclear.

Table 23 Reported Pharmacokinetic Metrics of Selected Species - Study 25532

Metric (unit)	^{14}C [asenapine equivalents]	Asenapine	Desmethyl-asenapine	Asenapine N-Oxide
Tmax (h)	4.00 (1.50-4.00)	0.75 (0.50-1.00)	3.50 (2.00-4.00)	0.75 (0.50-1.50)
Cmax (ng/mL)	78.4 (13.2)	8.40 (3.88)	2.07 (0.757)	0.211 (0.0543)
AUC_{0-12} (ng /mL x hr^{-1})	n.a.	36.9 (9.72)	17.9 (6.87)	n.c.
AUCtlast (ng /mL x hr^{-1})	1557 (284)	n.a.	n.a.	n.a.
AUC_{∞} (ng /mL x hr^{-1})	2020 (467)	n.a.	n.a.	n.a.
Clapp (L/h)	n.a.	293 (68.9)	n.a.	n.a.
Vz,app (L)	n.a.	11371 (2096)	n.a.	n.a.
t½ (h)	39.3 (7.55)	27.5 (4.97)	12.9 (4.46)	n.c.

Presented are median (minimum-maximum) for T_{max}; arithmetic mean (SD) for other PK parameters.
#: n=4; n.a..: Not applicable; n.c.: Not calculated.
Source Appendix BI, Table 5-3. Study Report 25532

5.4.2.5.3 HPLC System 2

Later the plasma from the 1 hour sample and from the remaining plasma from all of the plasma samples from 1.5 – 12 hours from all four subjects was pooled. Both pooled plasma samples were analyzed on HPLC system 2. The pooling of these samples was not performed quantitatively (i.e. the sponsor does not report the volumes) and therefore these chromatograms were only evaluated by the sponsor in a qualitative way.

In spite of this it should still be possible to infer approximate exposures to various metabolites since the samples are pooled over time.

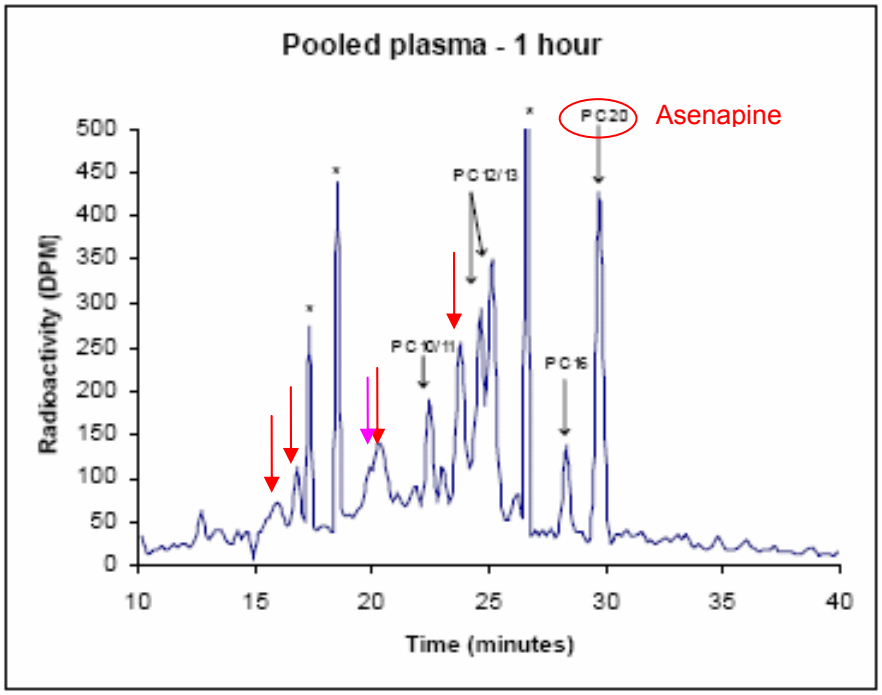
Figure 12 shows the pooled plasma chromatograms from the 1 hour sample and the combined 1.5 – 12 hour samples. The sponsor only labels asenapine and 4 metabolites as being of interest, (i.e. peaks labeled PC#), it's clear that the areas under the peaks identified by this reviewer with red arrows are nearly as great the peak area for asenapine in the pooled 1.5 to 12 hour sample.

Examination of the scale used for the peak heights used for the two different chromatograms reveal that the area under the smaller peaks in the 1.5 to 12 hour sample may be as great as the areas under peaks that appear visually taller in the 1 hour sample. In addition, since asenapine is declining yet radioactivity in plasma continues past 72 hours post dose the relative exposures to these metabolites may be even higher yet.

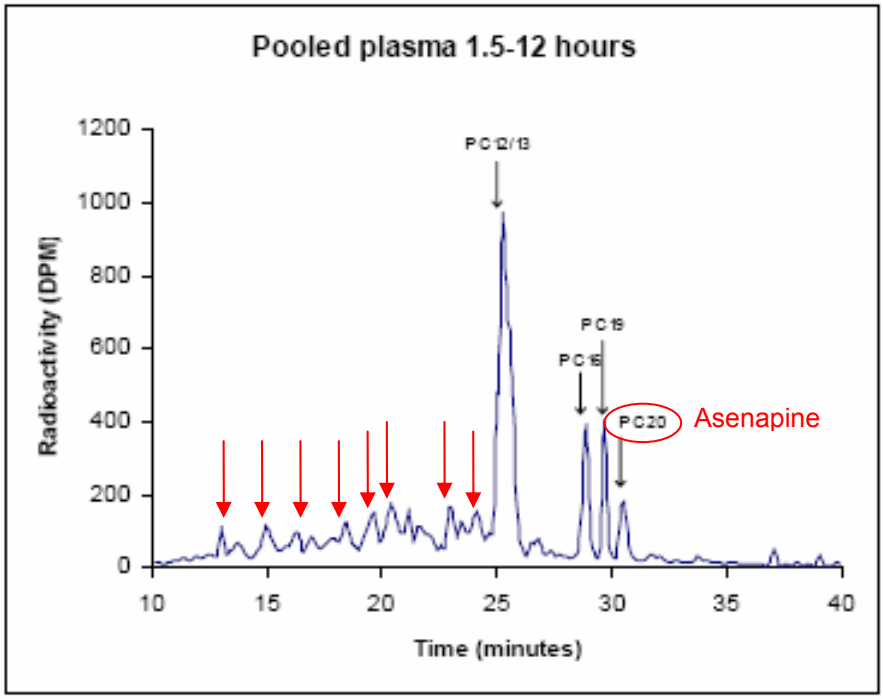
Although the sponsor claims that peaks identified in the 1 hour plasma sample with asterixes are not related to asenapine this seems suspect as they are so tall and the mode of detection is radioactivity. Consequently they should not only be due to the ^{14}C that was incorporated into asenapine. It's possible that their lack of detection in later samples may be secondary to their being formed by CYP2D6, which appears to be mechanistically inactivated by N-desmethyl-asenapine, and their subsequent rapid elimination.

In conclusion it appears that there may be a dozen or more unidentified metabolites circulating in plasma for which the plasma exposure is greater than 10% of the exposure to asenapine. Consequently, a large number of unidentified metabolites may still need to be qualified. The pharm/tox reviewer was also advised of this a few days after the midcycle meeting held at the end of Janurary 2008.

Figure 12 Representative HPLC Metabolite Profiles (HPLC system 2) of Pooled Plasma Samples of Male Human Volunteers after Sublingual Asenapine plus [^{14}C]-Asenapine – Study Report 40218



* These spikes are based on LC-MS analysis not related to asenapine.



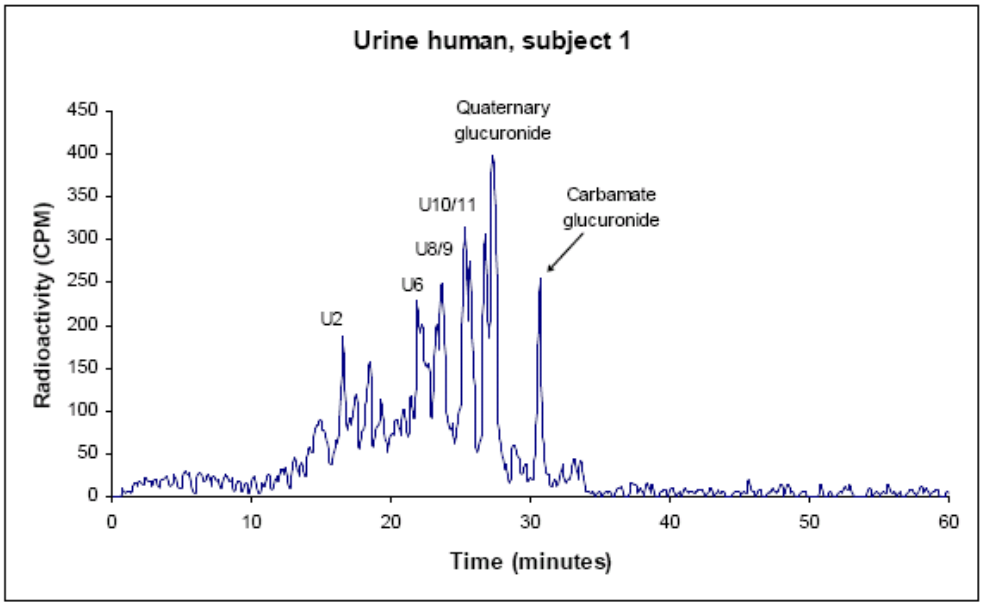
Peak PC10/11 contains at least the sulfate of the 11-hydroxy of asenapine
Peak PC12/13 are identified as the quaternary glucuronide of asenapine
Peak PC16 is identified as the carbamate glucuronide of the N(2)-des-methyl of asenapine
Peak PC19 is identified as the N(2)-des-methyl of asenapine
Peak PC20 is identified as asenapine

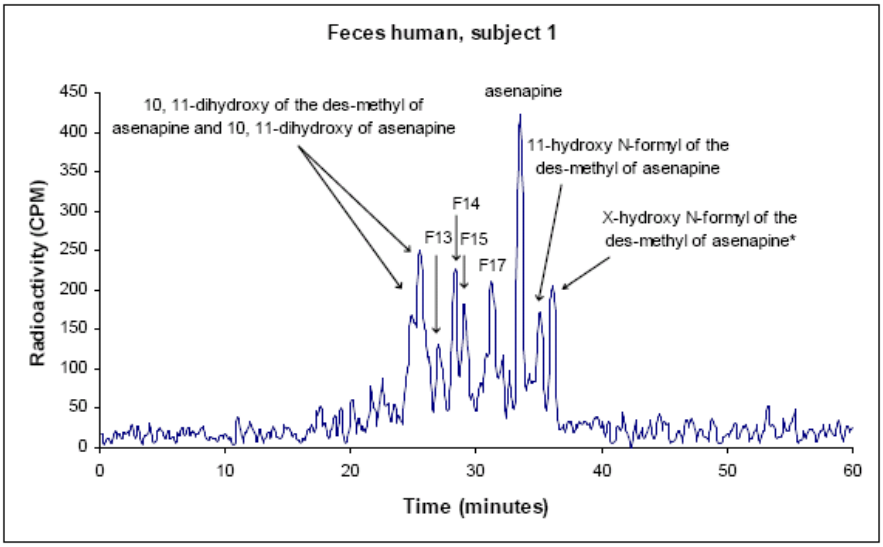
5.4.2.6 Recovery in Urine and Feces, Metabolic Scheme, & Mass Balance

5.4.2.6.1 Metabolites Identified in Urine and Feces

Figure 13 shows 'representative' HPLC system 2 metabolite profiles with separate urine and feces numbering of pooled urine and feces samples collected after sublingual administration of [^{14}C]-Asenapine to a healthy male volunteer in study 25532. Figure 14 on the following page shows 'representative' chromatograms of urine metabolites with HPLC system 2 for all subjects. The collection interval for these urine samples were not described, thus the sponsor's description as 'representative'. Yet it's clear that more than 20 potential peaks are visible yet the peak for asenapine (PC20) is not identifiable.

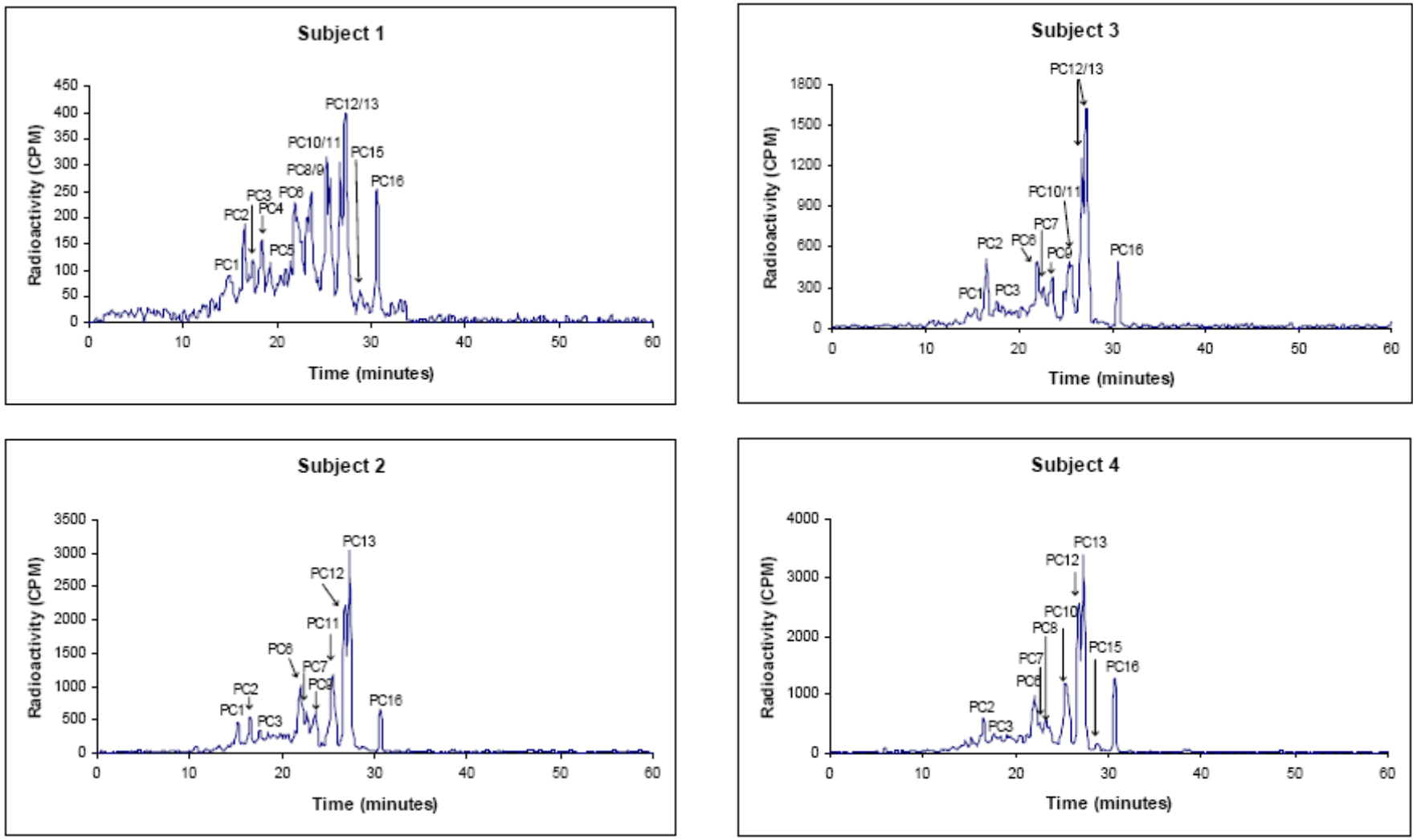
Figure 13 Representative HPLC Metabolite Profiles (HPLC system 2) of Urine and Feces Samples Collected after Sublingual Administration of [^{14}C]-Asenapine to a Healthy Male Volunteer





U2 is identified as the methoxy and glucuronide of the 10, 11-dihydroxy of the N-des-methyl of asenapine in which the position of the methoxy and glucuronide is 10, 11 and the reverse.
U6 is identified as the methoxy and sulphate of the 10, 11-dihydroxy of the N-des-methyl of asenapine in which the position of the methoxy and sulphate is 10, 11 or the reverse, the glucuronide of the 11-hydroxy of N-des-methyl of asenapine, the glucuronide of the 11-hydroxy of asenapine plus some other conjugated metabolites (sulphates and glucuronides).
U8/9 contained some conjugated metabolites (sulphates and glucuronides)
U10/11 is identified as the sulphate of the 11-hydoxy of asenapine plus some other conjugated metabolites (sulphates and glucuronides) of most probably the N-oxide of asenapine.
U12/13 is identified as the quaternary glucuronide of asenapine.
U16 is identified as the carbamate glucuronide of the N(2)-des-methyl of asenapine.
* the position of the hydroxyl group could not be assigned but it might be the 6-hydroxy

Figure 14 Representative HPLC Metabolite Profiles (HPLC System 2) of Pooled Urine Samples after Sublingual Administration of Radiolabeled and Unlabeled Asenapine – Study 25532

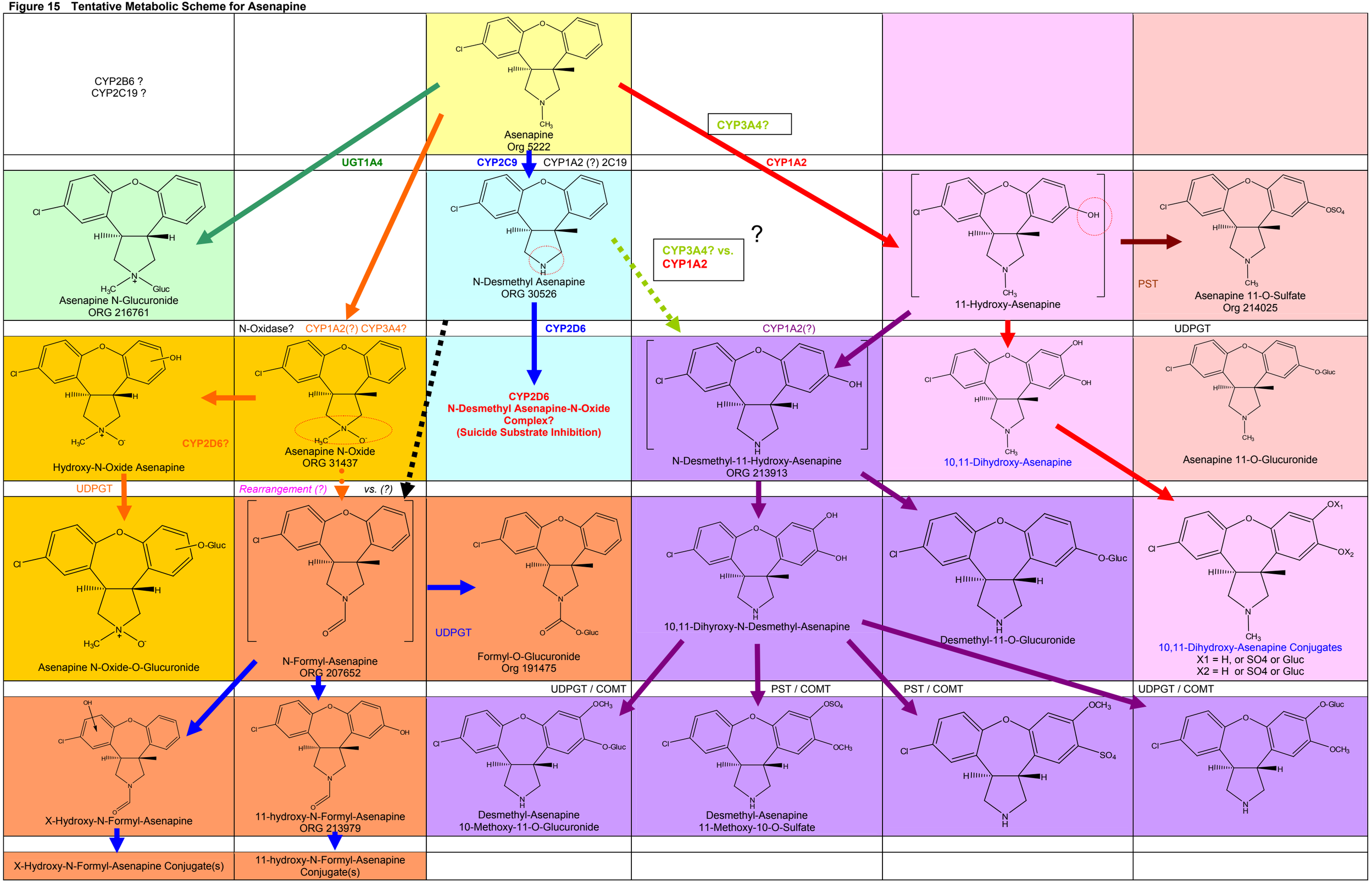


PC2 is identified as the methoxy and glucuronide of the 10, 11-dihydroxy of the N(2)-des-methyl of asenapine in which the position of the methoxy and glucuronide is 10, 11 and the reverse.
PC6 is identified as the methoxy and sulfate of the 10, 11-dihydroxy of the N(2)-des-methyl of asenapine in which the position of the methoxy and sulfate is 10, 11 or the reverse, the glucuronide of the 11-hydroxy of N(2)-des-methyl of asenapine, the glucuronide of the 11-hydroxy of asenapine plus some other conjugated metabolites (sulfates and glucuronides).
PC8/9 contained some conjugated metabolites (sulfates and glucuronides)
PC10/11 is identified as the sulfate of the 11-hydoxy of asenapine plus some other conjugated metabolites (sulfates and glucuronides) of most probably the N(2)-oxide of asenapine.
PC12/13 is identified as the quaternary glucuronide of asenapine.
PC16 is identified as the carbamate glucuronide of the N(2)-des-methyl of asenapine.

5.4.2.6.2 Metabolic Scheme (Tentative)

Figure 15 on the next page shows a tentative metabolic scheme. This scheme is based on the sponsor's more limited proposed scheme with the addition of metabolites only identified nominally by the sponsor, and with the addition of metabolites that can be inferred based on the available data. The scheme is only tentative as the data provided by the sponsor on certain secondary, tertiary and even lower level pathways cannot be identified with certainty. More importantly the enzymes or specific isozymes involved frequently cannot be identified. Consequently, pathways for which the enzymes or isozymes are relatively certain have been identified with bolded text.

Figure 15 Tentative Metabolic Scheme for Asenapine



5.4.2.6.3 Mass Balance

Table 25 on the following page shows the recovery of the radioactive dose by identified peak and by patient in both urine and feces, i.e. the reported mass balance.

Table 24 below summarizes the recovery of the radioactive dose reported in Table 25 and compares it to that reported by the sponsor. At least part of the discrepancy may be due to the radioactive peaks shown in Figure 12 that the sponsor claims was not associated with asenapine or any metabolites.

Table 24 % of Radioactive Dose Recovered in Urine and Feces as Determined from Individual Peaks and as Reported by the Sponsor

Reference	Description	Urine	Feces	Urine and Feces
Table 25	**Tally from Mass Balance Data provided by Sponsor**	43% 33% - 52%	32% 30 – 40%	75% 59% - 83%
Table 19	**Recovery of Radioactivity as Reported by Sponsor**	48.9% 37% - 59%	38.8% 35% – 47%	87.7% (72% – 96%)

Table 26 attempts to figure out relative contributions to the elimination of asenapine from each of the four primary metabolic pathways and shows only one possibility.

When the fraction of the dose that was not recovered, not accounted for, or not identified is totaled the fate of 37% - 56% (average 45%) of the dose is unknown.

Since multiple metabolites were identified for each peak, (see Table 25), and since the metabolic scheme is uncertain, (see Figure 15), except for direct glucuronidation by UGT1A4 which accounts for 12% - 21% of the dose and elimination of unchanged asenapine which accounts for 5% - 16% of the dose, the relative contribution of the 3 primary oxidative pathways cannot be definitively assigned. Thus the primary elimination pathways and enzymes have not been identified for 64.5% – 82.8% of the dose.

Table 25 Mass Balance Recovery of the Radioactive Dose by Identified Peak (HPLC System 2) for each Subject in both Urine and Feces – Study 25532

Peak No.	RT (min)	% of Radioactive Dose Recovered in Urine				% of Radioactive Dose Recovered in Feces				Nominal Description	% of Radioactive Dose Recovered in Urine & Feces			
		Subj 1	Subj 2	Subj 3	Subj 4	Subj 1	Subj 2	Subj 3	Subj 4		Subj 1	Subj 2	Subj 3	Subj 4
PC1	15.2	2.71	2.29	1.19							2.71	2.29	1.19	0
PC2	16.6	2.51	2.7	2.8	2.61					N(2)-des-methyl asenapine 10-Methoxy 11-O-Glucuronide & N(2)-des-methyl asenapine 10-O-Glucuronide 11-Methoxy	2.51	2.7	2.8	2.61
PC3	17.6	1.53	1.93	1.14	1.67						1.53	1.93	1.14	1.67
PC4	18.5	2.85									2.85	0	0	0
PC5	19.3	2.35									2.35	0	0	0
PC6/7	22	6.17	6.01	2.76	3.95					N(2)-des-methyl asenapine 10-methoxy 11-O-Sulfate & N(2)-des-methyl asenapine 10-O-Sulfate 11-Methoxy N-des-methyl asenapine 11-O glucuronide Asenapine-11-O-glucuronide Plus some other sulfates and glucuronides	6.17	6.01	2.76	3.95
PC7	22.7		2.35	1.56	1.86						0	2.35	1.56	1.86
PC8	23.3	2			3.1					U8/9 contained some conjugated metabolites (sulphates and glucuronides)	2	0	0	3.1
PC9	23.6	3.92	4.34	2.83							3.92	4.34	2.83	0
PC10	25.1	4.53		1.27	6.9	2.83	3.33	2.35	2.95	U10/11 Asenapine 11-O-Sulfate N-oxide asenapine sulphates and glucuronides	7.36	3.33	3.62	9.85
PC11	25.6	3.24	8.44	3.62		4.5	6.77	4.46	2.8	F10/11 10, 11-dihydroxy-des-methyl asenapine and 10, 11-dihydroxy-asenapine.	7.74	15.21	8.08	2.8
PC12	26.8	3.88	9.36	5.99	7.43					asenapine glucuronide	3.88	9.36	5.99	7.43
PC13	27.2	6.34	11.97	7.51	9.79	2.17			2.12	asenapine glucuronide	8.51	11.97	7.51	11.91
PC14	28.4					2.87	1.42	2.32	2.5		2.87	1.42	2.32	2.5
PC15	29	1.12			0.73	2.43	3.12	1.85	4.29		3.55	3.12	1.85	5.02
PC16	30.7	3.13	2.42	2.02	3.16			0.77		U16- N(2)-des-methyl asenapine glucuronide	3.13	2.42	2.79	3.16
PC17						3.79	4.05	2.6	2.81		3.79	4.05	2.6	2.81
PC18						1.13					1.13	0	0	0
PC19						0.92	1.65			N-desmethyl-asenapine	0.92	1.65	0	0
PC20						4.79	5.97	7.62	16.2	Asenapine	4.79	5.97	7.62	16.2
PC21							1.17	1.1	1.59		0	1.17	1.1	1.59
PC22						1.97	1.44	1.51	2.31	11-hydroxy N formyl N-desmethyl	1.97	1.44	1.51	2.31
PC23						2.7	1.88	1.71	2.82	X-hydroxy N-formyl of N-desmethyl	2.7	1.88	1.71	2.82
Cumulative Recovery (% of ^{14}C Dose)		46.3	51.8	32.7	41.2	30.1	30.8	26.3	40.4		**76.4**	**82.6**	**59.0**	**81.6**

Table 26 One Possibility for Relative Contributions by Primary Pathways to Mass Balance

Peak No.	Description	Subj 1	Subj 2	Subj 4	Subj 4
11 Hydroxylaton (CYP1A2)					
PC2	N(2)-des-methyl asenapine 10-Methoxy 11-O-Glucuronide & N(2)-des-methyl asenapine 10-O-Glucuronide 11-Methoxy	2.51	2.7	2.8	2.61
PC6	N(2)-des-methyl asenapine 10-methoxy 11-O-Sulfate & N(2)-des-methyl asenapine 10-O-Sulfate 11-Methoxy N-des-methyl asenapine 11-O glucuronide Asenapine-11-O-glucuronide Plus some other sulphates and glucuronides	6.17	6.01	2.76	3.95
PC10	Asenapine 11-O-Sulfate	7.36	3.33	3.62	9.85
PC11	N-oxide asenapine sulfates and glucuronides 10, 11-dihydroxy-des-methyl asenapine and 10, 11-dihydroxy-asenapine.	7.74	15.21	8.08	2.8
Subtotal		**23.78**	**27.25**	**17.26**	**19.21**
N-Demethylation ?					
PC22	11-hydroxy N formyl N-desmethyl asenapine	1.97	1.44	1.51	2.31
PC23	X-hydroxy N-formyl of N-desmethyl asenapine	2.7	1.88	1.71	2.82
PC19	N-desmethyl-asenapine	0.92	1.65	0	0
PC16	N(2)-des-methyl asenapine glucuronide	3.13	2.42	2.79	3.16
Subtotal	**N.B. it's uncertain if formyl metabolites should be included under N-Demethylation or not. Or alternatively under N-oxidation or even another pathway.**	**8.72**	**7.39**	**6.01**	**8.29**
quaternary glucuronide of asenapine UGT1A4					
PC12	asenapine. glucuronide	3.88	9.36	5.99	7.43
PC13	asenapine. glucuronide	8.51	11.97	7.51	11.91
Subtotal		**12.39**	**21.33**	**13.5**	**19.34**
Unidentified					
PC1		2.71	2.29	1.19	0
PC3		1.53	1.93	1.14	1.67
PC4		2.85	0	0	0
PC5		2.35	0	0	0
PC7		0	2.35	1.56	1.86
PC14		2.87	1.42	2.32	2.5
PC15		3.55	3.12	1.85	5.02
PC17		3.79	4.05	2.6	2.81
PC18		1.13	0	0	0
PC21		0	1.17	1.1	1.59
Subtotal		**20.78**	**16.33**	**11.76**	**15.45**
Unidentified Sulfate and Glucuronide Conjugates					
PC8	some conjugated metabolites (sulfates and glucuronides)	2	0	0	3.1
PC9	some conjugated metabolites (sulfates and glucuronides)	3.92	4.34	2.83	0
Subtotal		**5.92**	**4.34**	**2.83**	**3.1**
PC20	**Asenapine**	**4.79**	**5.97**	**7.62**	**16.2**
Total Recovery from Individual Peaks		**76.38**	**82.61**	**58.98**	**81.59**
	Identified	***49.68***	***61.94***	***44.39***	***63.04***
	Unidentified	26.7	20.67	14.59	18.55
	Not Accounted For in report of Urine and Feces Recovery	23.62	17.39	41.02	18.41
Total Recovery per Sponsor		**86.9**	**95.9**	**71.8**	**96.0**
	Not Recovered	13.1	4.1	28.2	4.0
Difference between amount reported as not recovered by sponsor and amount not accountable for in report of urine and feces recovery		10.52	13.29	12.82	14.41
Unidentified, Unaccounted, and Not Recovered		***50.32***	***38.06***	***55.61***	***36.96***
(Average)		***(45.2%)***			

5.4.3 *In Vitro* Drug Metabolism Studies

5.4.3.1 Hepatocytes

Metabolism in isolated human hepatocytes will be discussed first as the intact cells provides the best information on the overall metabolic profile as they include cytosolic enzymes in addition to microsomal enzymes. However it should be remembered that a hepatocyte system lacks the anatomical structure found *in vivo* and thus may not be accurate in terms of relative abundance of each metabolite or the importance of various metabolic pathways.

5.4.3.1.1 Study 5067 (1997) - AKA NCL Study

Study 5067 conducted in 1997 incubated [^{3}H]-Asenapine labeled at the 11 position, (see Figure 16), at a concentration of 149 ng/mL (521.4 nMol/L) for 3 hours with isolated human hepatocytes from a 41 yo female.

Results are shown in Table 27. Recoveries were reported for both the cell medium as well as the cell extract, unfortunately the relative amounts in the cell extract compared with the cell medium were not reported so only tentative conclusions may be drawn. The following tentative conclusions are made based upon the relative retention times:

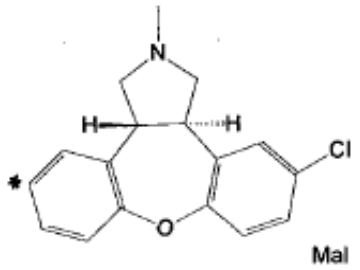
Peach Table Cells – greater amount found in cell medium and also eluting earlier, thereby indicating greater hydrophylicity and possible active secretion.
Yellow Table Cells - approximately equal amounts found in cell medium and cell extract possibly indicating passive diffusion.
Light Blue Table Cells - greater proportion found in cell extract indicating possible binding to cellular components or greater lipophilicity.

Table 27 Percent Radioactive Recovery by Peak after Asenapine Incubation with Human Hepatocytes at 521 nMol – Study 5067 (1997)

	H1	H2	H3	H4	H5	H6	H7	H8	H9	H10	H11	H12	H13 & H14	H15	Asenapine	H16
	Unknown												N-Oxides	Desmethyl Asenapine		Unknown
Cell Medium	37.7	9.3	3.2	12.5			2.8	6.9	11.9	1.1			9.1	4.0	1.6	
Cell Extract	3.1					2.1	3.9	8.2	12.0			3.9	10.4	46.7	9.6	

Metabolite H1 is highly polar and accounts for the majority of the recovery in the cell media. In addition 80% of the radioactivity in the cell media was volatile suggesting that much of the radioactivity was tritiated water. Taken together these facts suggest that the majority of asenapine's metabolism in this system is via is 11-oxidation and that H1 is likely the 11-O-sulfate.

Figure 16 Position of Asenapine ^{3}H Radiolabel - Study 5067



5.4.3.1.2 Study NL0060905 (2006)

Study NL0060905 conducted in 2006 incubated [^{14}C]-Asenapine at concentrations of 4.7 nMol/mL (µM) and 19.5 nMol/mL (µM) in a final ethanol concentration of 2% (v/v) performed in duplicate with isolated human male hepatocytes.

Results are shown in Table 28. Unfortunately only total recoveries were reported even though the sponsor stated that recoveries were determined in both the cell medium as well as the cell extract. Where feasible, recoveries that can be attributed to a single primary pathway are combined to show the relative importance of that primary pathway. This reveals that over 50% of asenapine's metabolism in this system proceeds via N-desmethylation.

Table 28 Fractional Recovery after Asenapine Incubation with Human Hepatocytes - Study NL0060905 (2006)

Peak			Total recovery	H1	H2	H3	H4	H5	H6	H7	H8	H9	H10	H11	H12	H13	H14	H15	H16	H17
m/z								384.1		464.2	290.1	450.2		274.1	288.1	318.1	304.1		302.1	
Code #														30526	5222		34137			
Nominal Structure								O-SO4		N-Gluc	OH-N-Des	N-Des-Gluc[c]		N-Des	As	N-formyl OH	N-oxide		N-formyl	
B	4.7 nMol/mL (µM)	Total	88.5	—[a]	—	5.17	3.76[b]	27.19	4.03	2.51	6.15	19.27	2.29	21.29	4.89	5.35	—	—	—	—
		Media	[redacted]																	
		extract																		
	Combined							31.2		2.5				52.0	4.9	5.35				
A	19.5 nMol/mL (µM)	Total	83.5	—	—	1.81	1.31	13.07	1.85	2.47	2.55	19.2	1.53	13.63	31.1	2.4	1.32	1.88	4.81	1.11
		Media	[redacted]																	
		extract																		
	Combined							15.0		2.5				42.7	31.1	7.2	3.1			

a – not detected
b - observed in only 1 duplicate
c –structure not identified by sponsor

It should be noted that the sponsor did not identify the structure of metabolite H9, however from the molecular weight it is readily apparent that it is the glucuronide conjugate of N-desmethyl-asenapine. By not identifying this structure, if this reviewer had not realized that the N-formyl metabolites proceed via N-desmethylation the relative contribution of N-desmethylation would have been capped at half of what the results truly show. Consequently the clinical importance of inhibition of this pathway would not have been as apparent.

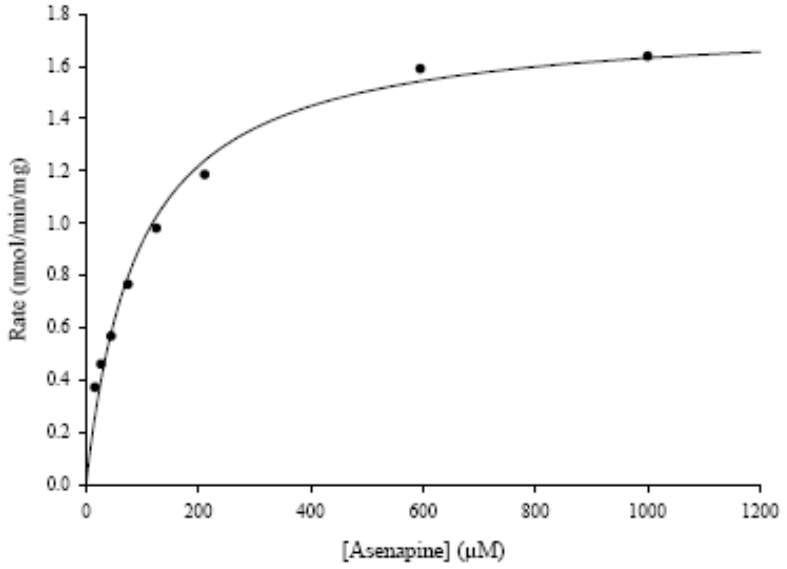
5.4.3.2 N-Glucuronication

The Uridine Glucuronosyl Transferase isozymes (UGT) involved in the N-glucuronidation of asenapine were identified in study DM2006-005222-013. Glucuronidation of metabolites was not examined.

Incubations were first conducted with pooled human liver microsomes (HLM-13) to determine apparent instrinsic enzyme kinetic parameters, followed by incubations with the recombinant UGT enzymes (UGT1A1, 1A3, 1A4, 1A6, 1A8, 1A9, 1A10, 2B4, 2B7, and 2B15). Incubation times were 1 hour, and the duration of incubation and the protein concentration used were established in preliminary experiments that assessed the linearity of the relationship with the reaction velocity. The formation of asenapine N-glucuronide was determined by mass spectrometry.

Data from incubations with pooled human hepatic microsomes were fit to a Michaelis-Menten model resulting in a Km of 92.6 μM and Vmax of 1.8 nMol / min / mg, (see Figure 17). Since asenapine's *in vivo* concentrations peak between 10 – 70 nMol/L glucuronidation should be a linear *in vivo*,

Figure 17 Mean Asenapine N-Glucuronide Formation Rate vs. Concentration in Pooled Human Hepatic Microsomes – Study DM2006-005222-013



After the apparent instrinsic kinetic parameters in pooled microsomes were determined, various recombinant UGT isozymes were incubated under nonlinear conditions with asenapine at a concentration equal to the apparent instrinsic Km, (i.e. 92 μM).

Based on these experiments UGT1A4 was identified as the isozyme with the greatest intrinsic affinity to glucuronidate asenapine, (see Table 29).

Table 29 Formation Rate of Asenapine N-Glucuronide by Recombinant UGT Isozymes at the Apparent Km (92 μM) – Study DM2006-005222-013

UGT Isozyme	1A1	1A3	1A4	1A6	1A8	1A9	1A10	2B4	2B7	2B15
Formation Rate[a] (nmol / min / mg)	<LLOQ	<LLOQ	0.49	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ

a LLOQ = 0.03 nmol/min/mg

UGT1A1 glucuronidates bilirubin and is also known as bilirubin-UGT-1 (BUGT1).

Despite high sequence identity, UGT1A3 and UGT1A4 differ in terms of substrate selectivity. UGT1A3 glucuronidates planar phenols such as 1-naphthol (1-NP) and 4-methylumbelliferone (4-MU). Whereas UGT1A4 converts the tertiary amines, such as lamotrigine (LTG) and trifluoperazine (TFP), to a quaternary ammonium glucuronide. Thus the finding that UGT1A4 glucuronidates asenapine is not surprising.

5.4.3.3 Microsomal Oxidative Metabolism

In vitro studies were conducted examining the microsomal oxidative metabolism of asenapine. Studies utilized the following test systems:

a) Human Liver Microsomes
b) Supersomes (i.e. microsomes from P450 isozyme specific cDNAh expressed in intact insect cells)

There were typically at least two study reports for each test system, an initial study conducted by Organon during their initial development, and a later study conducted by Pfizer within a few years of submission.

Unfortunately almost all of the studies were conducted at asenapine concentrations ~ 1000 fold higher than *in vivo* concentrations (2 – 28 nMol). Therefore results are somewhat suspect.

5.4.3.3.1 Human Liver Microsomes

The following three studies were conducted with human liver microsomes:

1) Study 2874 (1991)
2) NL0060848 (2005)
3) INT00003054 (2006)

5.4.3.3.1.1 Human Liver Microsomes – Study 2874 (1991)

Study 2874 examined the fractional recovery of radioactivity after incubation of 25 μM of ^{3}H-Asenapine in human liver microsomes from two Dutch males. Table 30 shows that recovery as metabolites is primarily as the N-Desmethyl. Three other metabolites including the diasteromeric N-oxide and 2 unidentified metabolites are recovered at lower fractions.

Table 30 Fractional Recoveries of Extracted Radioactivity after Incubation of ^{3}H-Asenapine 25 μM with Human Liver Microsomes for 30 Minutes – Study 2874

% of Extracted Radioactivity				
N-Oxide (Diastereomeric)	**M2**	**M3**	**Desmethyl-Asenapine**	**Asenapine**
5.8	8.3	4.5	12.7	68.9

5.4.3.3.1.2 Human Liver Microsomes – Study HLM NL0060848 (2005)

5.4.3.3.1.2.1 NADPH Dependence

In study NL0060848 (2005) male human liver microsomes (microsomal protein concentration: 500 μg/mL) were incubated for 15 minutes at 37°C with [^{14}C]-asenapine at 2 and 20 μmol/L in the presence and the absence of NADPH.

Table 31 shows that at lower asenapine concentrations of 2 μM biotransformation is NADPH dependent, indicating that only P450 is involved in oxidation of asenapine at clinical concentrations which are much lower. At higher concentrations of 20 μM asenapine turnover is not entirely NADPH dependent, likely indicating the involvement of FMO, in addition the turnover is lower than at 2 μM, indicating the possibility

of a mechanism based inhibitor. Based on the structure of asenapine and the likely involvement of FMO there is a good likelihood that this is an N-oxide metabolite.

Table 31 % Biotransformation of Asenapine in Human Liver Microsomes 500 mcg/ml – Study NL0060848 (2005)

[redacted]	2 µmol/L [^{14}C]-asenapine			20 µmol/L [^{14}C]-asenapine		
[redacted]	Sample-1	Sample-2	Mean	Sample-1	Sample-2	Mean
Control[a]	0.00	--	--	5.06	--	--
(-) NADPH	0.00	0.00	0.00	5.48	6.12	5.80
(+) NADPH	17.50	24.96	21.23	9.65	11.31	10.48

5.4.3.3.1.2.2 Inhibition by Isozyme Specific Inhibitors

Table 32 shows the degree of inhibition of asenapine biotransformation by CYP450 isozyme specific inhibitors in human liver microsomes. As expected the degree of inhibition is less at the higher asenapine concentrations as the I/Ki : C/Km ratio is smaller at the higher asenapine concentration. The results show that 3A4, 1A2, and likely 2D6 are involved in the metabolism of asenapine and 2D6 might cause autoinhibition at higher concentrations, (also possibly 2C19 but this is less certain). Plus inhibition of 3A4, 1A2, and 2D6 might occur *in vivo* but the importance of these can only be determined from *in vivo* data since the specific metabolites and relative importance of the pathways need to be considered.

Table 32 % Inhibition of Asenapine Biotransformation by CYP450 Isozyme Specific Inhibitors in Human Liver Microsomes - NL0060848 (2005)

Asenapine (µmol/L)	1.8	20.5	2.4	24.3	2.4	24.3	2.4	24.3	2.4	24.3	0.2	2	1.8	22.7
Isozyme	1A2		2B6		2B6		2C19		2C19		2D6		3A4	
Inhibitor (µM)	Furafylline		MPEP		Orphenadrine		Benzylnirvanol		Tranylcypromine		Quinidine		Ketoconazole	
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
0.1											1.84	2.66	55.76	3.23
0.2			10.04	3.23										
0.5							-9.17	1.32			17.62	2.91	59.53	5.08
1	11.51	2.39	15.16	-0.97			11.09	-4.71	11.29	12.66	19.93	0.15	77.37	13.26
2			10.34	7.30										
2.5					1.87	4.55								
5	45.83	10.90					6.98	-8.45	2.70	16.24			77.23	25.20
10	15.69	12.70	14.22	4.26			0.12	-10.02	4.60	17.03			86.14	36.08
11											24.32	2.96		
12.5					6.94	4.73								
20			14.08	4.44										
50	40.63	25.68			6.54	5.14	-12.92	-18.78	11.18	21.40				
53											31.71	7.72		
100	100.0	30.29												
125					11.96	6.69								
250									27.27	24.39				
500					7.29	6.28								

5.4.3.3.1.3 Human Liver Microsomes – Study INT00003054 (2006)

Study INT00003054 examined the fractional HPLC peak recoveries of radioactivity after Incubation of ^{14}C-Asenapine at ~ 5 and ~20 nMol/L with human liver microsomes at a protein concentration of 500 mcg/mL for 30 minutes.

Two sets of experiments were performed each using a different batch of microsomes. An initial set where the final concentration of ethanol used to dilute asenapine was 5% and a second set at a lower final ethanol concentration of 1%. The second set of experiments were conducted as ethanol interfered with the metabolism of asenapine and resulted in no turnover at the higher asenapine concentration.

The mechanism for alcohol's inhibition could be either nonspecific or specific inhibition of 2E1, 3A4, or alcohol and aldehyde dehydrogenase.

Similar to study 2874 (1971) the metabolites recovered included the N-desmethyl, the N-oxide and two other unidentified metabolites, (see Table 33).

Table 33 Fractional Recoveries of Radioactivity after Incubation of ^{14}C-Asenapine at ~ 5 and ~20 nMol/L with Human Liver Microsomes - Study INT00003054 (2006)

		EtOH	kBq	nMol/L	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M13	M14
											DesMe	Asenapine		N-Ox				
A	1	5%	10.5	5.5				2.5			1.5	94.5		1.5				
	2	1%	10.1	5.3			2.3	5.0			5.2	81.7		5.9				
B	1	5%	42.4	22.3								100						
	2	1%	35.8	18.8				10.5			10.9	63.8	6.0	8.8				

5.4.3.3.2 Supersomes

5.4.3.3.2.1 Supersome Study NL0010293 (1998)

5.4.3.3.2.1.1 Initial Formation Rates

The initial formation rates of asenapine N-oxide and desmethyl-asenapine from [^{3}H]-Asenapine by cDNAh P450 isozymes expressed in insect cells (i.e. Supersomes) was examined in study NL0010293.

[^{3}H]-Asenapine labeled in two positions as shown in Figure 18 was incubated with CYP1A2, CYP2A6, CYP2D6, CYP2E1, CYP2C9, CYP2C19 and CYP3A4 supersomes at a microsomal protein concentration of 250 µg/mL for 15 min at 37 °C at concentrations of 2 and 20 µM.

Results are shown in Table 34. From this data it appears that CYP1A2 is involved in the formation of the reactive N-Oxide as well as is the primary isozyme responsible for formation of the N-Desmethyl metabolite, although CYP2C19, which is polymorphic, and CYP3A4 may be involved. It should be noted that the actual importance of these isozymes will also depend on their relative abundance *in vivo*. Consequently, CYP3A4 may be more important than CYP2C19.

Figure 18 ^{3}H Radiolabeling of Asenapine Used in Study NL0010293 (1998)

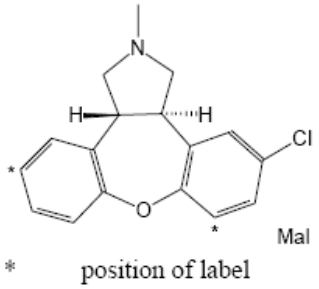


Table 34 Initial Formation Rates of Asenapine N-Oxide and Desmethyl-Asenapine by Supersomes - Study NL0010293 (1998)

Supersomes	Formation Rates[a] (pMol·/ nMol P450 x min^{-1})			
	Asenapine - N(2)-Oxide		N(2)-Desmethyl Asenapine	
[^{3}H]-Asenapine Conc.	2 µM	20 µM	2 µM	20 µM
CYP1A2	*	*	376.91	1277.17
CYP2A6	–	–	–	–
CYP2C9	–	–	–	123.73
CYP2C19	–	–	85.77	725.44
CYP2D6	–	–	–	181.30
CYP2E1	–	–	–	–
CYP3A4	–	*	10.52	155.82

a Data are presented as mean values of duplicate incubations
– Below limit of detection
* Showed activity.

According to the sponsor, *'It was not possible to quantify the formation of the N(2)-oxide metabolite of Org 5222, because in the HPLC metabolite profiles of the higher substrate concentration an impurity was present at a detectable level, which eluted at the retention time of the N(2)-oxide metabolite of Org 5222. However the activity of CYP1A2 towards the N(2)-oxidation was higher as compared with CYP3A4 activity.'*

5.4.3.3.2.1.2 Enzyme Kinetic Parameters

Enzyme kinetic parameters for the formation of the N-oxide and the N-desmethyl metabolites were also determined for each of these isozymes, and the results are shown in Table 35. This data tends to confirm the previous conclusions.

Table 35 Enzyme Kinetic Parameters for the Formation of Asenapine N(2)-oxide and N(2)-Desmethyl Asenapine by CYP1A2, CYP2C19 and CYP3A4 Supersomes - Study NL0010293 (1998)[a]

Supersome Isozyme	Enzyme Kinetic Parameter	N(2)-oxide	N(2)-Desmethyl Asenapine
CYP1A2	Vmax (pMol / min / nMol P450)	942 ± 47	1556 ± 251
	Km (nMol/mL) (μM)	0.7 ± 0.2	16.6 ± 8.4
	Clint ($L/hr \times \mu Mol^{-1}$)	83.3	5.62
CYP2C19	Vmax	—[b]	6052 ± 6 42
	Km	—	99.1 ± 14.7
	Clint ($L/hr \times \mu Mol^{-1}$)	—	3.66
CYP3A4	Vmax	572 ± 67	5735 ± 1156
	Km	77.0 ± 27.9	453.5 ± 166.0
	Clint ($L/hr \times \mu Mol^{-1}$)	0.44	0.78

a Values are presented as mean ± standard error (SE) of the fit.
b not determined

5.4.3.3.2.1.3 Correlation of Asenapine Metabolite Formation with Isozyme Activity

Spearman Rank correlations between the formation of the asenapine metabolites N-oxide asenapine and N-desmethyl asenapine and the metabolism of cytochrome P450 enzyme selective substrates also tend to confirm the rank order of activity of these isozymes toward the formation of the N-oxide and N-desmethyl metabolite, (see Table 36).

Table 36 Spearman Rank Correlations between the Formation of Asenapine N-oxide asenapine and N-Desmethyl asenapine and the Metabolism of Cytochrome P450 Isozyme Selective Substrates - Study NL0010293 (1998)

Cytochrome P450	Substrate	Reaction	Asenapine N(2)-Oxide		N(2)-Desmethyl Asenapine	
			2 µM	20 µM	2 µM	20 µM
CYP1A2	Phenacetin	O-DeEthyl	0.78**	0.71*	0.92***	0.79**
CYP2A6	Coumarin	7-OH	-0.23	0.07	-0.37	0.09
CYP2C	S-mephenytoin	4-OH	0.28	0.59	0.45	0.56
CYP2D	Dextromethorphan	O-DeMethyl	-0.32	-0.07	-0.22	0.12
CYP2E	Chlorzoxazone	6-OH	-0.23	-0.20	-0.23	-0.33
CYP3A	Testosterone	6β-OH	0.41	0.45	0.48	0.53

Statistical significance: *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

5.4.3.3.2.1.4 Effect of Isozyme Selective Inhibitors on Metabolite Formation

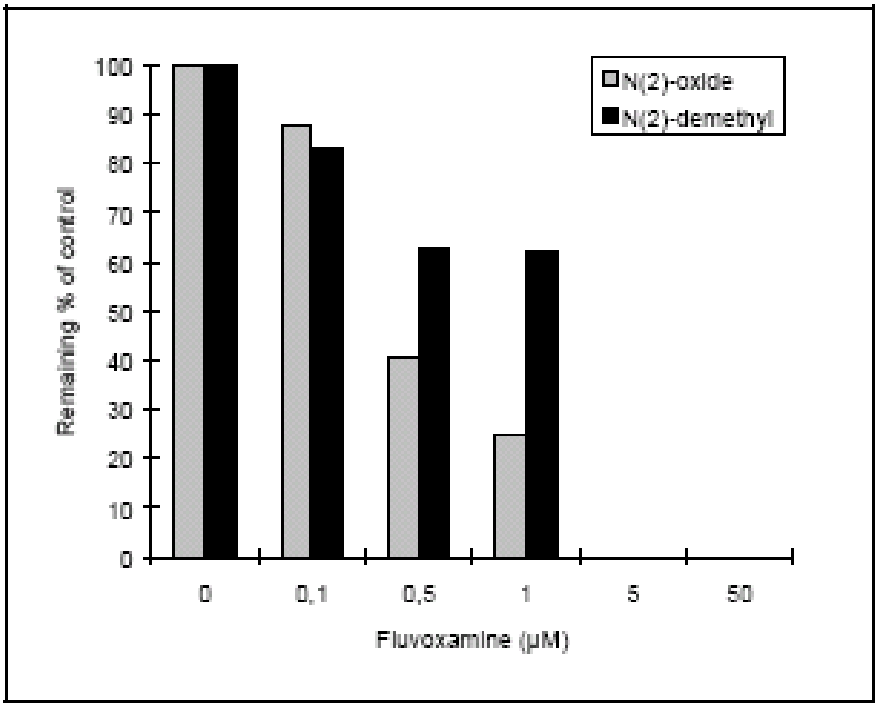
Microsomal incubations with 2 µM and 20 µM of [^{3}H]-asenapine were performed with five different inhibitor concentrations, (0.1, 0.5, 1, 5, 50 µM), of fluvoxamine and ketoconazole, selective inhibitors for CYP1A2 and CYP3A, respectively.

The sponsor's results are shown in Figure 19 and Figure 20. The asenapine concentrations shown in the figures appear to be transposed, as there is less inhibition at lower asenapine concentrations. If we assume that the concentrations are transposed, then the results would be consistent with the other experiments in supersomes which would not be surprising and all the results using the same experimental system should be consistent.

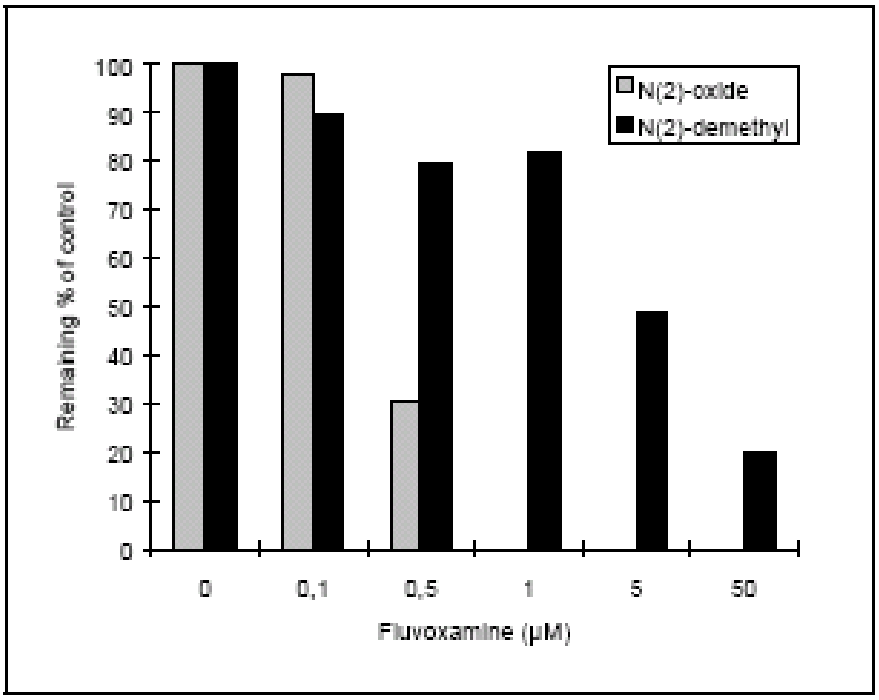
This should be remembered in assessing the weight of evidence for *in vitro* data showing the specific isozymes involved.

Figure 19 Inhibition of N(2)-Oxide and N(2)-Desmethyl Asenapine Formation by the CYP1A2 Selective Inhibitor Fluvoxamine – Study NL0010293 (1998)[a]

- 2 nmol·mL^{-1} Org 5222



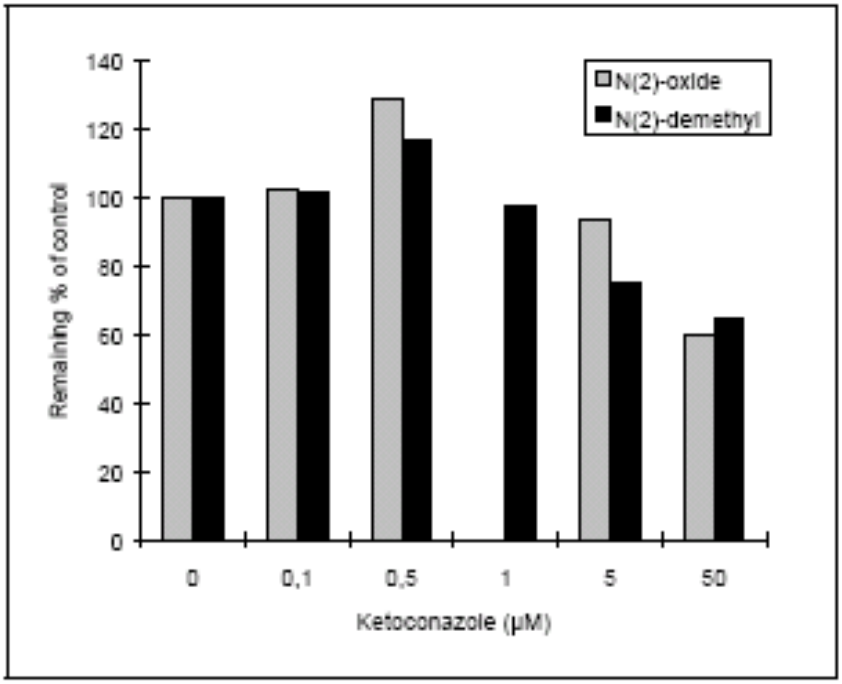
- 20 nmol·mL^{-1} Org 5222



a Asenapine concentrations 2 and 20 µM (nMol/mL))

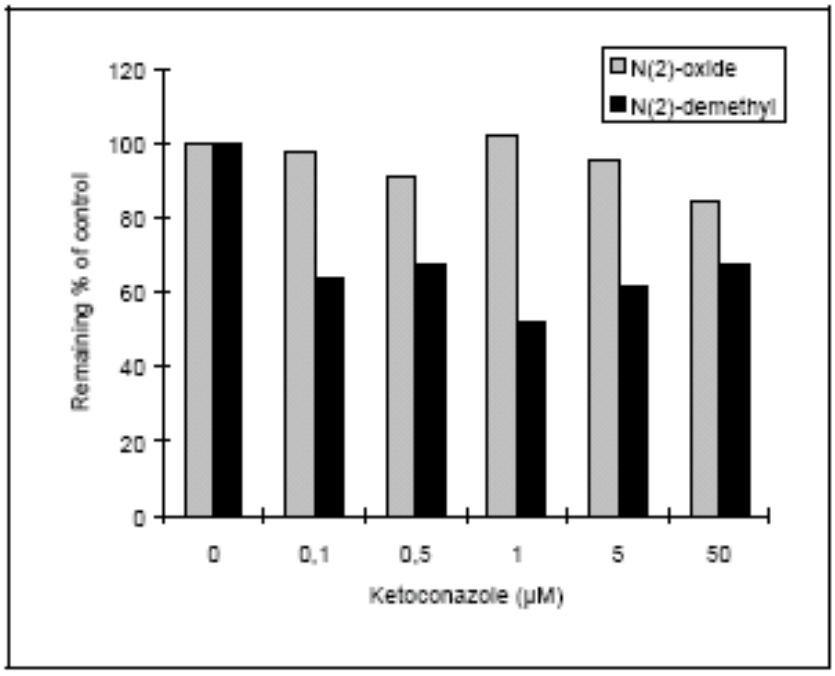
Figure 20 Inhibition of N(2)-Oxide and N(2)-Desmethyl Asenapine Formation by the CYP3A Selective Inhibitor Ketoconazole – Study NL0010293 (1998)

- 2 nmol·mL^{-1} Org 5222



* No reliable data were obtained for the N(2)-oxidation at 1 µM ketoconazole.

- 20 nmol·mL^{-1} Org 5222



a Asenapine concentrations 2 and 20 µM (nMol/mL)

5.4.3.3.2.2 Supersome Study NL0060848 (2005)

The objective of this study was to estimate and/or to confirm if human cytochrome P450 enzyme CYP1A2, CYP2B6, CYP2C19, CYP2D6 and CYP3A4 are involved in the Phase-I biotransformation of asenapine (Org 5222) *in vitro*. It was conducted from December 2005 to January 2006. It appears to have been conducted in response to the finding that asenapine is a potent CYP2D6 inhibitor in the *in vivo* paroxetine drug-drug interaction study, (25525), conducted from August to December 2005.

5.4.3.3.2.2.1 Turnover of Asenapine by Specific P450 Supersomes

Incubations of the asenapine were conducted with Supersomes selectively expressing human CYP1A2, CYP2B6, CYP2C19, CYP2D6 and CYP3A4 in order to select and/or confirm the enzymes involved in the metabolism of asenapine.

CYP1A2, CYP2B6, CYP2C19 and CYP3A4 (cytochrome P450 concentration: 100 pMol/mL) supersomes were incubated for 15 minutes at 37°C with two different concentrations of [^{14}C]-asenapine, approximately 2 and 20 µMol/L.

For CYP2D6 supersomes, [^{3}H]-asenapine was used at final concentrations of approximately 2 nMol/L and 2 µMol/L, the incubations with CYP2D6 were performed for 5 and 15 min at 37°C. The 2 nMol/L concentration is near the *in vivo* trough concentration.

Results are shown in Table 37.

Table 37 Biotransformation of Asenapine (%) by Supersomes[a] - NL0060848 (2005)

Supersome Isozyme	Asenapine Concentration	Biotransformation of Asenapine % of Baseline			
CYP1A2		Supersome Concentration			
		Control[b]	10 pMol	25 pMol	100 pMol
	1.84 µM		24.7	53.5	
	19.2 µM		10.7	15.6	
	2.16 µM	0.00			82.3
	20.7 µM	6.80			34.3
CYP2B6[c]		Control[b]	CYP2B6 Activity		
	2.05 µM	0.00	48.8		
	20.3 µM	6.72	42.5		
CYP2C19[c]		Control[b]	2C19 Activity		
	2.16 µM	0.00	30.2		
	20.7 µM	6.80	23.0		
CYP2D6[c]		5 min Control[b]	5 min CYP2D6	15 min Control[b]	15 min CYP2D6
	1.4 nMol	9.81	27.0	12.6	67.6
	2 µM	3.93	6.47	4.64	11.4
CYP3A4[c]		Control[b]	3A4 Activity		
	2.16 µM	0.00	12.5		
	20.7 µM	6.80	22.6		

a Biotransformation was expressed as percentage of total radioactivity not eluting as asenapine.
b Control Supersomes were Supersomes with no detectable cytochrome P450 activity. Incubations were performed in duplicate except for the incubations with control Supersomes.
c Experiments were performed with 100 pMol P450.

Table 37 shows that at supratherapeutic concentrations, (i.e. approximately 100 - 1000x *in vivo* concentrations of 10 – 70 nMol/L), CYP1A2 is the most important isozyme followed by CYP2B6 and then CYP2C19. However, at therapeutic concentrations CYP2D6 results in nearly as much turnover as CYP1A2 at supratherapeutic concentrations. In addition to this, the activity of CYP1A2, CYP2D6, and possibly CYP2C19 is lower at the higher asenapine concentration indicating the possible presence of an inhibitory metabolite.

Figure 21 to Figure 25 on the following page shows HPLC chromatograms for each supersome incubation at the high substrate concentration. CYP1A2 clearly shows the formation of the N-oxide, however it also shows a number of other metabolites. Consequently the degree on inhibition in a 15 minute incubation may not be predictive of more chronic administration. For CYP2B6, CYP2C19, and CYP3A4 it's clear there's activity but little evidence of N-oxide formation, whereas for CYP2D6 there's little metabolism and only the N-desmethyl metabolite is evident. Unfortunately without chromatograms from the lower substrate concentration incubations for comparison no conclusions can be reached based on these chromatograms.

Figure 21 CYP1A2 Supersomes & Asenapine 20 µM

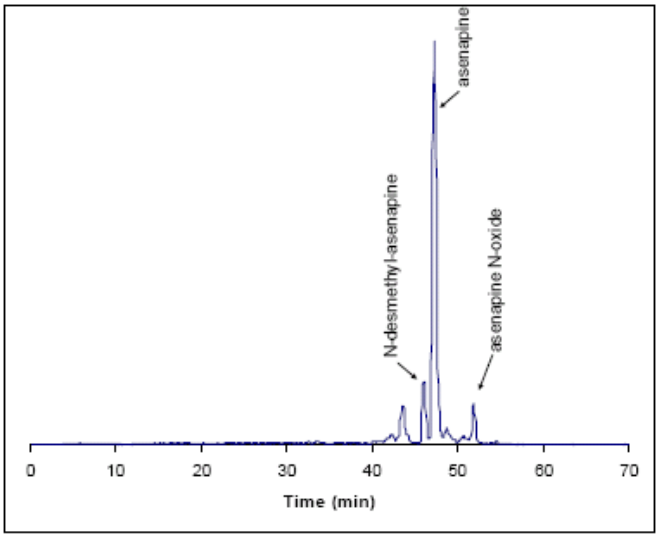


Figure 22 CYP3A4 Supersomes & Asenapine 20 µM

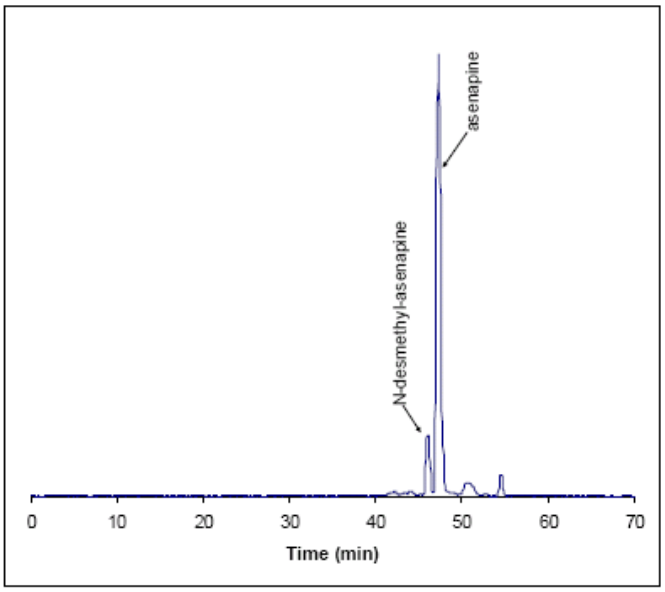


Figure 23 CYP2B6 Supersomes & Asenapine 20 µM

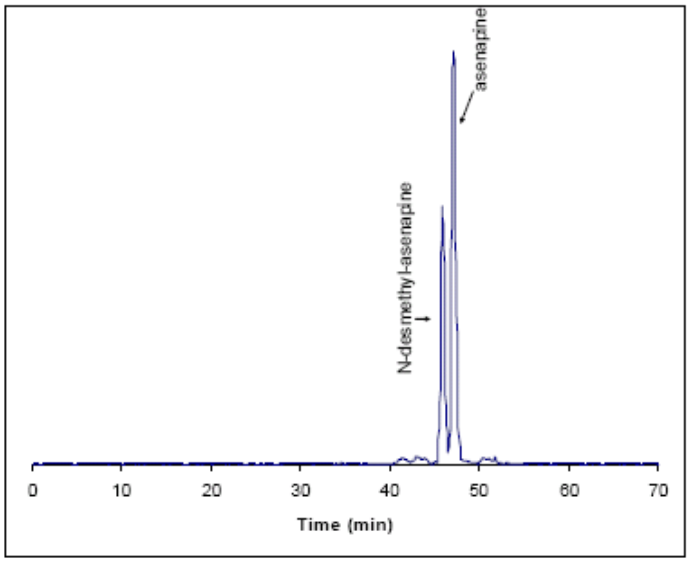


Figure 24 CYP2C19 Supersomes & Asenapine 20 µM

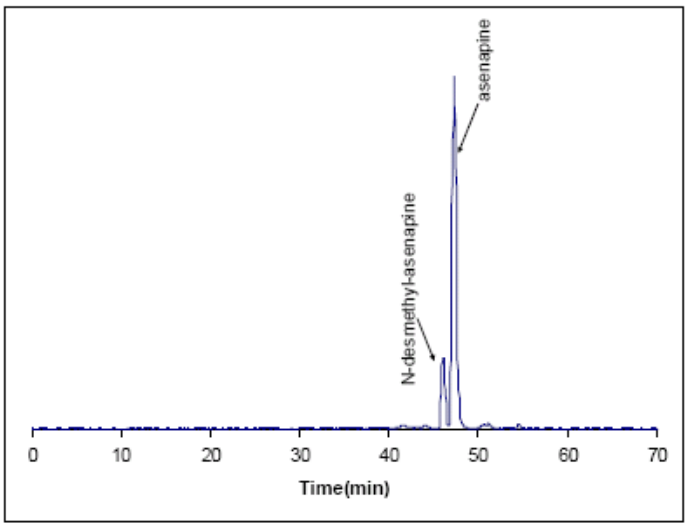
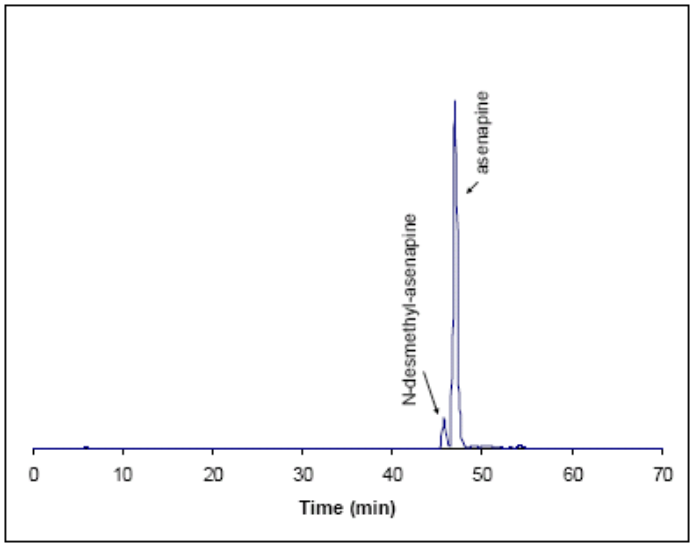


Figure 25 CYP2D6 Supersomes & Asenapine 2 µM



5.4.3.3.2.2.2 Protein Bound Metabolites with CYP2D6 Supersomes

For CYP2D6 the recovery of radioactivity was also determined by liquid scintillation counting (LSC) of the incubation fraction before the addition of acetonitrile and obtaining the supernatant. In each case recovery after centrifugation was less after incubation of CYP2D6, and even in the presence of CYP2D6 the recovery was greater at the higher asenapine concentration, (see Table 38).

Taken together this indicates binding of a reactive metabolite to the microsomal protein which is concentration dependent. The most likely candidate for a chemically reactive metabolite due to asenapine is the (N2-oxide).

Table 38 Radioactivity Bound to Microsomal Protein after Incubation of Asenapine with CYP2D6 - NL0060848 (2005)

Incubation Time (minutes)	Supersome	Asenapine Concentration	Replicate	Activity before acetonitrile (kBq)	Activity after centrifugation (kBq)	Recovery (%)
5 min	CYP2D6	1.4 nMol/L	A	1.5	1.2	77
			B	1.6	1.2	73
	Inactive Control	1.4 nMol/L	–	1.4	1.2	90
	CYP2D6	2 µMol/L	A	205.0	165.3	81
			B	206.1	166.3	81
	Inactive Control	2 µMol/L	–	206.1	183.9	89
15 min	CYP2D6	1.4 nMol/L	A	1.4	1.0	72
			B	1.5	1.0	70
	Inactive Control	1.4 nMol/L	–	1.3	1.2	88
	CYP2D6	2 µMol/L	A	199.0	156.0	78
			B	208.1	159.9	77
	Inactive Control	2 µMmol/L	–	197.8	167.5	85

Consequently, asenapine appears to be a suicide substrate inhibitor for CYP2D6 at supratherapeutic concentrations such as would occur on first pass after oral administration. As a suicide substrate, inhibition of CYP2D6 would be due to a decrease in the total amount of enzyme and would result in inhibition in CYP2D6 poor metabolizers as well as in extensive metabolizers and would not be overcome with increasing substrate concentrations. In addition, recovery might take several weeks until the enzyme has had time to regenerate, thus there would be issues with administering other CYP2D6 substrates even after asenapine could no longer be detected in plasma. This would make switching from asenapine to many other antipsychotics or addition of other psychoactive drugs problematic.

5.4.3.3.2.2.3 Supersome Enzyme Kinetic Parameters

Next the sponsor determined of the Km and Vmax using supersomes expressing selected human CYPs.

Km and Vmax determinations were performed for CYP1A2, CYP2B6, CYP2C19, CYP2D6 and CYP3A4. Supersomes were incubated for 15 minutes at 37°C with different concentrations of [^{14}C]-asenapine or [^{3}H]-asenapine in the case of CYP2D6. Asenapine concentrations used were as follows:

CYP1A2	0.5, 1, 2, 5, 10, 20, 50, and 100 µmol/L
CYP2B6	0.5, 1, 2, 5, 10, 20, 50, 100, 250, and 500 µmol/L
CYP2C19	0.5, 1, 2, 5, 10, 20, 50, and 100 µmol/L µmol/L
CYP2D6	1, 2, 5, 10, 20, 50, 100, 200, 500 and 2000 µmol/L
CYP3A4	0.5, 1, 2, 5, 10, 20, 50, 100, 250, and 500 µmol/L

Results are shown in Table 39. The sponsor only reported Vmaxs and Kms and since the same amount of microsomal protein was used in each experiment the sponsor only focused on the Km. However when intrinsic clearances are calculated the relative importance is more easily discernable. In addition when the relative abundance of these isozymes *in vivo* are considered CYP3A4 is likely to be even more important especially with oral administration.

Table 39 Enzyme Kinetic Parameters of Asenapine Disappearance in Supersomes – Study NL0060848 (2005)

Supersome Isozyme	Vmax (pMol/min x pMol P450^{-1})	Km (µMol/L)	Clint (L/min x pmol P450^{-1})
CYP1A2	10.2	24.5	**41,626**
CYP2B6	100.1	333.5	30,015
CYP2C19	15.9	68.5	23,212
CYP2D6	0.18	0.30	**60,000**
CYP3A4	139.7	936.6	14,916

5.4.3.4 Other Enzyme Systems

Other enzyme systems that might be expected to further metabolize asenapine and its metabolites based on the *in vivo* data and information from other drugs were not examined. These include:

Sulfation	Phenol Sulfotransferases
N-oxidation	Cytosolic N-Oxidases
Methylation	Catechol O-Methyl-Transferases.

Based on the *in vitro* information, NADPH independent oxidation by FMO does not appear to be a significant at clinical concentrations.

Other enzyme systems involved with detoxification of the N-oxide were also not examined.

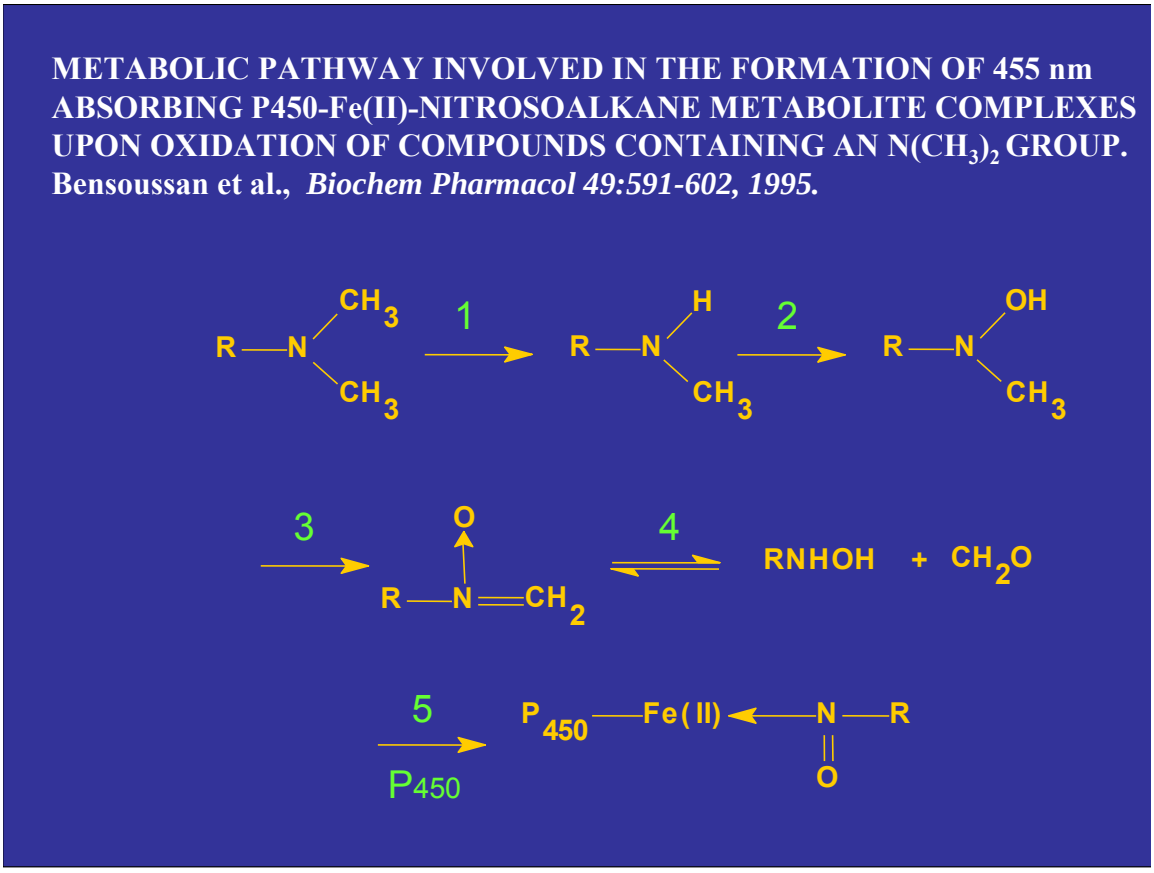
5.4.3.5 *In Vitro Inhibition by Asenapine and Metabolites*

Inhibition by asenapine and selected metabolites were examined *in vitro* in pooled human liver microsomes, (study DM2005-005222-009) and in GENTEST insect derived supersomes of human CYPs in studies NL0017588, NL0013163, NL0048836, NL0050059, and NL0050307.

Results of these studies indicate that asenapine, N-desmethyl-asenapine, and asenapine N-oxide, are all potent inhibitors of CYP2D6 with Ki's in the range of 6 – 85 nMol/L, which are at or somewhat above therapeutic concentrations. However, more important than the Kis is the fact that the N-desmethyl-metabolite is a noncompetitive inhibitor, i.e. a suicide substrate. Thus even with low doses inhibition will increase over time until a steady-state is reached. However if asenapine is swallowed the high concentrations achieved with such rapid delivery will result in a much greater degree of inhibition.

N-oxides are known to be potent suicide substrate inhibitors as shown by Figure 26. Although Figure 26 shows inactivation of by a nitrosoalkane whereas asenapine is a heterocyclic N-oxide, the evidence clearly points to suicide inactivation by asenapine regardless of whether the exact mechanism is the same or not.

Figure 26 Slide from FDA Presentation on N-Oxide Suicide Substrate Inhibition – Article from 1995



In addition a 1999[4] article on inhibition of CYP2D6 by antipsychotics, most of the antipsychotics examined were competitive inhibitors, although several were partial competitive and cis-thiothixene, and clozapine had greater inhibition with pre-incubation, and inhibition by metabolites was not examined.

[4] DMD (1999), Vol 27, no. 9 1078 – 1083.

This indicates that clozapine or a metabolite is also a mechanism based inhibitor of CYP2D6. See Figure 27 and Figure 28 for a comparison of the structures of these two dibenzo antipsychotics.

Figure 27 Structure of Asenapine

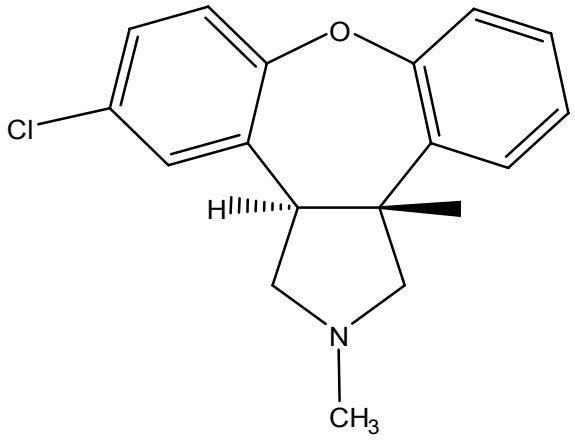
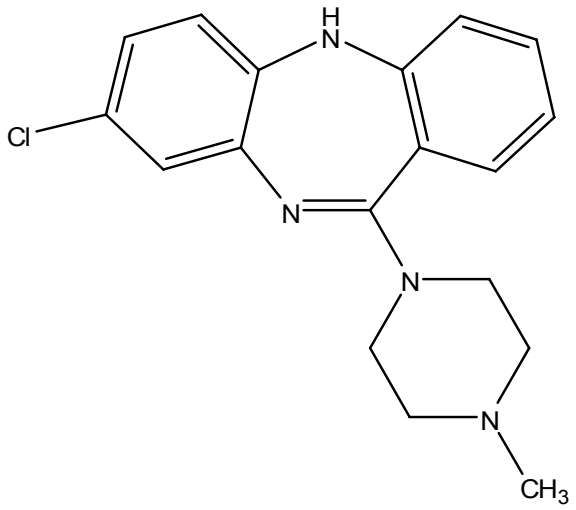


Figure 28 Structure of Clozapine



5.4.3.5.1 *In Vitro* Inhibition of P450 CYPs in Supersomes

A summary of the sponsor's results and the enzyme kinetic parameters reported may be found in Table 41 and Table 42 respectively.

It should be noted that no units were reported for Vmax. Consequently intrinsic clearances cannot be calculated.

In addition, since only 2 concentrations were examined and since high substrate inhibition is expected, fitting of the data to a Michaelis-Menton Model, the estimates of the apparent enzyme kinetic parameters, and the proposed mechanism of inhibition derived from nonlinear regression and the fit to a structural model cannot be considered reliable. However even if an adequate range of concentrations were studied this reviewer is uncertain of the advantages and disadvantages of the use of nonlinear regression as compared to other methods for determining the mechanism of inhibition, but believes that other methods would be preferable. In spite of this the totality of the data suggests that noncompetitive with CYP2D6 is likely.

In spite of the examination of the N-desmethyl-asenapine and asenapine N-oxide metabolites, the lack of information on the 11 and 7 – O asenapine metabolites limits the interpretability of the results.

Experimental conditions for supersomes were fairly similar across studies so they will be reviewed together rather than separately

GENTEST insect derived supersomes of human CYPs were incubated at 37 ^{o}C with their specific substrates in the presence or absence of asenapine, asenapine metabolites or specific reference inhibitors. The substrates and reference inhibitors used are shown in Table 40.

Table 40 CYP P450 Enzyme Specific Substrates and Reference Inhibitors used in Supersome Experiments

Study	Isozyme	Substrate	Product	Control Inhibitor
NL0017588	1A2	7-ethoxy-3-cyanocoumarin (CEC)	7-ethoxy-3-hydrocoumarin (CHC);	furafylline
NL0017588 NL0048836 NL0050307	2D6	3-[2-(N,N-diethyl-N-methylamino)-ethyl]-7-methoxy-4-methylcoumarin (AMMC)	3-[2-(N,N-diethylamino)-ethyl]-7-hydroxy-4-methylcoumarin (AHMC)	quinidine
NL0013163	2C19	mephenytoin	4-Hydroxy-mephenytoin	tranylcypromine
	3A4 (a) 3A4 (b)	testosterone	6ß-hydroxytestosterone	ketoconazole
NL0050059	1A2	7-ethoxy-3-cyanocoumarin (CEC)	7-ethoxy-3-hydrocoumarin (CHC)	furafylline
	2A6	Coumarin	7-hydroxycoumarin (7-HC)	tranylcypromine
	2C8	D benzylfluorescein (DBF)	fluorescein	quercetin
	2C9	7-methoxy-4-trifluoromethylcoumarin (MFC)	7-hydroxy-4-trifluoromethylcoumarin (HFC)	sulfaphenazole
	2C19	D benzylfluorescein (DBF)	fluorescein	tranylcypromine
	3A4 (1)	Benzyloxyresorufin (BzRes)	resorufin	ketoconazole
	3A4 (2)	7-benzyloxyquinoline (BQ)	7-hydroxyquinoline (7-HQ)	ketoconazole

An early study assessed linearity of CYP2D6 activity with different buffers, and experiments used different buffer systems. The final % of organic solvent used to dissolve substrates was generally not reported. In earlier experiments mentioned in previous sections this was a problem but it appears that this may have been taken care of for most of the supersome experiments.

For the most part information was not provided on the preliminary experiments to establish conditions, however it appears the sponsor was aware of the issues involved and even if the actual enzyme kinetic parameters are off this should not effect the general conclusions.

Studies NL0048836 and NL0050307 that assessed the ability of asenapine, N-desmethyl-asenapine, and asenapine N-oxide(s) to inhibit CYP2D6 utilized NADPH regenerating systems whereas other studies only used NADPH itself.

For study NL0013163 product formation of 4-OH-mephenytoin and 6ß-hydroxytestosterone were quantified by HPLC, whereas for other experiments the fluorescent products formed during the enzymatic incubation were quantified using a fluorometer to determine the initial formation rates.

In each study two sets of experiments were performed for each inhibitor.

First the IC_{50} values for asenapine, asenapine metabolites, and the reference inhibitors for the individual cytochrome P450 enzymes were determined using a series of increasing asenapine, metabolite or reference inhibitor concentrations, and then the IC_{50} was calculated by interpolation using the following formula:

IC50 = (50% Inhibition - % Inhibition at First Incubate concentration < IC50) / (%Inhibition at First Incubate Concentration > IC50 - % Inhibition at First Incubate concentration) x (Conc at First Conc > IC50 – Conc at First Conc < IC50) % Inhibition + Conc at First Conc < IC50

An example follows:

Figure 29 Example of IC_{50} Determinations in a Supersome Experiment

Table 8.1.1 IC50 determination Org 10968 for CYP2D6

Concentration Org 10968 ($nmol \cdot L^{-1}$)	Concentration AMMC ($\mu mol \cdot L^{-1}$)	AHMC production (units/pmol CYP2D6/min)	Inhibition (%)
250	1.5	50.667	88.9
125	1.5	108.07	76.3
62.5	1.5	201.37	55.8
31.3	1.5	301.08	33.8
15.6	1.5	377.84	17.0
7.8	1.5	406.63	10.6
3.9	1.5	410.52	9.8
2.0	1.5	427.97	6.0
0.98	1.5	421.28	7.4
0	1.5	455.09	0.0

Incubations were performed in duplicate.

IC50 calculation :

$((50-33.8)/(55.8-33.8)x(62.5-31.3))+ 31.3\ nmol \cdot L^{-1} = \mathbf{54.27\ nmol \cdot L^{-1}}$

Based on these IC50 values, two asenapine or two asenapine metabolite and two reference inhibitor concentrations were chosen in the final inhibition experiments with increasing substrate concentrations for the CYP isozyme. An example of the type of data generated follows:

Figure 30 Example of the Type of Data Generated for Enzyme Kinetic Inhibition Parameter Estimates

Table 8.2.1 CYP2D6 inhibition by Org 10968

	AHMC production (units/pmol CYP2D6/min)		
Concentration AMMC ($\mu mol \cdot L^{-1}$)	0 $nmol \cdot L^{-1}$ Org 10968	2 $nmol \cdot L^{-1}$ Org 10968	20 $nmol \cdot L^{-1}$ Org 10968
10	796.03	875.10	722.42
5	666.33	677.18	582.11
2.5	564.74	567.88	469.61
1.25	458.76	436.23	351.03
0.625	318.93	323.30	246.92
0.313	219.45	202.08	160.22
0.156	130.39	129.38	91.083

Incubations were performed in duplicate.

From these final experiments the inhibition constants (Ki) as well as the type of inhibition (competitive, non- competitive, mixed competitive or uncompetitive) were determined using the curve-fitting program for the analysis of enzyme kinetic data "EZ-FIT"[5].

[5] Perrella FW (1988) EZ-FIT: A practical curve-fitting microcomputer program for the analysis of enzyme kinetic data on IBM-PC compatible computers. Analytical Biochemistry, 174(2):437-47.

Table 41 Summary of Results of *In Vitro* Cytochrome P450 Inhibition Studies with Asenapine and Selected Metabolites

Study	Date	Test System	Isozyme	Inhibitor	Ki	Claimed Type of Inhibition
NL0017588	Dec 1999	Supersomes	1A2	Asenapine	2.6 µMol	Competitive
			2D6		6.75 nMol	Competitive
NL0013163	April 1999	Supersomes	2C19	Asenapine	25.15	uncompetitive
			3A4 (a) 3A4 (b)		91.4 125.59	Mixed-competitive ? ?
NL0048836	Aug 2003	Supersomes	2D6	Asenapine	16.2 nMol	Competitive
				30526 N-Desmethyl	62.08 nMol	Noncompetitive
				31437 N-Oxide	82.62 nMol	Competitive
NL0050059	Oct 2003	Supersomes	1A2	Asenapine (N.B. CYP2D6 not studied)	1.5 µMol	Competitive
			2C8		360.44 µMol	Noncompetitive
			2C9		105.19 µMol	Uncompetitive
			2C19		2.0 µMol	Competitive
			3A4 (1)		33.24 µMol	Noncompetitive
			1A2	30526 N-Desmethyl-Asenapine (N.B. CYP2D6 not studied)	1.4 µMol	Noncompetitive
			2A6		70.31 µMol	Competitive
			2C8		80.33 µMol	Noncompetitive
			2C9		172.34 µMol	Noncompetitive
			2C19		1.78 µMol	Competitive
			3A4 (1)		3.53 µMol	Competitive
			1A2	31437 N-oxide (N.B. CYP2D6 not studied)	No inhibition	
			2A6			
			2C8			
			2C9			
			2C19			
			3A4 (1)			
			3A4 (2)			
NL0050307	Oct 2003	Supersomes	2D6	10968 N(2)-Oxide	26.72 nMol	Competitive
			2D6	10969 N(2)-Oxide	12.43 nMol	Competitive
DM2005-005222-009	Dec 2005	Pooled Human Liver Microsomes (HLM)	CYP1A2	Asenapine	6.9 µMol[a]	
			CYP2B6		> 30 µMol[a]	
			CYP2C8		> 30 µMol[a]	
			CYP2C9		> 30 µMol[a]	
			CYP2C19		> 30 µMol[a]	
			CYP2D6		44 nMol[a]	
			CYP3A		> 30 µMol[a]	
			CYP3A		> 30 µMol[a]	

a IC50

Table 42 Reported Enzyme Kinetic Parameters from *In Vitro* Cytochrome P450 Inhibition Studies with Asenapine and Selected Metabolites

Study	CYP	Substrate	Org 5222 (µmol/L)	Km (µmol/L)	Vmax (units/pmol CYP1A2/min)	Model	Km (µmol/L)	Vmax (units/pmol CYP1A2/min)	Ki (µmol/L)	AIC	Runs test
NL0017588	1A2	Asenapine	0	2.69	157.9	***Competitive***	***3.08***	***165.9***	***2.06***	***119.3***	***Passes***
			1.5	7.92 a	196.7 b	***Non-Competitive***	***4.63***	***185.7***	***8.90***	***134.1***	***Fails***
			3	6.56 a	156.6 b	***Mixed Competitive***	***3.09***	***165.9***	***2.06***	***121.3***	***Passes***
						Uncompetitive	5.37	189.7	7.41 ***3916***	141.2	Fails
	2D6	**Asenapine**	**Org 5222 (nmol/L)**	**Km (µmol/L)**	**Vmax (units/pmol CYP2D6/min)**	**Model**	**Km (µmol/L)**	**Vmax (units/pmol CYP2D6/min)**	**Ki (nmol/L)**	**AIC**	**Runs test**
			0	0.72	7.03	***Competitive***	***0.71***	***6.97***	***6.75***	***3.78***	***Passes***
			4	1.10 a	6.84 b	Non-Competitive	0.99	7.52	35.3	16.2	Passes
			6	1.35 a	7.03 b	Mixed Competitive	0.72	6.99	6.93 843.8	5.76	Passes
						Uncompetitive	1.08	7.56	32.7	21.8	Fails
NL0013163	**2C19**	**Asenapine**	**Org 5222 (µmol/L)**	**Km (µmol/L)**	**Vmax (pmol/pmol CYP2C19/min)**	**Model**	**Km (µmol/L)**	**Vmax (pmol/pmol CYP2C19/min)**	**Ki (µmol/L)**	**AIC**	**Runs test**
			0	33.87	0.37	Competitive	28.00	0.35	7.49	90.4	Passes
			5	36.02 a	0.33 b	Non-Competitive	38.67	0.38	30.83	92.0	Passes
			7.5	52.15 a	0.33 b	Mixed Competitive	33.02	0.37	12.98 50.43	91.6	Passes
						Uncompetitive	***43.97***	***0.39***	***25.16***	***88.4***	***Passes***
	3A4	**Asenapine**	**Org 5222 (µmol/L)**	**Km (µmol/L)**	**Vmax (pmol/pmol CYP3A4/min)**	**Model**	**Km (µmol/L)**	**Vmax (pmol/pmol CYP3A4/min)**	**Ki (µmol/L)**	**AIC**	**Runs test**
			0	29.54	1.67	Competitive	23.02	1.51	34.87	0.48	Passes
			25	36.49 a	1.49 b	Non-Competitive	31.45	1.70	114.27	1.8	Passes
			40	29.73 a	1.22 b	***Mixed Competitive***	***30.25***	***1.69***	***91.40 125.59***	***0.21***	***Passes***
						Uncompetitive	36.98	1.76	86.44	1.3	Passes
NL0048836	**2D6**	**Asenapine**	**Org 5222 (µmol/L)**	**Km a (µmol/L)**	**Vmax b (units/pmol CYP2D6/min)**	**Model**	**Km (µmol/L)**	**Vmax (units/pmol CYP2D6/min)**	**Ki (nmol/L)**	**GoF**	**Runs test**
			0	0.83	521.17	***Competitive***	***0.77***	***497.90***	***16.02***	***-0.05***	***Passes***
			2	0.87	483.36	Non-Competitive	0.90	518.97	66.00	-0.04	Passes
			8	1.03	483.81	Lin. Mixed Competitive	0.82	508.44	C C	0.98	Passes
						Uncompetitive	0.94	522.68	56.02	0.01	Passes
	2D6	**Org 30526 N-Desmethyl-Asenapine**	**Org 30526 (nmol/L)**	**Km a (µmol/L)**	**Vmax b (units/pmol CYP2D6/min)**	**Model**	**Km (µmol/L)**	**Vmax (units/pmol CYP2D6/min)**	**Ki (nmol/L)**	**GoF**	**Runs test**
			0	1.41	665.71	Competitive	0.79	535.21	19.35	1.05	Passes
			10	0.59		***Non-Competitive***	***1.07***	***600.96***	***62.08***	***0.88***	***Passes***
			20	1.60	413.06	Lin. Mixed Competitive	0.79	535.23	C C	2.10	Passes
					542.47	Uncompetitive	1.26	625.65	45.15	0.89	Passes

			Org 30526 (nmol/L)	Km a (µmol/L)	Vmax b (units/pmol CYP2D6/min)	Model	Km (µmol/L)	Vmax (units/pmol CYP2D6/min)	Ki (nmol/L)	GoF	Runs test
	2D6	Org 31437 Asenapine N-Oxide	0	0.90	531.46	***Competitive***	***0.95***	***542.66***	***82.62***	***0.62***	***Passes***
			40	1.42	549.46	Non-Competitive	1.29	582.14	419.8	0.77	Passes
			80	2.07	560.41	Lin. Mixed Competitive	0.95	542.69	82.67 C	1.2	Passes
						Uncompetitive	1.41	586.54	C	1.3	Passes
NL0050059			**Org 5222 (µmol/L)**	**Km a (µmol/L)**	**Vmax b (units/pmol CYP1A2/min)**	**Model**	**Km (µmol/L)**	**Vmax (units/pmol CYP1A2/min)**	**Ki (µmol/L)**	**GoF**	**Runs test**
	1A2	**Asenapine**	0	1.29	2479	***Competitive***	***1.42***	***2610***	***1.50***	***-1.010***	***Passes***
			0.3	1.62	2672	Non-Competitive	1.68	2667	c	-0.135	Passes
			0.6	2.40	2734	Lin. Mixed Inhibition	1.42	2610	1.50 C	-0.438	Passes
						Uncompetitive	1.71	2644	C	- 0.067	Passes
			Org 5222 (µmol/L)	**Km a (µmol/L)**	**Vmax b (units/pmol CYP2C8/min)**	**Model**	**Km (µmol/L)**	**Vmax (units/pmol CYP2C8/min)**	**Ki (µmol/L)**	**GoF**	**Runs test**
	2C8	**Asenapine**	0	0.51	268	Competitive	0.44	254	120.91	0.466	Passes
			10	0.52	265	***Non-Competitive***	***0.51***	***270***	***360.44***	***0.250***	***Passes***
			80	0.49	219	Lin. Mixed Inhibition	0.52	271	C c	1.297	Passes
						Uncompetitive	0.55	274	279.78	0.273	Passes
			Org 5222 (µmol/L)	**Km a (µmol/L)**	**Vmax b (units/pmol CYP2C9/min)**	**Model**	**Km (µmol/L)**	**Vmax (units/pmol CYP2C9/min)**	**Ki (µmol/L)**	**GoF**	**Runs test**
	2C9	**Asenapine**	0	14.76	536	Competitive	10.96	501	24.65	-0.108	Passes
			5	10.24	485	Non-Competitive	13.71	530	118.42	-0.187	Passes
			20	18.40	480	Lin. Mixed Inhibition	12.27	519	41.54 C	0.278	Passes
						Uncompetitive	14.56	533	105.19	-0.362	Passes
			Org 5222 (µmol/L)	**Km a (µmol/L)**	**Vmax b (units/pmol CYP2C19/min)**	**Model**	**Km (µmol/L)**	**Vmax (units/pmol CYP2C19/min)**	**Ki (µmol/L)**	**GoF**	**Runs test**
	2C19	**Asenapine**	0	1.18	104	***Competitive***	***1.22***	***103***	***2.00***	***-2.086***	***Passes***
			0.05	1.24	100	Non-Competitive	1.32	106	6.56	-1.779	Passes
			0.5	1.61	106	Lin. Mixed Inhibition	1.22	103	2.00 C	-1.420	Passes
						Uncompetitive	1.35	106	5.55	-1.579	Passes
			Org 5222 (µmol/L)	**Km a (µmol/L)**	**Vmax b (units/pmol CYP3A4/min)**	**Model**	**Km (µmol/L)**	**Vmax (units/pmol CYP3A4/min)**	**Ki (µmol/L)**	**GoF**	**Runs test**
	3A4	**Asenapine**	0	2.60	767	Competitive	2.24	736	9.77	-1.393	Passes
			1	2.47	747	***Non-Competitive***	***2.55***	***768***	***33.24***	***-2.749***	***Passes***
			4	2.59	686	Lin. Mixed Inhibition	2.54	768	31.10 (a=1.09)d	-2.655	Passes
						Uncompetitive	2.68	774	27.84	-2.474	Passes

	1A2	Org 30526 N-Desmethyl-Asenapine	Org 30526 (µmol/L)	Km a (µmol/L)	Vmax b (units/pmol CYP1A2/min)	Model	Km (µmol/L)	Vmax (units/pmol CYP1A2/min)	Ki (µmol/L)	GoF	Runs test
			0	0.96	1919	Competitive	0.7	1722	0.30	0.383	Passes
			0.2	1.07	1683	***Non-Competitive***	***1.03***	***1935***	***1.40***	***-0.835***	***Passes***
			0.6	1.15	1396	Lin. Mixed Inhibition	0.96	1911	0.90 (a=1.77)c	-0.802 -	Passes
						Uncompetitive	1.18	1972	1.18	0.396	Passes
	2C8	Org 30526 N-Desmethyl-Asenapine	Org 30526 (µmol/L)	Km a (µmol/L)	Vmax b (units/pmol CYP2C8/min)	Model	Km (µmol/L)	Vmax (units/pmol CYP2C8/min)	Ki (µmol/L)	GoF	Runs test
			0	0.58	243	Competitive	0.52	230	21.06	-0.502	Passes
			10	0.87	238	***Non-Competitive***	***0.71***	***255***	***80.33***	***-0.836***	***Passes***
			30	0.76	190	Lin. Mixed Inhibition	0.63	247	41.98 c	-0.371	Passes
						Uncompetitive	0.81	261	62.57	-0.465	Passes
	2C9	Org 30526 N-Desmethyl-Asenapine	Org 30526 (µmol/L)	Km a (µmol/L)	Vmax b (units/pmol CYP2C9/min)	Model	Km (µmol/L)	Vmax (units/pmol CYP2C9/min)	Ki (µmol/L)	GoF	Runs test
			0	6.82	381	Competitive	5.00	352	c	1.994	Passes
			20	7.67	367	***Non-Competitive***	***6.92***	***388***	***172.34***	***1.152***	***Passes***
			40	6.09	300	Lin. Mixed Inhibition	7.15	389	C C	2.198	Passes
						Uncompetitive	7.67	393	149.58	1.161	Passes
	2C19	Org 30526 N-Desmethyl-Asenapine	Org 30526 (µmol/L)	Km a (µmol/L)	Vmax b (units/pmol CYP2C19/min)	Model	Km (µmol/L)	Vmax (units/pmol CYP2C19/min)	Ki (µmol/L)	GoF	Runs test
			0	1.51	110	***Competitive***	***1.47***	***107***	***1.78***	***-1.753***	***Passes***
			0.04	1.46	103	Non-Competitive	1.55	109	4.82	-1.700	Passes
			0.3	1.70	107	Lin. Mixed Inhibition	1.47	107	C C	-0.531	Passes
						Uncompetitive	1.59	110	c	-1.063	Passes
	3A4	Org 30526 N-Desmethyl-Asenapine	Org 30526 (µmol/L)	Km a (µmol/L)	Vmax b (units/pmol CYP3A4/min)	Model	Km (µmol/L)	Vmax (units/pmol CYP3A4/min)	Ki (µmol/L)	GoF	Runs test
			0	1.93	659	***Competitive***	***1.97***	***658***	***3.53***	***-0.068***	***Passes***
			0.8	2.57	659	Non-Competitive	2.35	679	c	0.545	Passes
			1.6	2.75	657	Lin. Mixed Inhibition	1.97	658	C C	0.980	Passes
						Uncompetitive	2.42	677	c	0.598	Passes
NL0050307	2D6	Org 10968 Asenapine N-Oxide (1)	Org 10968 (nmol/L)	Km a (µmol/L)	Vmax b (units/pmol CYP2D6/min)	Model	Km (µmol/L)	Vmax (units/pmol CYP2D6/min)	Ki (nmol/L)	GoF	Runs test
			0	1.02	834.73	***Competitive***	***1.06***	***858.27***	***26.72***	***-0.593***	***Passes***
			2	1.34	924.83	Non-Competitive	1.25	900.75	104.15	-0.563	Passes
			20	1.53	796.19	Lin. Mixed Competitive	1.13	878.09	39.42 C	-0.100	Passes
						Uncompetitive	1.33	910.58	84.51	-0.386	Passes
		[redacted]									

			Org 10969 (nmol/L)	Km a (µmol/L)	Vmax b (units/pmol CYP2D6/min)	Model	Km (µmol/L)	Vmax (units/pmol CYP2D6/min)	Ki (nmol/L)	GoF	Runs test
		Org 10969 Asenapine N-Oxide (2)	0	0.97	814.66	***Competitive***	***0.92***	***794.55***	***12.43***	***-0.791***	***Passes***
			3	1.21	804.28	Non-Competitive	1.16	847.30	51.94	-0.722	Passes
			11	1.43	742.33	Lin. Mixed Competitive	1.00	817.92	18.07 C	-0.321	Passes
						Uncompetitive	1.26	858.59	42.69	-0.488	Passes

a : apparent Km
b : apparent Vmax
c : Redundant
d : a = factor between inhibition constant 1(=Ki) and inhibition constant 2 in the linear mixed inhibition model
GoF : Goodness of Fit. The model giving the lowest value of GoF is considered the best fit.
Michaelis-Menten Model v = Vmax*([S]/(Km + [S]))

5.4.3.5.2 *In Vitro* Inhibition of P450 CYPs by Asenapine in Pooled Human Liver Microsomes- Study DM2005-005222-009

Asenapine was examined for effects on several drug metabolizing enzyme activities in pooled human liver microsomes. Seven concentrations ranging from 0.0952 - 30.0 μM or 0.00952 - 3.00 μM, including 0, were evaluated in duplicate and IC_{50}s were determined by interpolation. Other incubation conditions are shown in Table 43.

Table 43 Incubation Conditions with Human Liver Microsomes – Study DM2005-005222-009

Enzyme	Marker Substrate Activity	Substrate Concentration (μM)	Microsomal Protein Concentration (mg/mL)	Incubation Time (min)	Termination Solvent[a]
CYP1A2	Phenacetin O-Deethylase	50 μM	0.03	30	5/92/3
CYP2B6	Bupropion Hydroxylase	80 μM	0.05	20	5/92/3
CYP2C8	Amodiaquine N-Deethylase	1.9 μM	0.025	10	5/92/3
CYP2C9	Diclofenac 4'-Hydroxylase	4 μM	0.03	10	5/92/3
CYP2C19	S-Mephenytoin 4'-Hydroxylase	60 μM	0.2	40	5/92/3
CYP2D6	Dextromethorphan O-Demethylase	5 μM	0.03	10	5/92/3
CYP3A	Felodipine Oxidase	2.8 μM	0.01	10	50/47/3
CYP3A	Midazolam 1'-Hydroxylase	2.5 μM	0.03	4	92/5/3
CYP3A	Testosterone 6β-Hydroxylase	50 μM	0.03	10	5/92/3

a Termination solvent ratio = Acetonitrile/Water/Formic Acid

The percent activity remaining at the maximum concentration studied (30 mM) and the estimated IC_{50}s are shown in Table 44.

Asenapine demonstrated marked inhibition of CYP2D6 and moderate inhibition of CYP1A2 activities with respective IC_{50}s of 44 and 610 nMol/L, and little or no inhibition of CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A. This suggests that the greatest potential for an interaction with asenapine is with compounds cleared by CYP2D6 followed by compounds cleared by CYP1A2, (see Table 44). However it should be remembered that metabolites have not been tested in this system.

Table 44 Summary of IC_{50} Data for Asenapine in Human Liver Microsomes – Study DM2005-005222-009

Enzyme	Marker Substrate Activity	% of control at [I] = 30 μM	IC50 (μM) Mean ± SE	IC50 (nM)
CYP1A2	Phenacetin O-Deethylase	6.9	0.61 ± 0.05	610
CYP2B6	Bupropion Hydroxylase	91	>30	
CYP2C8	Amodiaquine N-Deethylase	78	>30	
CYP2C9	Diclofenac 4'-Hydroxylase	95	>30	
CYP2C19	S-Mephenytoin 4'-Hydroxylase	84	>30	
CYP2D6	Dextromethorphan O-Demethylase	3.3a	0.044 ± 0.001	44
CYP3A	Felodipine Oxidase	65	>30	
CYP3A	Midazolam 1'-Hydroxylase	120	>30	
CYP3A	Testosterone 6β-Hydroxylase	58	>30	

a % of Control at 3 μM

5.4.3.6 Induction by Asenapine In Vitro

5.4.3.6.1 Induction of CYP1A2 and CYP3A4

In vitro experiments in 4 batches [2 fresh (HU cell lines) and 2 cryopreserved] of human hepatocytes were performed by Pfizer to evaluate the potential for asenapine to induce of CYPs 1A2 and 3A4. No evidence of induction was found. However, asenapine metabolites were not assessed nor were the effects on transporters or other enzyme systems, (e.g. glucuronosyl-transferases).

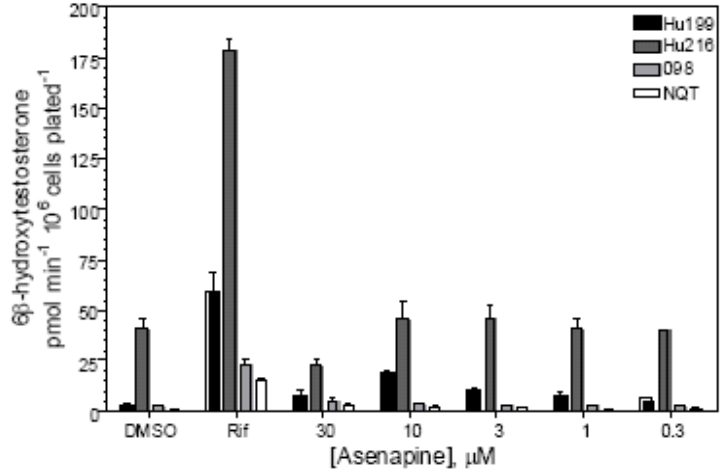
Results for CYP3A4 are shown in Figure 31 and Figure 32, and results for CYP1A2 are shown in Figure 33 and Figure 34.

The following information on the methodology used is from the sponsor:

'To evaluate the potential of a compound to induce drug metabolizing enzymes, we have implemented several assays to measure specific cytochrome P450 levels in vitro. These assays focus on induction of CYP3A4 and CYP1A2, and measure both enzyme activity and mRNA levels in freshly isolated and/or cryopreserved human hepatocytes. These assays include 10 µM rifampin as a positive control for CYP3A4 and 10 µM lansoprazole as a positive control for CYP1A2. Background controls treated with vehicle are included, and viability is measured at the conclusion of the experiment. Asenapine was tested at 5 concentrations (0.3 to 30 µM) in freshly isolated and cryopreserved hepatocytes from 4 separate donors. The rate of product formation was determined for each lot by LC-MS/MS, and results are normalized to percent of positive control using background (vehicle) as 0, and positive control as 100 (%control = (activity of test article mean background)/(mean activity of positive control - mean background) × 100). A compound is considered to be an in vitro inducer if it reaches 40% of the positive control with a dose-dependent increase in enzyme activity in 3 of the 4 hepatocyte lots tested.3 Measurement of CYP3A4 and CYP1A2 mRNA levels were performed using the TaqMan assays from Applied Biosystems, and fold increase over background (vehicle) was determined using relative quantification (RQ) based on cycle threshold (CT). Results of the TaqMan assay are not used alone to infer in vitro induction, but are used in support of enzyme activity data.'

Figure 31 A) Rate of 6β−Hydroxytestosterone Formation for Controls and Asenapine at 0 to 30 µM in Human Hepatocytes; B) Fold Induction for CYP3A4 for Controls and Asenapine at 0 to 30 µM in Human Hepatocytes - Study RR 764-04914

A)



B)

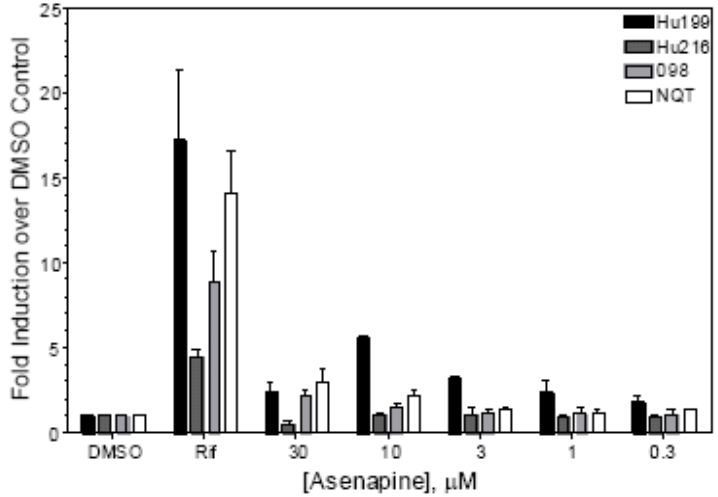
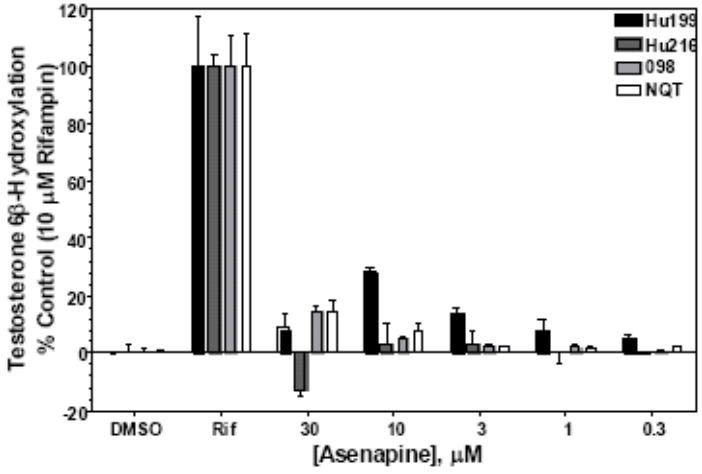


Figure 32 A) Rate of 6β-Hydroxytestosterone Formation Normalized to Percent of Positive Control for Controls and Asenapine at 0 to 30 µM in Human Hepatocytes; B) Mean Rate of 6β-Hydroxytestosterone Formation Normalized to Percent of Positive Control and Relative Quantitation (RQ) Values of CYP3A4 mRNA for Controls and Asenapine at 0 to 30 µM in Human Hepatocytes - Study RR 764-04914

A)



B)

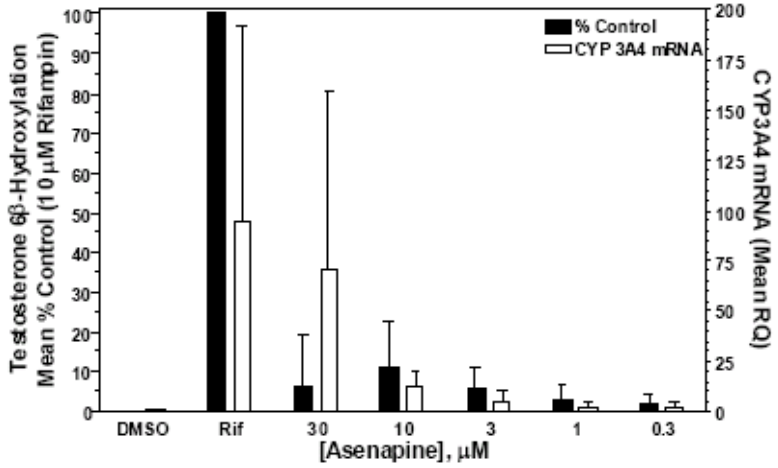
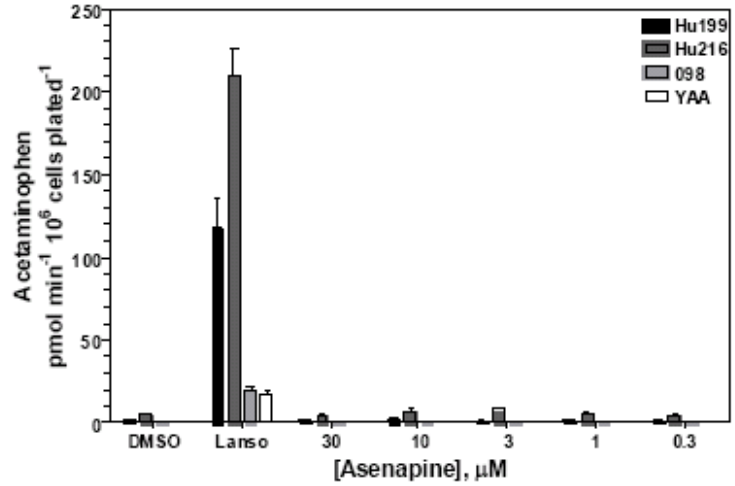


Figure 33 A) Rate of Acetaminophen Formation for Controls and Asenapine at 0 to 30 µM in Human Hepatocytes; B) Fold Induction for CYP1A2 for Controls and Asenapine at 0 to 30 µM in Human Hepatocytes

A)



B)

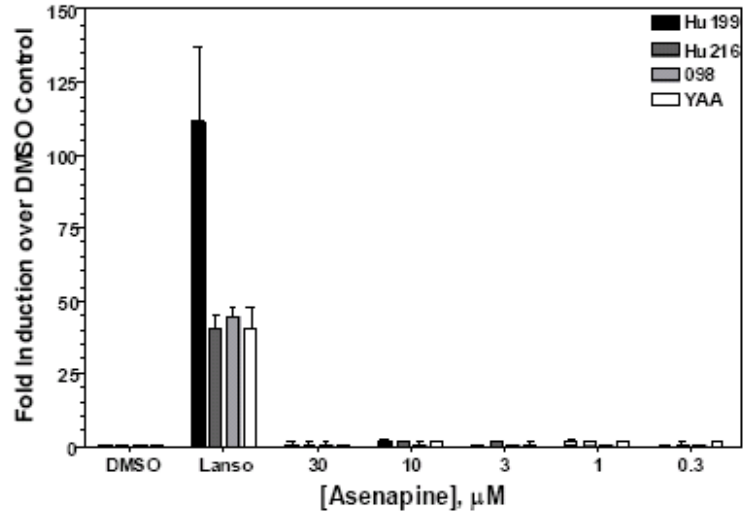
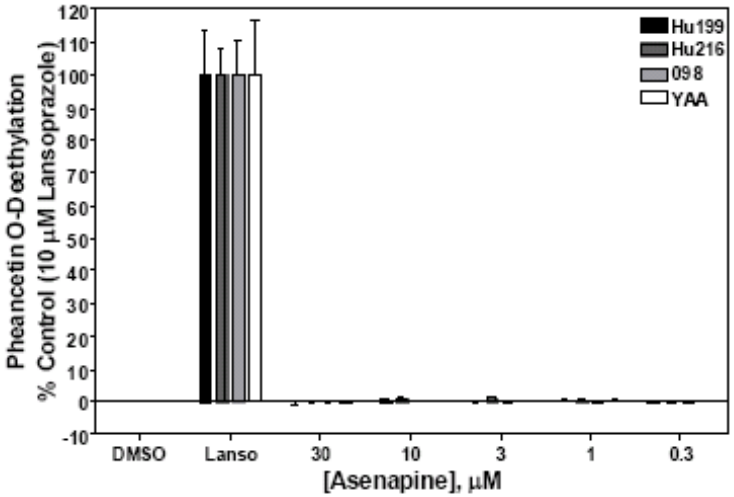


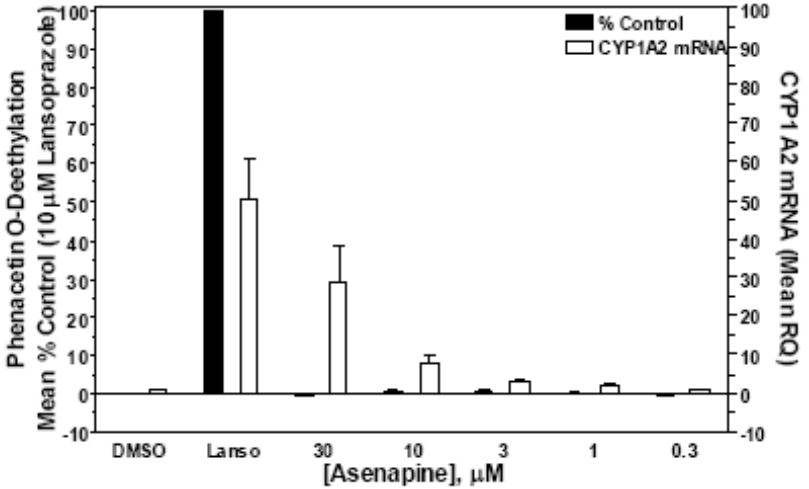
Figure 34 A) Rate of Acetaminophen Formation Normalized to Percent of Positive Control for Controls and Asenapine at 0 to 30 µM in Human Hepatocytes; B) Mean Rate of Acetaminophen Formation Normalized to Percent of Positive Control and

Relative Quantitation (RQ) Values of CYP1A2 mRNA for Controls and Asenapine at 0 to 30 µM in Human Hepatocytes

A)



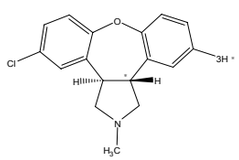
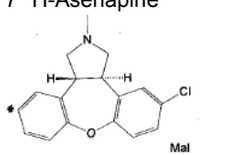
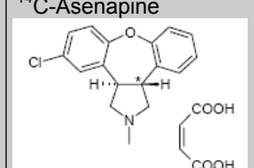
B)



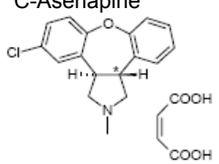
5.4.3.7 *Cross Species Comparison of Metabolites Detected In Vitro*

The following table was created for the scoping meeting to respond to a request from the Pharmacology/Toxicology reviewer in order to determine whether all human metabolites have been observed in toxicology studies. Coding for metabolites are per each individual study report. In general H*i* or M*i* stands for the *i*th metabolite by retention time from hepatocytes or microsomal incubations respectively. Where identification of metabolites was possible they are nominally shown below the metabolite code, in addition when metabolites with different codes (e.g. H15 and M7 can be identified in different experiments as the same metabolite they have been lined up.Species in red are human metabolites that can be matched to an animal metabolite and pink species are human metabolites that cannot be matched to animal metabolites. Species in blue are animal metabolites that were also detected as human metabolites in the same study and experimental conditions, whereas green indicates an animal metabolite that was also detected as a human metabolite in the same study but not under the same experimental conditions. Species in brown are amimal metabolites that cannot be matched to a human metabolite. Where available, the % recovery is included otherwise an X indicates the metabolite was detected and a **bold X** indicates that this was one of the dominant species recovered. By looking across columns it appears that most of the human metabolites here have been seen in animal species. In addition at the midcycle meeting held at the end of Janurary 2008 the pharm/tox reviewer again requested if there was any any new metabolism information that would be of interest to the pharm/tox reviewer. A few days later OCP was able to identify that 99.9% of the circulating radioactivity in humans had not been identified and that there were a number of unidentified metabolites that accounted for greater than 10% of the circulating exposures to asenapine.

Table 45 Cross Species Comparison of Metabolites Detected *In Vitro*

Study	System Studied	Radiolabeled Substrate	Conc	Species	Metabolite																
2874	Hepatic Microsomal incubation	7,11 ^{3}H, ^{14}C - Asenapine 	[redacted]				H1	H2	H3	H4	H5	H6	H7	H8	H9	H10	H11	H12	H13 H14	H15	As	H16
					Met 2	Met 3	11-O-SO_4(?)												N-oxide (diasteromers 1 & 2) Org 31437	N(2)-desmethy Org30526		
				Human	5.4 – 8.3	3.5 – 4.5													3.6 - 5.8	8.1 - 12.7		
			25 nMol/ml	Wistar Rat															74.8	5.8		
			25 μM	Dog															31.7	32.2		
5067	Hepatocyte Cell Medium	7 ^{3}H-Asenapine 	149 ng/ml	Human			37.7	9.3	3.2	**12.5**			2.8	6.9	11.9	1.1			9.1	4.0	1.6	
			219 ng/ml	Rat			10.8	7.1	5		2.8	1.7			6.0	2.7	1.7		6.8	5.4	49.4	1.2
	Hepatocyte Cell Extract		149 ng/ml	Human			3.1					2.1	3.9	8.2	12.0			3.9	10.4	46.7	9.6	
			219 ng/ml	Rat			1.9												2.7	31.5	60.7	3.4
INT 00003054	Hepatic Microsomes	^{14}C-Asenapine 	A1 5% EtOH 5.5 nMol		M1	M2	M3	M4	M5	M6	M9	M11	M12	M13	M14	M15	M16		M10	M7	M8	
				Human				X											X	X	**94.5**	
				Mouse ICR/CD-1				X			X	X	X	X	X				X	X	X	
				SD Rat				X			X	X		X	X				X	X	X	
				NZ White Rabbit				X				X		X	X				X	X	X	
				Beagle Dog	X	X	X	X	X	X	X	X	X	X	X				X	X	X	

			B1 5% EtOH 22.3 nMol	Human																		100	
				Mouse								X		X						X	X	X	
				Rat							X	X		X	X					X	X	X	
				Rabbit										X	X					X	X	X	
				Dog							X	X								X	X	X	
			A 2 1% EtOH 5.3 nMol	Human			X	X												X	X	81.7	
				Mouse										X						X	X	X	
				Rat			X							X						X	X	X	
				Rabbit			X	X	X											X	X	X	
				Dog				X												X	X	X	
			B2 1% EtOH 18.8 nMol	Human				X			X									X	X	63.8	
				Mouse			X													X	X	X	
				Rat																X	X	X	
				Rabbit			X	X						X						X	X	X	
				Dog																X	X	X	

					H1	H2	H3	H4	H5	H6	H7	H8	H9	H10	H11	H12	H13	H14	**H15**	**H16**	**H17**	
									O-SO4	O-SO4	N-Gluc	OH-N-DesMe			Org30526 N(2) desMe	As	N(2) formyl hydroxy	Org 31437	Org 31437 N(2) oxide	**N(2) formyl**		
NL 0060905	Cyropreserved Hepatocytes	^{14}C-Asenapine 	B	Mouse ICR/CD-1									X	X	X	X		X	X	X	X	
				Rat SD											X	X		X	X	X	X	
				Rabbit NZ white									X		X	X		X	X	X	X	
				Dog Beagle	X	X							X	X	X	X		X	X			
				Human			X	X	X	X	X	X	X	X	X	X	X					
			A	Mouse									X	X	X	X		X	X	X	X	
				Rat											X	X		X	X	X	X	
				Rabbit									X		X	X		X	X	X	X	
				Dog	X	X							X	X	X	X		X	X	X	X	
				Human			X	X	X	X	X	X	X	X	X	X	X	X	X			

5.5 Pharmacokinetics - Sublingual

5.5.1 Single Dose Pharmacokinetics - Dose Linearity

Two studies in young healthy males were dedicated to examining sublingual single rising dose (SRD) pharmacokinetics of asenapine. Study 25509 used subtherapeutic doses of up to 0.3 mg and study 25542 used doses of 2 mg and 5 mg. Due to the limited amount of data that this provided this reviewer also looked at the first and single dose data from several other studies shown below.

Study No.	Design	Population	Doses Studied
25509	SRD S/T Study	young healthy males	10 – 300 mcg, (0.01 – 0.3 mg)
25514	First Dose (MD)	young healthy males	200 mcg
25542	SRD & MD S/T	young healthy males	2 mg, 5 mg
25533	SD Absolute Bioavailability	young healthy males	5 mg
25540	SD w/wo charcoal	young healthy males	5 mg

Study 25509 was a single rising dose study of sublingual asenapine in young healthy male volunteers over a dose range of 10 – 100 mcg, (0.01 – 0.1 mg),

In addition mean single dose Cmax and AUC data for healthy volunteers from an additional number of studies (but not all studies) were examined.

Plots of single dose mean concentration vs. time profiles both of raw and dose normalized concentrations on linear and semi-log scales for doses of 2 mg and 5 mg from study 25542 show that sublingual asenapine exhibits linear 2-compartment pharmacokinetics over this dose range, (see Figure 35 to Figure 38).

When administered sublingually, linearity over the range of 0.02 mg to 5 mg is confirmed by the mean Cmax and AUC data from a number of other studies, (see Figure 39 and Figure 40).

Asenapine pharmacokinetic metrics from the five studies listed above are shown in Figure 41, Table 46 and Table 47. These metrics indicate that asenapine is a high intrinsic clearance drug with an intrinsic clearance that is likely equal to hepatic blood flow when bioavailability is considered, has an extremely large volume of distribution of roughly 100 L/kg, and an initial phase half-life of around 5 hours with a terminal phase half-life of around 24 hours.

For desmethyl-asenapine the reported Cmaxs are around 20% those of asenapine and the reported AUCs are around 40% of the parent, (see Table 47). Desmethyl-asenapine's shorter reported half-life doesn't make sense and is most likely due to lack of assay sensitivity. Based on this single dose data desmethyl-asenapine likely has formation-rate-limited pharmacokinetics. Thus the estimated clearances, volumes, and half-lives for desmethyl-asenapine are likely in error.

Figure 35 Mean Single Dose Asenapine Concentration vs. Time Profiles – Study 25542

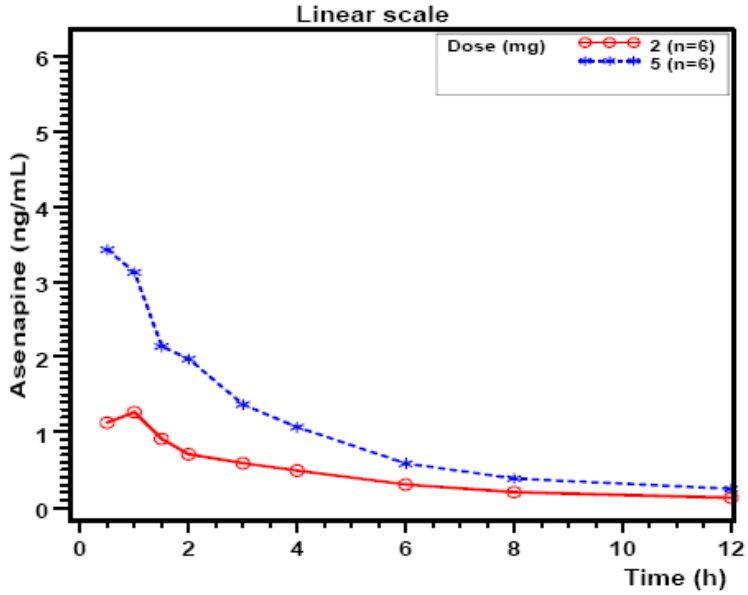


Figure 36 Mean Single Dose Asenapine Dose-Normalized Concentration vs. Time Profiles – Study 25542

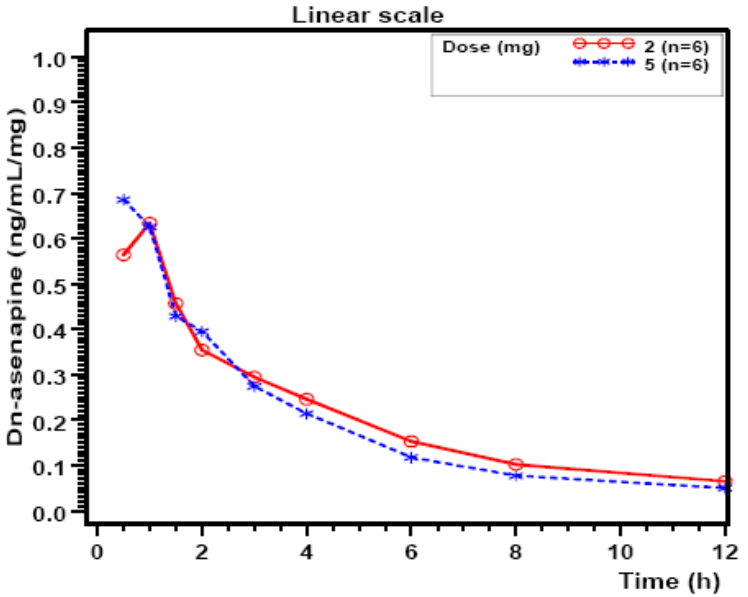


Figure 37 Mean Single Dose Asenapine Semi-log Concentration vs. Time Profiles – Study 25542

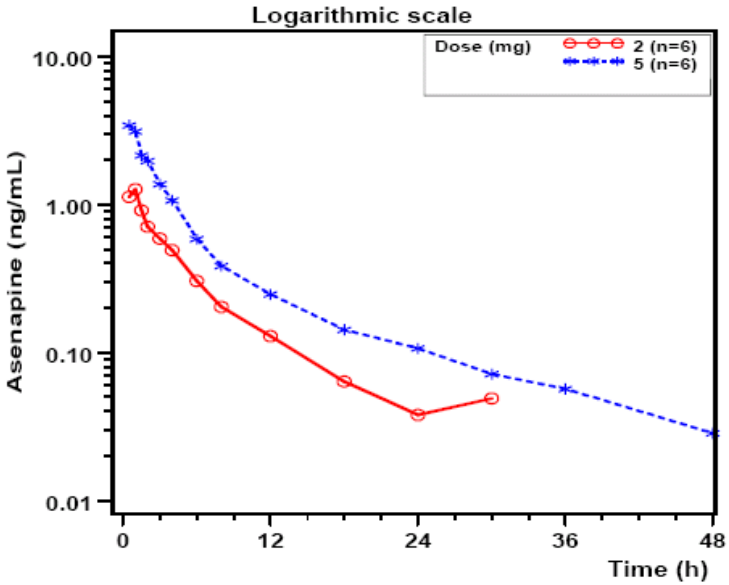


Figure 38 Mean Single Dose Asenapine Semi-log Dose-Normalized Concentration vs. Time Profiles – Study 25542

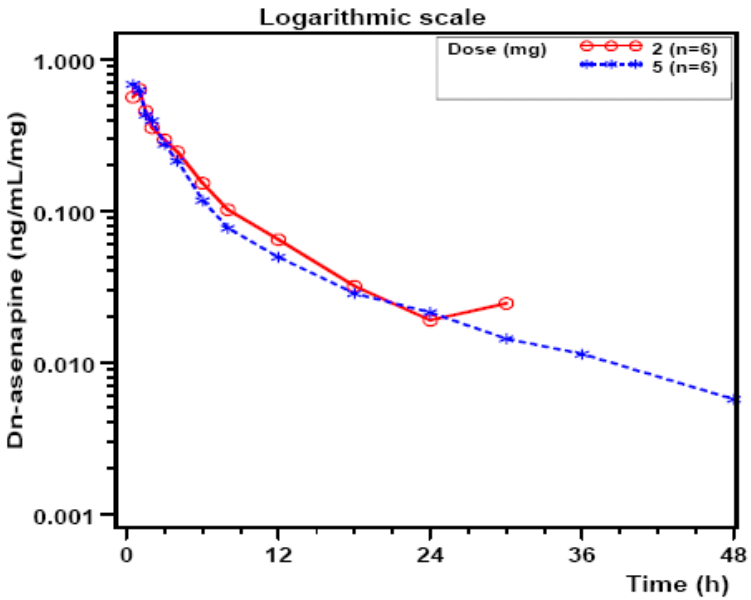

Logarithmic scale
Dose (mg)
2 (n=6)
5 (n=6)
1.000
0.100
0.010
0.001
Dn-asenapine (ng/mL/mg)
0
12
24
36
48
Time (h)

Figure 39 Asenapine Single Dose Mean Cmax vs. Dose from Multiple Studies

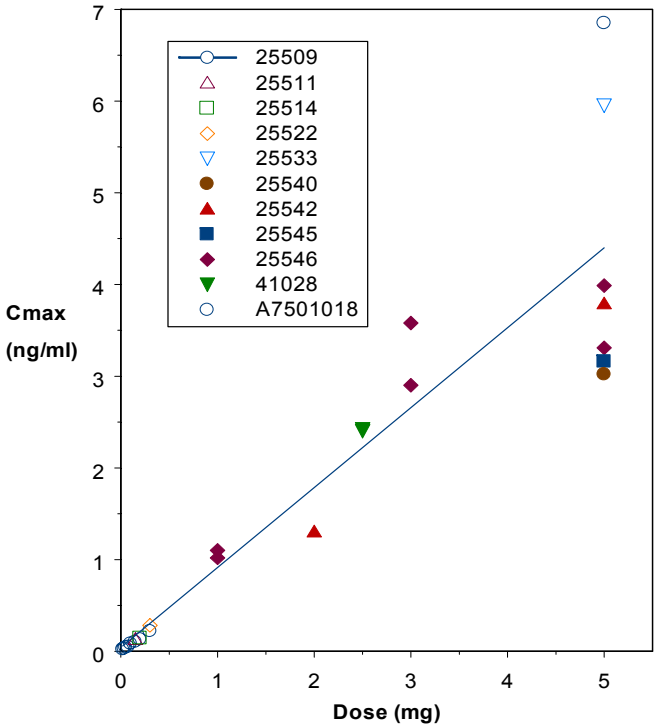


Figure 40 Asenapine Single Dose Mean AUC vs. Dose from Multiple Studies

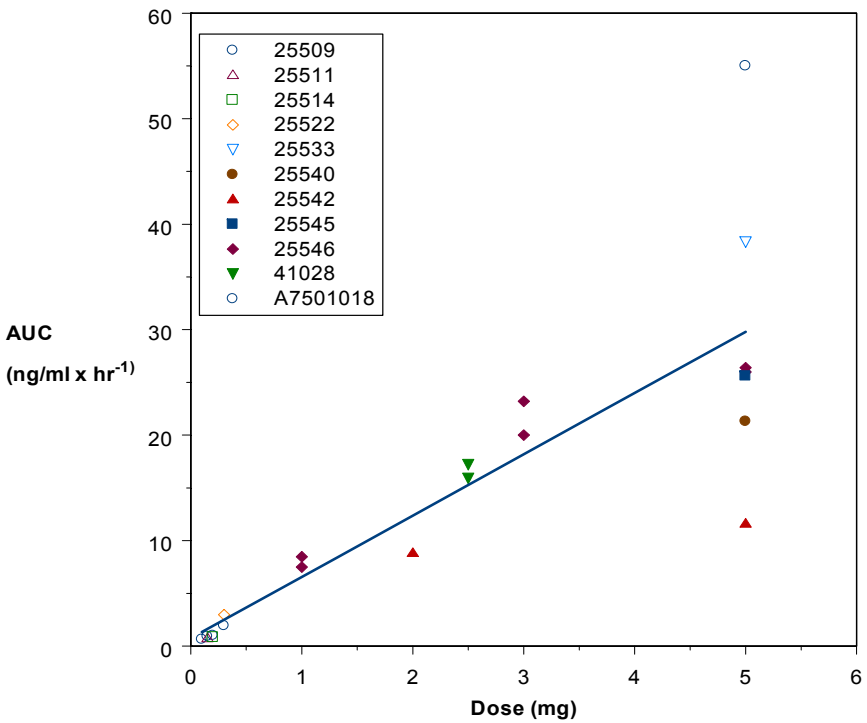


Figure 41 Pharmacokinetic Metrics (Mean ± SD) for Single Rising Doses of Sublingual Asenapine in Healthy Young Males - Study 25509

Dose group (µg)	C_{max} (pg/ml)	t_{max} (h)	$AUC_{0-\infty}$ (pg·h/ml)	AUC_{0-tfix} (pg·h/ml)	CL_{app} (l/h/kg)	$t_{½}$ (h)
10*	-	-	-	-	-	-
20**	21.37	1	-	-	-	-
35***	28.47±5.60	2.00±0.91	-	-	-	-
50	40.85±9.75	1.70±0.25	-	-	-	-
75	47.73±18.14	2.25±1.00	-	217±78	-	-
100	84.26±11.11	1.63±0.92	635±73	413±52	1.9±0.3	5.0±1.1
150	103.10±16.49	2.13±0.83	916±131***	533±108	2.2±0.2***	5.7±1.1***
200	129.32±37.59	1.69±0.65	1023±358	639±220	2.9±1.0	5.1±1.0
300	220.16±75.42	1.75±0.96	1932±651	1031±297	2.2±0.4	7.9±3.6

* N=0 (all levels below the lower limit of quantification) ** N=1 *** N=7 All other groups N=8

Table 46 Asenapine Pharmacokinetic Metrics after the First 200 mcg SL Dose – Study 25514[a]

N	Tmax (hrs)	Cmax (pg/mL)	AUC_{0-12} (pg/mL x hr^{-1})	Clapp (L/hr/kg)	dn-Cmax (pg/mL x hr^{-1})	dn-AUC_{0-12} (pg/mL x hr^{-1})	t½ (hrs)
12	1.67 ± 0.81 0.5 - 4.0	142.2 ± 49.3 62.5 - 220.6	848.4 ± 189.2 542.0 - 1127.9	3.33 ± 0.99 2.1 - 5.5	0.71 ± 0.25 0.31 - 1.1	4.24 ± 0.95 2.71 - 5.64	4.3 ± 0.9 2.7 - 5.6

a Values are mean ± SD and range.

Table 47 Asenapine and Desmethyl-Asenapine Sublingual Pharmacokinetic Single Dose Metrics – Studies 25542 and 25533[a]

Analyte	Asenapine				Desmethyl-Asenapine			
Study	25542		25533	25540	25542		25533	25540
Asenapine Dosage	2 mg	5 mg	5 mg	5 mg	2 mg	5 mg	5 mg	5 mg
N	6	6	8	7	6	6	8	7
Tmax (h)	[1.0] 0.50 - 1.0	[0.78] 0.5 - 1.0	[1.0] (0.5 - 3.0)	1.0 (0.5 - 2.0)	[5.0] 1.5 - 8.0	[3.0] 3.0 - 6.0	[6.0] (2.0 - 12.0)	6.0 (4.0 - 8.0)
Cmax (ng/mL)	1.30 ± 0.459	3.79 ± 1.21	5.95 (40.7) 2.05 - 8.64	3.02 (1.38)	0.237 ± 0.0485	0.571 ± 0.076	0.463 (14.0) 0.321 - 0.532	0.428 (0.210)
dn - Cmax (ng/mL/mg)	0.648 ± 0.229	0.758 ± 0.242			0.119 ± 0.0242	0.114 ± 0.015		
$AUC_{0-12\ (t)}$ (ng /mL x hr^{-1})	4.99 ± 1.48	11.6 ± 2.94	37.0 (24.2) 19.6 - 44.6	20.3 (5.75)	1.98 ± 0.472	4.74 ± 0.68	7.76 (21.70 6.08 - 11.0	7.59 (4.13)
dn – AUC_{0-12} (ng /mL x hr^{-1} / mg)	2.49 ± 0.742	2.32 ± 0.587			0.990 ± 0.236	0.949 ± 0.136		
$AUC_{0-\infty}$ (ng /mL x hr^{-1})	8.82* ± 2.51*	16.9 ± 4.35	38.3 (24.1) 19.9 - 46.6	21.3 (6.11)	4.01* ± 1.43*	11.5** ± 3.18**	8.85 (22.5) 6.99 - 12.7	10.3 (3.34†
dn - $AUC_{0-\infty}$ (ng /mL x hr^{-1} / mg)	4.41* ± 1.25*	3.38 ± 0.870			2.01* ± 0.715*	2.30** ± 0.636**		
CLapp (L/h)	241* ± 71.0*	316 ± 101	141 (34.6) 107 - 251		—	—	559 (19.9) 374 - 681	
wn - CLapp (L/h/kg)	3.27* ± 1.09*	4.24 ± 1.38			—	—		
Vz,app (L)	7180* ± 4874*	13689 ± 9438	3713 (42.7) 2070 - 6847		—	—	8311 (31.1) 5918 - 13941	
wn - Vz,app (L/kg)	95.6* ± 65.1*	182 ± 124			—	—		
t½ (h)	24.8* ± 23.8*	29.6 ± 15.9	19.7 (44.2) 7.68 - 31.0	15.9 (5.04)	7.97* ± 2.58*	17.1** ± 8.69**	10.7 (38.8) 6.34 - 20.2	15.1 (4.32)†

a Values are [Median] range, mean ± SD, mean (%CV) and range, or mean (%CV); * n = 4; ** n =5; † n = 6

5.5.2 Multiple Dose Pharmacokinetics - Dose Linearity, Time Invariance, Diurnal Variation, Dose Titration and Maximally Tolerated Dose Evaluation

Six studies were conducted that evaluated multiple dose pharmacokinetics. These included studies to evaluate the multiple dose pharmacokinetics, various dose titration regimens, and the maximally tolerated dose after sublingual administration, as-well-as proof of concept and PK/P. Descriptions of the study populations, study designs, and maximum dosages examined are shown in Table 48.

Studies 41001, 41007, 25542, and 41012 examined various titration schedules and dosages up to 20 mg BID and the titration schedules and study cohorts for these studies are shown in Table 49 to Table 52.

Studies 25511 and 25514 used subtherapeutic doses of 0.15 – 0.3 mcg BID and the metrics are included only for completeness in the last table in this section, Table 56.

Study 41001 also used a subtherapeutic dose of 0.8 mg BID and the sponsor only reported pharmacokinetic metrics dose normalized to 1 mg. Thus the results of this study are not reported or reviewed here. This was also a proof-of-concept study in patients with schizophrenia or schizoaffective disorder, however as the dose was subtherapeutic no evidence of efficacy was observed.

Studies 41007 and 25542 examined multiple doses in the range of 4.8 – 10 mg BID, as well as higher. As the proposed therapeutic dose range is 5 mg to 10 mg BID the focus of this review section will be on these studies. Study 41007 also included a PET sub-study in healthy volunteers at a dose of 4.8 mg and study 25542 also examined diurnal variation. Asenapine pharmacokinetic summary metrics from these studies are shown in Table 53.

The pharmacokinetic metrics from these studies reveal the following:

a) absorption is rapid with a median Tmax of 0.5 – 1.0 hours

b) Dose normalized Cmaxs at 5 mg BID and below are around 0.8 ng/ml per mg (~ 4 ng/ml total) with lower Cmaxs and delayed Tmaxs at higher doses (10 mg BID) probably due to swallowing

c) High intrinsic clearances approximating hepatic blood flow

d) Large volumes of distribution averaging 150 – 200 L/kg

e) Long terminal half-lives averaging around 1 day in one study and 1 – 1½ in others and ranging up to 2½ days in the PET study.

f) No significant diurnal variation in the overall profile however predose concentrations show clear diurnal variation when dose normalized.

Desmethyl-asenapine pharmacokinetics from study 25542 are shown in Table 54 and show Cmaxs around 30% of asenapine's at 5 mg BID and below, and around 60% of asenapine's at 10 mg BID. AUCs of desmethyl-asenapine average 85% of asenapine's at doses of 5 mg BID, and 110% at 10 mg BID. Although the half-lives for desmethyl-asenapine are shorter than asenapine's, this is probably due to assay insensitivity and most likely desmethyl-asenapine has formation rate limited kinetics.

Figure 42 and Figure 44 show steady-state asenapine mean concentration vs. time profiles after morning and evening doses. When the concentrations are transformed to the log scale they demonstrate biphasic kinetics during a single dosage interval, (see Figure 43 and Figure 45), and if the dose is high enough and sampling is sufficiently long a triphasic elimination profile indicating 3 compartment pharmacokinetics is observed, (see Figure 45).

For desmethyl-asenapine, Figure 46 and Figure 48 reveal monoexponential decline during a single dosage interval. However when dose-normalized concentration vs. time profiles are examined there is clear nonlinearity indicating saturable absorption, (see Figure 47 and Figure 49).

In addition, dose normalized pre-dose concentrations for asenapine reveal a degree of diurnal variation, (see Figure 50), although examination of Figure 47 and Figure 49 reveal that this is mainly in the 2nd phase kinetics and that the amount of diurnal variation is small and thus does not raise any obvious concerns especially as dosing is BID.

Asenapine and desmethyl-asenapine pharmacokinetics at doses of 10 – 20 mg BID from study 41012 are shown in Table 55. Asenapine's Cmax again appears to plateau, but only above 10 mg BID and there is a decrease in dose normalized AUC. The ratio of desmethyl-asenapine to asenapine in this study and study 25532 (Table 22) is also similar but somewhat lower than the ratios in study 25542, (see Table 54). The most likely explanations are the small number of subjects in these studies and whether subjects swallowed drug or not. In study 41012 there were also cases of severe oral dystonia at the 15 mg BID dose.

Plots of Cmax's and AUC's vs. dose from a number of multiple dose studies also appear to show possible plateauing at doses above 5 mg BID, (see Figure 51 and Figure 52), and plots of dose normalized values versus dose confirm this, although the cutoff for linearity is not clear, (see Figure 53).

As mentioned earlier, studies 25511 and 25514 used subtherapeutic doses of 0.15 – 0.3 mcg BID and are included in Table 56 on the last page in this section simply for completeness,

Table 48 Study Populations, Designs, and Maximum Dosages Examined in Phase I Multiple Dose Clinical Pharmacology Studies

No.	Nominal Design	Population	Design	Cohort	N	Maximum Dosage
25511	MD	Young healthy male volunteers	Rand, DB, PBO controlled, parallel grp, MD study	1	6	150 mcg SL BID x 6.5 days
				2	12	or 150 mcg SL BID x 13.5 days
25514	MD	Young healthy male volunteers	Rand, DB, PBO controlled, parallel grp, MRD study	1	12	200 mcg SL BID x 2 days then 300 mcg SL BID x 4.5 day
41001	MRD	M/F patients with schizophrenia or schizoaffective disorder	Rand, DB PBO controlled 3-way sequential design S/T MTD PK proof of concept study	1	10	up to 0.8 mg BID over 5 days
				2	10	up to 0.8 mg BID over 6 days
				3	10	up to 0.8 mg BID over 9 days
41007	MRD	Young otherwise healthy subjects with schizophrenia or schizoaffective disorder (PET substudy also included healthy subjects)	Rand, DB, PBO controlled, sequential design, MRD, S/T MTD PK study with PK/PD PET sub-study	Grp 1	6	2.4 mg BID x 5 days
				Grp 2	6	2.4 mg BID x 5 days
				Grp 3A	3	4.8 mg BID x 5 days
				Grp 3B	3	4.8 mg BID x 5 days
25542	MRD	Young healthy male volunteers	Rand, DB, PBO controlled, 5-way parallel design MRD study	1	6	up to 3 mg BID x 6 days
				2	6	up to 5 mg BID x 6 days
				3	6	up to 10 mg BID x 6 days
				4	6	up to 15 mg BID x 6 days
	SRD			5	6	2 mg and 5 mg SD
41012	MRD	M/F patients with schizophrenia or schizoaffective disorder	S/T MTD titration study in Rand DB PBO controlled 3-way sequential design	1	6	up to 15 mg BID x 5 days
				2	6	up to 15 mg BID x 5 days
				3	6	up to 20 mg BID x 5 days

Table 49 Dose Titration Schedules - Study 41001

Grp	N	Day																total # days
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	
1	10	0.2 mg BID x 3 days			0.3 mg BID x 3 days			0.4 mg BID x 3 days			0.6 mg BID x 3 days			0.8 mg BID x 5 days					17
2	10	0.2 mg BID x 2 days			0.3 mg BID x 2 days			0.4 mg BID x 2 days		0.6 mg BID x 2 days			0.8 mg BID x 6 days						14
3	10	0.2 mg BID x 1 day	0.3 mg BID x 1 day	0.4 mg BID x 1 day	0.6 mg BID x 1 day	0.8 mg BID x 9 days													13

Table 50 Dose Titration Schedules - Study 25542

Group	Day											total # days
	1	2	3	4	5	6	7	8	9	10	11	
1	0.3 mg BID x 1 day	0.6 mg BID x 1 day	1 mg BID x 1 day	3 mg BID x 6 days								9
2	0.3 mg BID x 1 day	1 mg BID x 1 day	3 mg BID x 1 day	5 mg BID x 6 days								9
3	1 mg BID x 1 day	3 mg BID x 1 day	5 mg BID x 1 day	10 mg BID x 6 days								9
4	1 mg BID x 1 day	3 mg BID x 1 day	5 mg BID x 1 day	10 mg BID x 1 day	15 mg BID x 6 days							11
5	2 mg SD							5 mg SD				

Table 51 Dose Titration Schedules - Study 41007

Grp	Day																total # days
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17 18	
1	0.2 mg BID x 1 day	0.4 mg BID x 1 day	0.6 mg BID x 1 day	0.8 mg BID x 1 day	1.2 mg BID x 3 days			1.6 mg BID x 3 days			2.0 mg BID x 3 days		2.4 mg BID x 5 days					18
2	0.3 mg BID x 1 day	0.6 mg BID x 1 day	0.8 mg BID x 1 day	1.2 mg BID x 1 day	1.6 mg BID x 1 day	2.0 mg BID x 1 day	2.4 mg BID x 5 days											11
3A	0.4 mg BID x 1 day	0.8 mg BID x 1 day	1.2 mg BID x 1 day	1.6 mg BID x 1 day	2.0 mg BID x 1 day	2.4 mg BIDx 2 days		3.2 mg BID x 2 days		4.0 mg BID x 2 days		4.8 mg BID x 5 days						16
3B	0.6 mg BID x 1 day	1.2 mg BID x 1 day	1.6 mg BID x 1 day	2.0 mg BID x 1 day	2.4 mg BID x 1 day	3.2 mg BID x 1 day	4.0 mg BID x 1 day	4.8 mg BID x 5 days										12

Table 52 Dose Titration Schedules – Study 41012

Grp	Day										total # days
	1	2	3	4	5	6	7	8	9	10	
1	2 mg BID x 1 day	3 mg BID x 1 day	5 mg BID x 1 day	8 mg BID x 1 day	10 mg BID x 1 day	15 mg BID x 5 days					10
2	3 mg BID x 1 day	5 mg BID x 1 day	8 mg BID x 1 day	10 mg BID x 1 day	15 mg BID x 5 days						9
3	5 mg BID x 1 day	10 mg BID x 1 day	15 mg BID x 1 day	20 mg BID x 5 days							8

Table 53 Asenapine Steady-State Pharmacokinetic Metrics – Studies 41007 and 25542

Study	41007	25542		41007	25542			
Dosage	2.4 mg	3 mg		4.8 mg	5 mg		10 mg	
Dose	Morning	Morning	Evening	Morning	Morning	Evening	Morning	Evening
N	8	5	5	4	6	6	5	5
Tmax[a] (h)	1.6 ± 0.4 (26.7) 1 - 2 [1.5]	[0.5] 0.5 - 1.0	[1.0] 0.5 - 1.0	2.0 ± 1.4 (67.7) 1.0 - 4.0 [1.5]	[0.5] 0.5 - 1.5	[0.5] 0.5 - 1.0	[1.0] 0.52 - 1.5	[0.5] 0.5 - 0.5
Cmax (ng/mL)	2.0 ± 1.7 (88.6) 0.9 - 6.2 [1.4]	2.76 ± 1.48	2.95 ± 1.76	3.6 ± 1.8 (50.8) 1.0 - 5.3 [4.1]	3.59 ± 1.27	3.46 ± 1.62	4.9 ± 1.9	5.57 ± 2.36
dn - Cmax (ng/mL/mg)	0.8 ± 0.7 (88.5) 0.4 - 2.6 [0.6]	0.92 ± 0.49	0.98 ± 0.58	0.8 ± 0.4 (50.9) 0.2 - 1.1 [0.9]	0.72 ± 0.26	0.69 ± 0.32	0.49 ± 0.19	0.557 ± 0.236
AUC0 - 12 (ng/mL *hr^{-1})	11.5 ± 7.1 (61.4) 6.1 - 27.2 [9.6]	11.0 ± 2.91	12.8 ± 4.75	22.4 ± 10.0 (44.6) 8.1 - 30.9 [25.3]	15.5 ± 5.47	14.6 ± 5.42	24.4 ± 13.0	28.2 ± 16.0
dn - AUC0 - 12 (ng/mL *hr^{-1} / mg)	4.8 ± 2.9 (61.20 2.6 - 11.3 [4.0]	3.68 ± 0.97	4.27 ± 1.58	4.7 ± 2.1 (44.7) 1.7 - 6.4 [5.3]	3.11 ± 1.09	2.92 ± 1.08	2.4 ± 1.3	2.82 ± 1.60
Clapp (L/h)	251 ± 89 (35.6) 88.3 - 392 [251]	284 ± 61.2	261 ± 92.0	283 ± 209 (73.8) 155.0 - 595.0 [191]	349 ± 94.4	405 ± 218	485 ± 187	449 ± 223
wn - CLapp (L/h/kg)		3.71 ± 0.76	3.42 ± 1.26		5.02 ± 1.28	5.84 ± 3.02	6.20 ± 2.68	5.80 ± 3.19
Vz,app (L)	10830 ± 3710 (34.3) 7410 - 16560 [9900]			14515 ± 10679 (74) 7265 - 30355 [10219]				
dn - Cmin,av (ng/mL/mg)		0.188 ± 0.017	0.115 ± 0.02		0.151 ± 0.045	0.096 ± 0.024	0.136 ± 0.101	0.084 ± 0.056
t½ (hr)	30.9 ± 12.5 (40.4) 20.3 - 58.2 [27.1]	—	18.2 ± 6.98	36.2 ± 8.3 (23.0) 24.8 - 43.3 [38.4]	—	18.8 ± 10.6	—	20.4 ± 6.70
Tss(protocol day)		6	6		5	4	5	4

a Mean ± SD, except, Median and range for Tmax, and Mean for Tss (Time to steady - state).

Table 54 Desmethyl-Asenapine Steady-State Pharmacokinetic Metrics – Study 25542

		Asenapine 3 mg		Asenapine 5 mg		Asenapine 10 mg	
		Morning (n=5)	Evening (n=5)	Morning (n=6)	Evening (n=6)	Morning (n=5)	Evening (n=5)
Tmax (h)		[6.0] 3.0 - 6.0	[3.0] 1.0 - 12.0	[2.0] 1.50 - 4.0	[1.75] 1.07 - 6.0	[4.0] 1.50 - 4.0	[3.0] 1.0 - 8.0
Cmax (ng/mL)		0.805 ± 0.312	0.701 ± 0.317	1.49 ± 0.312	1.16 ± 0.346	3.41 ± 1.18	2.59 ± 0.874
dn - Cmax (ng/mL/mg)		0.268 ± 0.104	0.234 ± 0.106	0.297 ± 0.0625	0.233 ± 0.0693	0.341 ± 0.118	0.259 ± 0.0874
AUC_{0-12} (ng*h/mL)		7.63 ± 3.24	6.77 ± 2.94	14.0 ± 3.58	11.6 ± 3.38	31.8 ± 14.3	25.7 ± 11.4
dn - AUC_{0-12} (ng*h/mL/mg)		2.5 ± 1.08	2.26 ± 0.982	2.79 ± 0.715	2.32 ± 0.675	3.18 ± 1.43	2.57 ± 1.14
dn - Cmin,av (ng/mL/mg)		0.150 ± 0.0742	0.168 ± 0.0780	0.168 ± 0.0383	0.180 ± 0.0516	0.191 ± 0.102	0.193 ± 0.105
t½ (h)		—	17.2 ± 8.51	—	15.0 ± 3.68	—	14.9 ± 4.80
Tss (Day)		6	6	5	4	7	5
Ratio DesMe-Asenapine: Asenapine	**Cmaxs**	0.29	0.24	0.41	0.34	0.70	0.46
	AUCs	0.69	0.53	0.9	0.79	1.3	0.91

Figure 42 Mean Steady-State Asenapine Concentration vs. Time Profiles after a Morning Dose – Study 25542

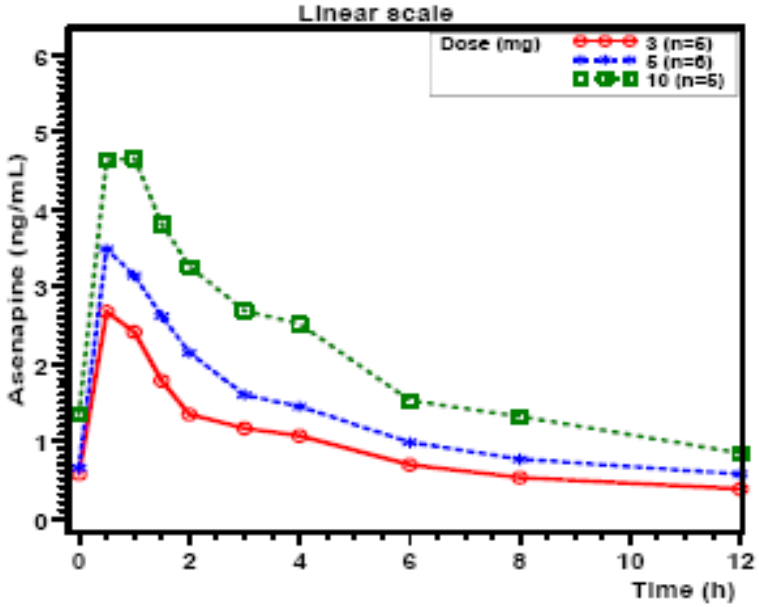


Figure 43 Mean Steady-State Asenapine Semi-log Concentration vs. Time Profiles after a Morning Dose – Study 25542

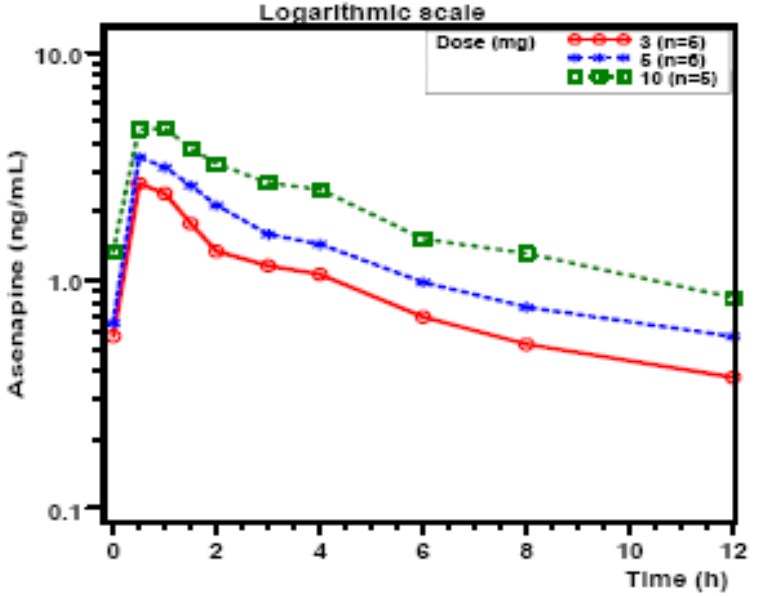


Figure 44 Mean Steady-State Asenapine Concentration vs. Time Profiles after an Evening Dose – Study 25542

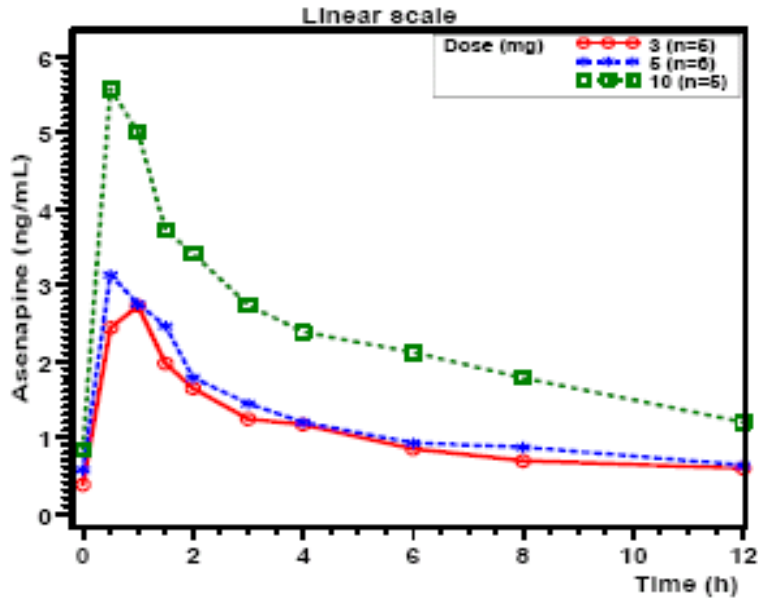


Figure 45 Mean Steady-State Asenapine Semi-log Concentration vs. Time Profiles after an Evening Dose – Study 25542

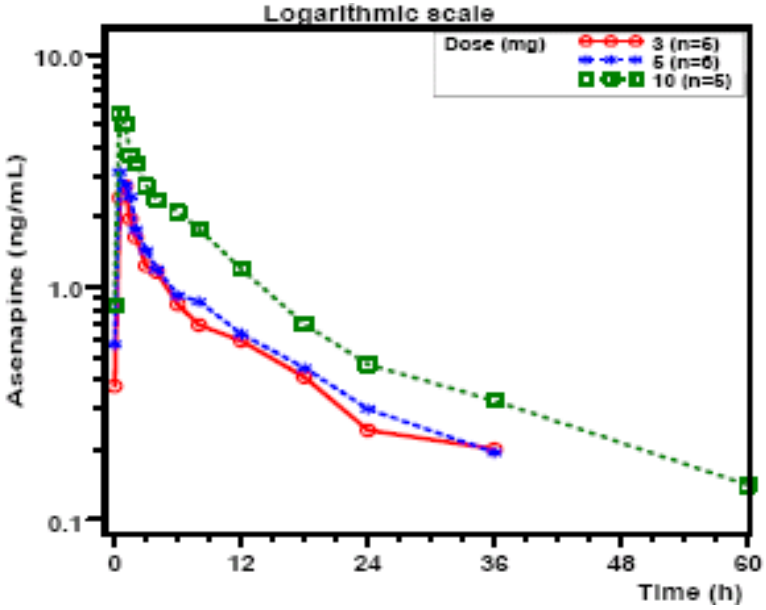


Figure 46 Mean Steady-State Desmethyl-Asenapine Concentration vs. Time Profiles after a Morning Dose – Study 25542

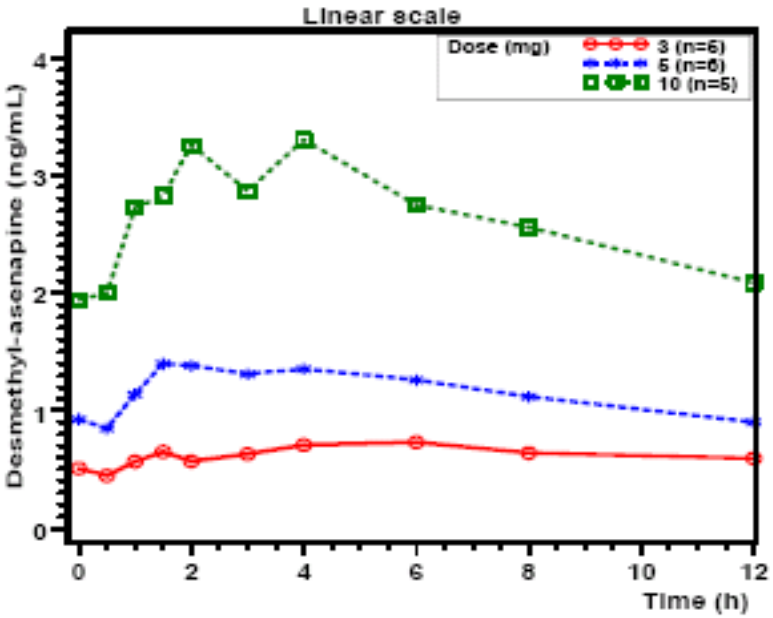


Figure 47 Mean Steady-State Dose-normalized Asenapine Concentration vs. Time Profiles after a Morning Dose – Study 25542

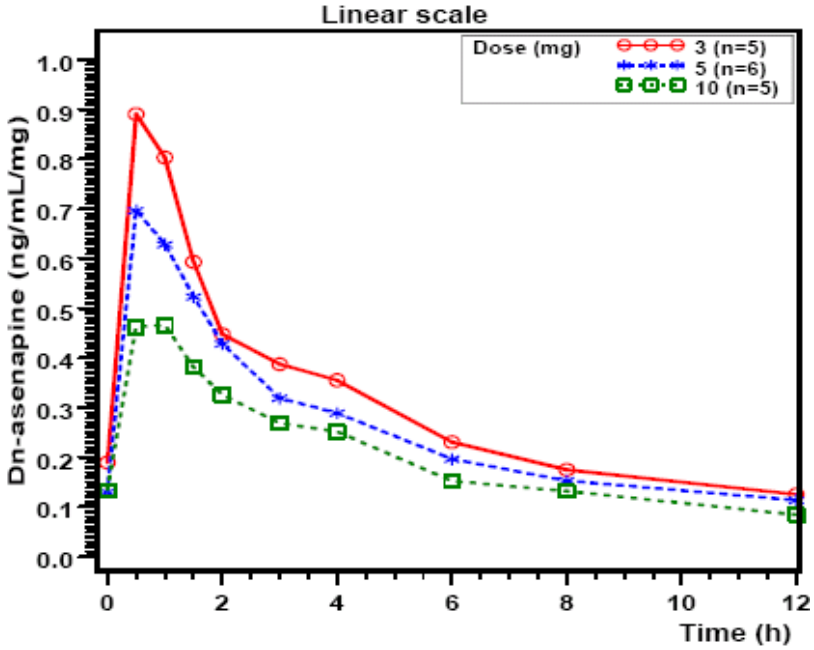


Figure 48 Mean Steady-State Desmethyl-Asenapine Semi-log Concentration vs. Time Profiles after a Morning Dose – Study 25542

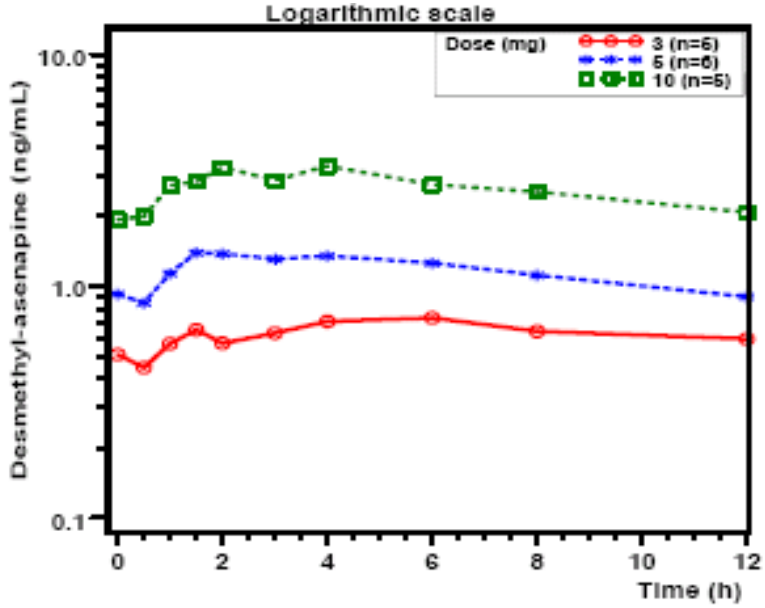


Figure 49 Mean Steady-State Dose-normalized Asenapine Concentration vs. Time Profiles after an Evening Dose – Study 25542

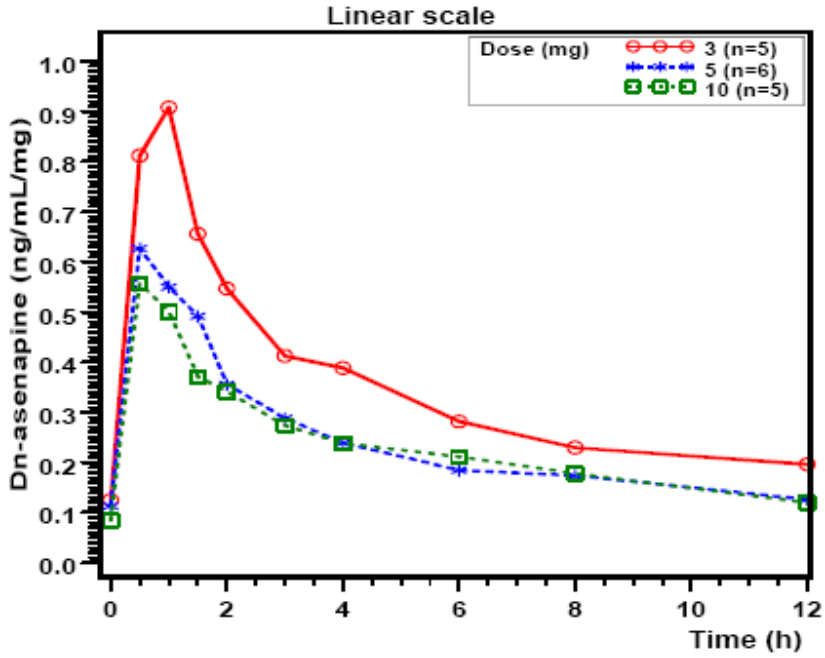


Figure 50 Mean Dose-Normalized Asenapine and Desmethyl-Asenapine pre-Dose Concentration Fluctuations from Days 4 to 10 of Dosing – Study 25542

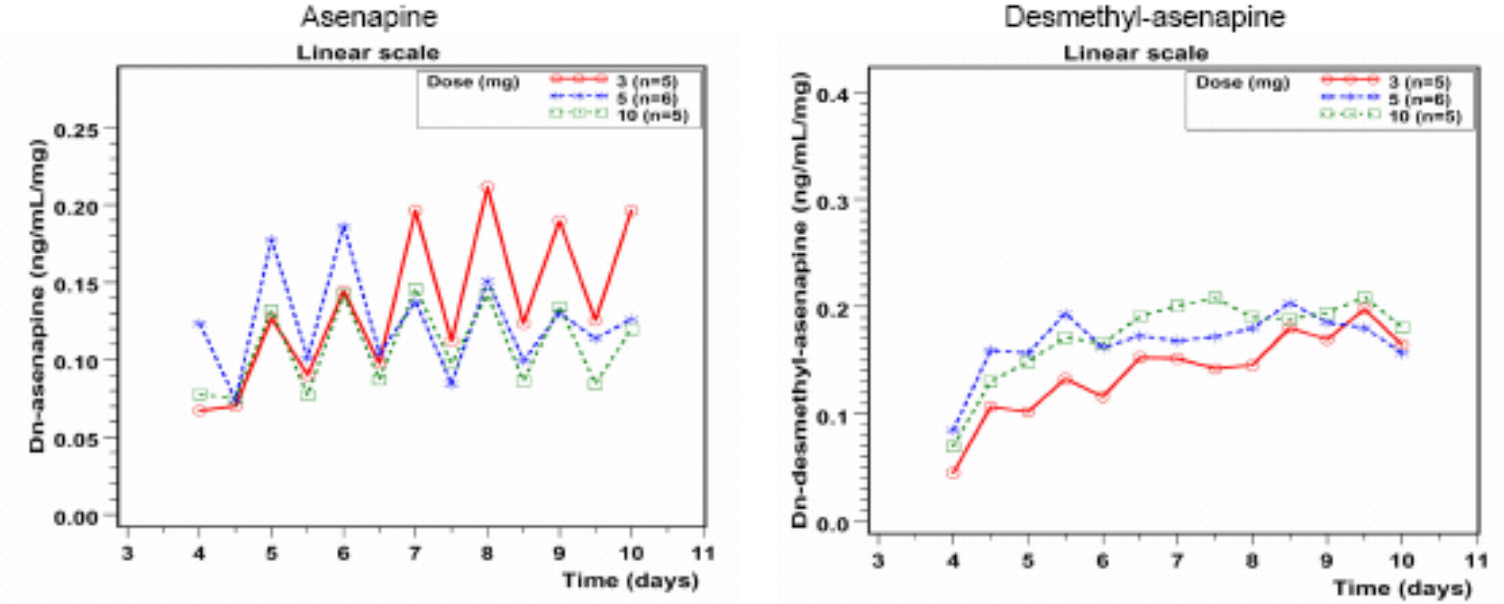


Table 55 Multiple Dose Asenapine Pharmacokinetic Metrics –Study 41012

	Asenapine			Desmethyl-Asenapine			Ratio of Means Desmethyl-Asenapine : Asenapine		
Dose	**10 mg BID**	**15 mg BID**	**20 mg BID**	**10 mg BID**	**15 mg BID**	**20 mg BID**	**10 mg BID**	**15 mg BID**	**20 mg BID**
n	2	12	3	2	12	3			
Tmax (h)	[1.25] 1.00 - 1.50	[1.05] 0.97 – 4.00	[1.03] 1.00 - 2.03	[4.00] 4.00 – 4.00	[2.05] 1.00 – 4.37	[1.50] 1.03 - 2.03			
Cmax (ng/mL)	8.84 2.17 - 15.5	7.80 ± 3.54 1.42 - 11.8	8.28 ± 3.72 4.17 - 11.4	1.33 1.23 - 1.42	3.18 ± 1.31 1.71 - 5.96	2.92 ± 0.67 2.46 - 3.69	0.15	0.41	0.35
AUC_{0-12} (ng * h/mL)	37.3 16.5 - 58.1	49.5 ± 18.9 11.4 - 76.7	55.7 ± 34.9 21.2 - 91.0	12.7 11.0 - 14.4	29.1 ± 14.8 13.1 - 62.3	23.8 ± 2.39 21.5 - 26.3	0.34	0.59	0.43
Cmin,av (ng/mL)	1.30 0.964 - 1.64	2.64 ± 1.17 1.24 - 5.01	2.74 ± 1.71 1.13 - 4.54	0.853 0.693 - 1.01	1.90 ± 1.11 0.874 - 4.49	1.33 ± 0.131 1.19 - 1.45			
dn - Cmax (ng/mL)/mg	0.884 0.217 - 1.55	0.52 ± 0.24 0.09 - 0.79	0.414 ± 0.186 0.209 - 0.570	0.133 0.123 - 0.142	0.212 ± 0.088 0.114 - 0.397	0.146 ± 0.033 0.123 - 0.185			
dn - AUC_{0-12} (ng * h/mL)/mg	3.73 1.65 - 5.81	3.30 ± 1.26 0.76 - 5.11	2.78 ± 1.75 1.06 - 4.55	1.27 1.10 - 1.44	1.94 ± 0.984 0.870 - 4.15	1.19 ± 0.120 1.08 - 1.32			
t½ (h)	38.1[a] 38.1	39.0[b] ± 26.1 18.5 - 109	31.0 ± 10.6 20.7 - 41.9	15.4 13.9 - 17.0	18.1 ± 5.18 11.4 - 28.5	15.2 ± 4.20 11.7 - 19.9			

a n = 1
b n = 11

Figure 51 Mean Asenapine Multiple Dose Cmaxs vs. Dose from Various Studies

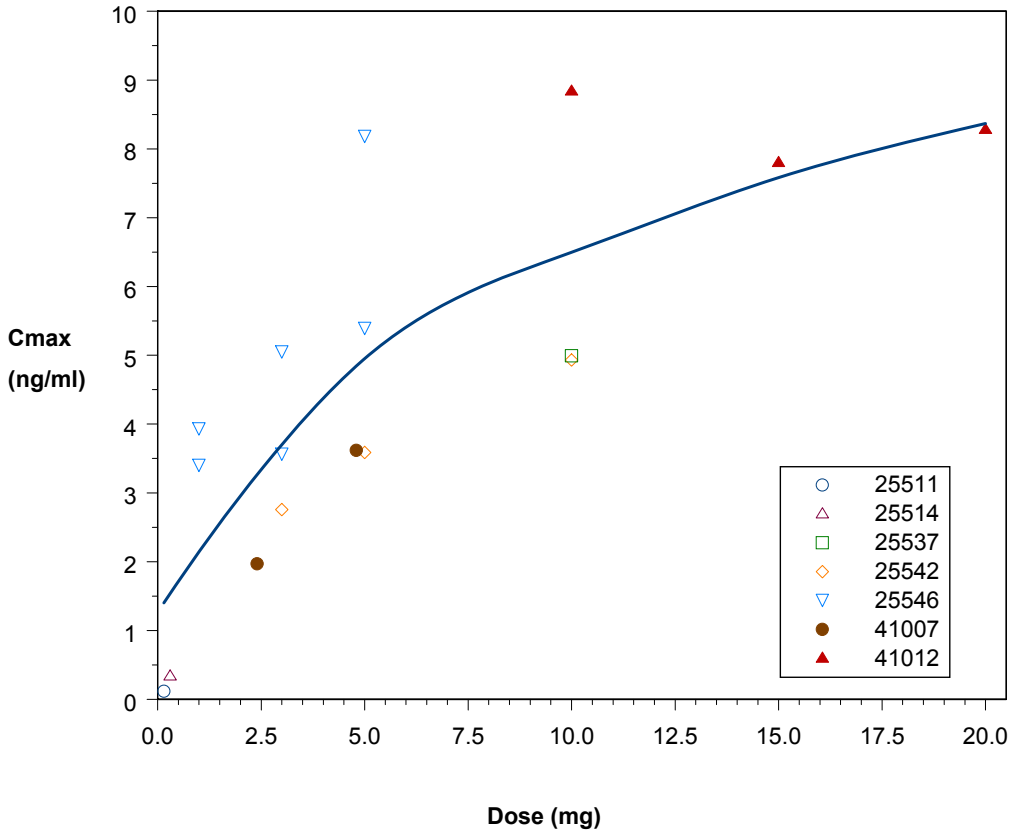


Figure 52 Mean Asenapine Multiple Dose AUCs vs. Dose from Various Studies

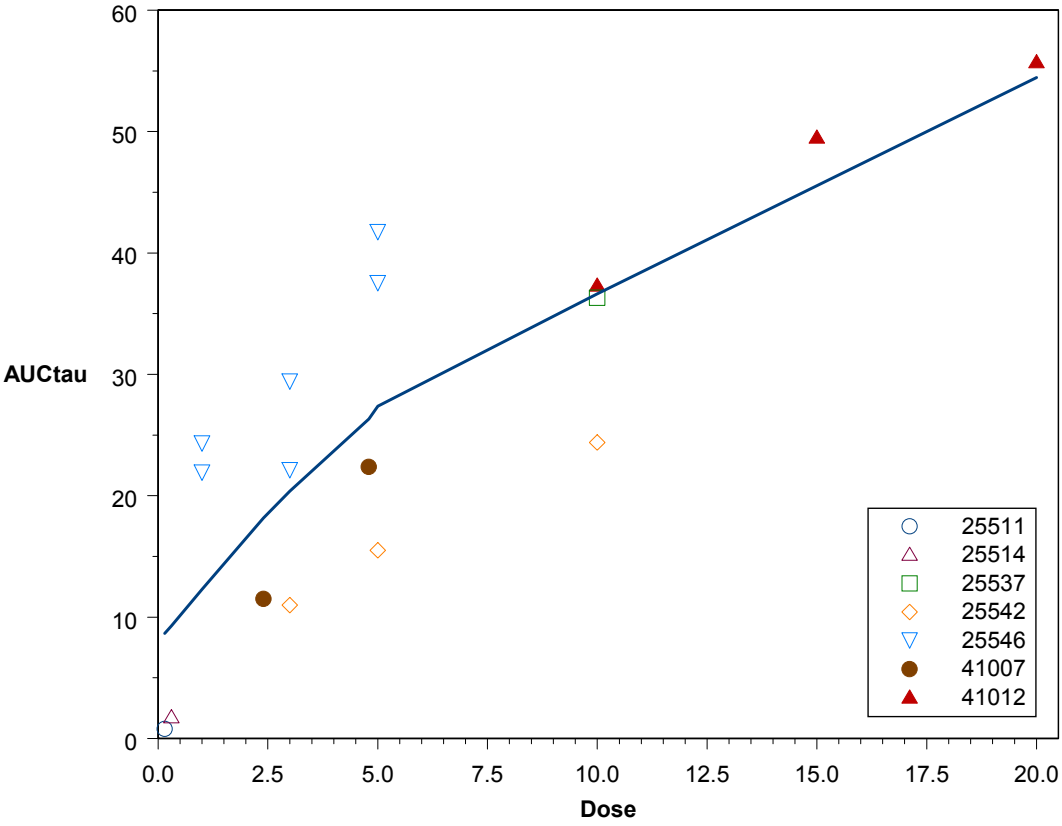


Figure 53 Mean Asenapine Dose Normalized Cmaxs and AUCs vs. Dose from Various Multiple Dose Studies

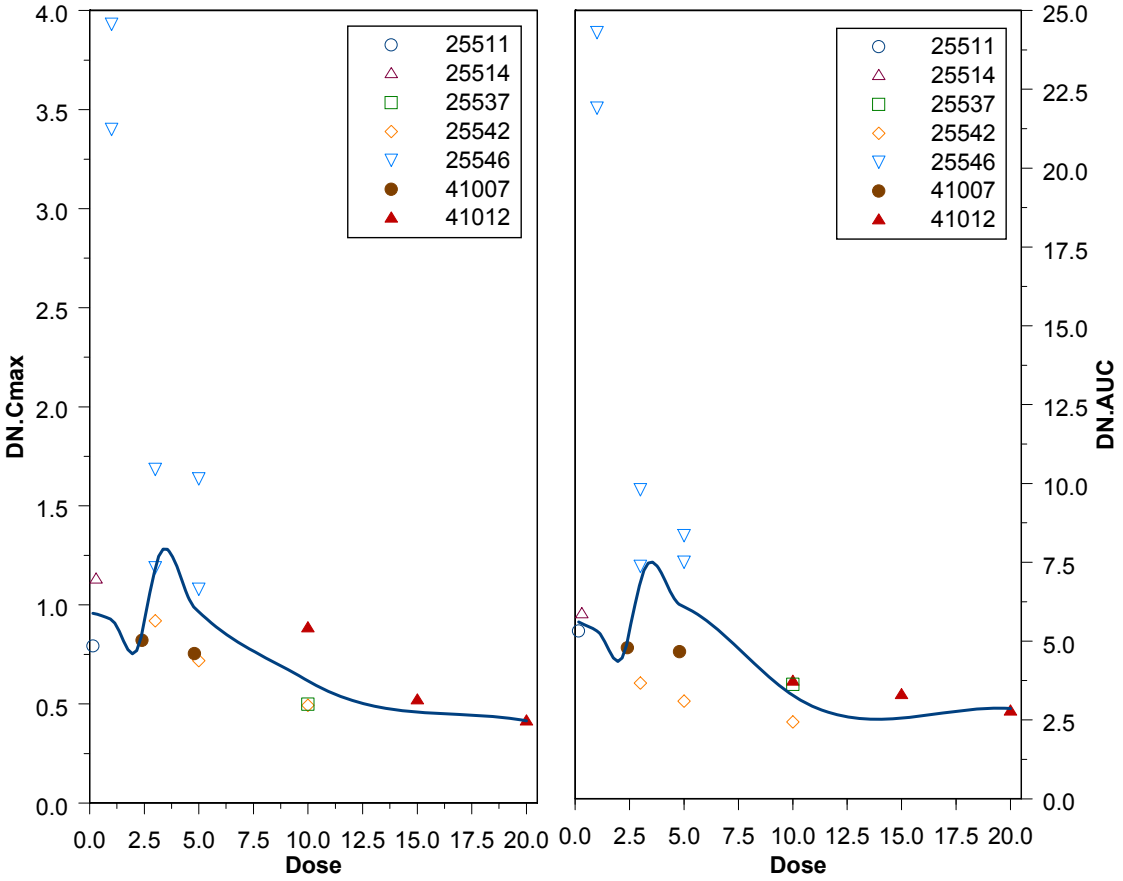


Table 56 Asenapine SL Multiple Dose Pharmacokinetic Metrics in Young Healthy Male Volunteers - Studies 25511 and 25514

Study	25511							25514
Dosage	150 mcg SL BID							300 mcg SL BID
Day No.	1	3	5	7	10	12	14	
N	18	12-17	12-17	17	6	6	6	12 (11)
Tmax (hr)	1.6 ± 0.6 1.0 - 3.1	1.3 ± 0.6 1.0 - 3.0	1.5 ± 0.6 1.0 - 3.0	1.5 ± 0.8 0.5 - 4.0	1.0 ± 0.00 1.0 - 1.0	1.2 ± 0.3 1.0 - 1 5	1.3 ± 0.5 0.75 - 2.0	1.2+0.3 0.75-1.5
Cmax (pg/ml)	127.8 ± 38.5 61.4 - 192.2	106.4 ± 42.1 61.1 - 118.0	103.4 ± 34.0 68.6 - 193.0	141.6 ± 48.1 80.1 - 23 9.5	106.0 ± 35.9 70.8 - 159.1	112.0 ± 27.8 75.2 - 150.3	143.5 ± 42.0 86.0 - 183.4	340+99.3 188.4-495.
AUC_{0-12} (pg/ml x hr^{-1})	730.4 ± 284.7 372.9 - 1476.7	—	—	832.0 ± 216.2 589.0 - 1335.1	—	—	765.4 ± 242.4 444.3 - 1064.0	1759.5+442.9 1168.5-2737.5
Clapp (L/hr x kg^{-1})	3.2 ± 1.3 1.4 - 5.9	—	—	2.6 ± 0.7 1.4 - 3.8	—	—	3.1 ± 1.3 1.7 - 4.9	2.41+0.68 1.53-4.06
t½ (h)	4.2 ± 1.4 2.0 - 7.3	—	—	7.7 ± 5.6 4.1 - 28.4	—	—	8.4 ± 7.3 2.8 - 22.7	16.2+4.75 10.8-24.3
	—	—	—	(6.4) ± (1.8) (4.1) - (11.8)	—	—	(5.5) ± (2.3) (2.8) - (8.8)	5.6+1.2 4.0-8.3
Css,min (pg/ml)	—	36.8 ± 18.3 0.00 - 61.6	47.9 ± 15.9 23.2 - 85.0	43.6 ± 10.4 28.4 - 64.5	42.3 ± 9.6 30.2 - 53.1	42.9 ± 12.04 30.8 - 63.5	33.9 ± 9.3 24.0 - 44.4	—
Css,av (pg/ml)	—	—	—	69.3 ± 18.0 49.1 - 111.3	—	—	63.8 ± 20.2 37.0 - 88.7	146.6+36.9 97.4-228.1
DF (%)	—	—	—	136.7 ± 39.5 81.5 - 202.7	—	—	176.7 - 59.5 102.8 - 248.3	179.8+39.2 108.1-268.5

5.5.3 Enantiomer Pharmacokinetics - Single Dose

Study 41028 was a single dose pharmacokinetic study in eight healthy male volunteers. Subjects received one 2.5 mg tablet of the (R,R) – asenapine enantiomer (Org 10968) and one 2.5 mg tablet of the $^{13}C_6$ labeled (S,S) – asenapine enantiomer (Org 10969) administered simultaneously.

Table 57 Comparison of Asenapine Enantiomer Pharmacokinetic Metrics after Simultaneous Single Oral Doses of 2.5 mg of each Asenapine Enantiomer in Healthy Male Volunteers – Study 41028

[redacted]	Summary Statistics		Geometric Means		Geometric Mean Ratios of (S,S)-asenapine : (R,R)-asenapine (95% confidence interval)
	(S,S)-asenapine	(R,R)-asenapine	(S,S)-asenapine	(R,R)-asenapine	
Tmax (h)	[0.63] 0.5 - 1.0	[0.75] 0.5 - 1.0	—	—	—
Cmax (ng/mL)	2.40 ± 0.948	2.42 ± 0.949	2.20	2.23	0.99 (0.95 - 1.02)
$AUC_{0-\infty}$ ($ng/mL \times hr^{-1}$)	15.9 ± 5.90	17.2 ± 5.94	14.7	16.2	0.91 (0.85 - 0.98)
$AUC_{0-tlast}$ ($ng/mL \times hr^{-1}$)	15.2 ± 5.70	16.3 ± 5.52	14.1	15.3	0.92 (0.85 – 0.998)
$t_{1/2}$ (h)	10.2 ± 4.25	12.6 ± 5.58	9.43	11.6	0.81 (0.58 - 1.13)

Table 58 Comparison of Desmethyl - Asenapine Enantiomer Pharmacokinetic Metrics after Simultaneous Single Oral Doses of 2.5 mg of each Asenapine Enantiomer in Healthy Male Volunteers – Study 41028

[redacted]	Summary Statistics		Geometric Means		Geometric Mean Ratios of N-desmethyl-(S,S)–asenapine : N-desmethyl-(R,R)-asenapine (95% CI)
	N-desmethyl - (S,S)-asenapine	N-desmethyl - (R,R)-asenapine	N-desmethyl - (S,S)-asenapine	N-desmethyl - (R,R)-asenapine	
Tmax (h)	[6.0] 3.0 - 8.07	[12.0] 6.0 - 12.0	—	—	—
Cmax (ng/mL)	0.328 ± 0.139	0.109 ± 0.0326	0.308	0.105	2.9 (2.46 - 3.48)
$AUC_{0-tlast}$ (ng*h/mL)	3.55 ± 2.21	1.71 ± 1.29	3.06	1.32	2.3 (1.52 - 3.52)

The following is the sponsor's assessment of the results of this study.

*"The plasma concentrations of the (S,S) - and (R,R) - enantiomers of asenapine are similar after simultaneous single sublingual doses of 2.5 mg of the (S,S) - enantiomer and 2.5 mg of the (R,R) - enantiomer of asenapine. The mean AUC of the (S,S) - enantiomer was 8 - 9% lower than that of the (R,R) - enantiomer. This difference in mean AUC is not considered clinically relevant, although it was statistically significant due to a very low within subject variation on AUC (6.5%). When adding up the AUC0 - ∞ values of both enantiomers the result (33.1 ng*h/mL) is similar to that found in other clinical pharmacology studies with a single sublingual dose of 5 mg of the racemate, e.g. 38.5 ng*h/mL in study 041 - 029 (4).*

*Formation of the N - desmethyl metabolite seems to be enantioselective, i.e. the (S,S)-enantiomer is converted to more than two - fold higher N - desmethyl - asenapine concentrations than the (R,R)-enantiomer based on AUC0 - tlast. Although the C - t profiles of the N - desmethyl metabolites contained sometimes only a few measurable data points, the plasma concentrations of N - desmethyl - (S,S) - asenapine were consistently higher in all subjects. In two subjects (subjects 02 and 05) the N-desmethyl metabolite could be followed for at least 24 h, both for the (S,S) - and (R,R) - enantiomer: 24 h and 36 h respectively. Adding up the AUC0 - tlast values for these subjects gives 11.5 ng*h/mL and 9.6 ng*h/mL respectively. These values are similar to those found in other clinical pharmacology studies with a single sublingual dose of 5 mg of the racemate, e.g. a mean of 8.6 ng*h/mL with median tlast = 41 h in study 041 - 029 (4).*

Compared to asenapine the N - desmethyl - asenapine shows a much lower binding affinity for therapeutically relevant receptors (see Investigator Brochure). Combined with the low level of exposure to the N - desmethyl metabolite, this indicates that this metabolite does not contribute substantially to the pharmacological effects of asenapine. Thus the difference in AUC between the N - desmethyl - (R,R) - asenapine and the N - desmethyl - (S,S) - asenapine is considered to be of no clinical relevance."

This reviewer does not agree with the sponsor's assessment as the difference in exposure to the two N-desmethyl metabolites might indicate either a difference in volume of distribution due to differences in tissue penetration or binding or more likely a difference in clearance with increased exposure to other metabolites.

Lower exposure to the R,R desmethyl metabolite in spite of a higher exposure to parent may mean more exposure to the potentially toxic to N-oxide, or it may mean greater metabolism of the R,R N-desmethyl-asenapine by CYP2D6 at least initially. Although exposure to the S,S enantiomer is slightly lower, exposure to the N-desmethyl metabolite is significantly greater. Consequently, increased exposure to the S,S N-desmethyl metabolite could mean that it preferentially inhibits CYP2D6. In addition, if metabolism of N-desmethyl-asenapine by CYP2D6 is the mechanism of toxicity then this could be the more clinically important finding. Presently it's not possible to determine what the clinical consequences might be without further *in vitro* and possibly *in vivo* testing. These results might indicate a difference in risk : benefit ratio for the different enantiomers if administered separately.

5.5.4 Bioavailability

5.5.4.1 Absolute Bioavailability

Two studies were conducted to determine asenapine's absolute bioavailability. In study 25533 the IV dose was too low to result in reliable determinations of asenapine concentrations and in study 41036 even thought the IV dose was increased, concentrations were still too low to determine the terminal elimination rate, and based on estimates of half-lives from other studies the amount of error would have been more than 10% so this study was terminated prematurely. Subsequently the sponsor combined the IV pharmacokinetics from the two studies and based on estimated terminal half-lives from a number of studies as well as AUCs from these studies was able to obtain an overall estimate of average absolute bioavailability for a single 5 mg dose of approximately 35%.

Descriptions of these study reports and their conclusions follow.

5.5.4.1.1 Study 25533 - Absolute Bioavailability

In study 25533 eight healthy adult male subjects were simultaneously administered a single sublingual dose of asenapine 5 mg and 10 µg (200 nCi) of ^{14}C-asenapine by intravenous push. Analyses for the radio - labeled asenapine and N-desmethyl-asenapine were performed by accelerator mass spectrometry.

Asenapine and desmethyl-asenapine kinetics for unlabeled species were determined, however the plasma concentrations of ^{14}C-asenapine and ^{14}C-N-Desmethyl-asenapine could not be reliably determined due to insufficient reproducibility of the method used. For this reason no results were reported for the radiolabeled component and IV pharmacokinetic metrics and bioavailability were not determined. Reportable metrics from study 25533 are shown in Table 59.

According to the sponsor unchanged ^{14}C-labeled asenapine was detected in feces, lthough the exact quantity could not be determined. Based on the presence of unchanged ^{14}C-labeled asenapine in feces biliary excretion is likely.

Table 59 Pharmacokinetic Metrics after a Single Simultaneous Administration of Asenapine 5 mg Sublingually and 10 mcg (200 nCi) ^{14}C-Asenapine IV Push – Study 25533

Parameter (unit)	Asenapine		N - Desmethyl - Asenapine	
N	8		8	
Route	SL	IV	SL	IV
Tmax (h)	[1.0] (0.5 - 3.0)	—[a]	[6.0] (2.0 - 12.0)	—[a]
Cmax (ng/mL)	5.95 (40.7) 2.05 - 8.64	—	0.463 (14.0) 0.321 - 0.532	—
$AUC_{0-tlast}$ (ng·h/mL)	37.0 (24.2) 19.6 - 44.6	—	7.76 (21.70 6.08 - 11.0	—
AUC_{0-inf} (ng·h/mL)	38.3 (24.1) 19.9 - 46.6	—	8.85 (22.5 6.99 - 12.7	—
CL/f (L/h)	141 (34.6) 107 - 251	—	559 (19.9) 374 - 681	—
Vz/f (L)	3713 (42.7) 2070 - 6847	—	8311 (31.1) 5918 - 13941	—
$t_{1/2}$ (h)	19.7 (44.2) 7.68 - 31.0	—	10.7 (38.8) 6.34 - 20.2	—

a Not reported. Based on sponsor's report it appears concentrations were too low to be reliably determined.

5.5.4.1.2 Study 41036 - Absolute Bioavailability

Study 41036 was intended as a single dose 2-way cross-over absolute bioavailability study in healthy adult males. It was preceded by a pilot study of 0.5 mg asenapine administered over 1 hour intravenously in three subjects. Due to the low dose and insufficient assay sensitivity, concentrations could only be determined out to 37 hours. With a half-life of 24 hours extrapolating to AUC_{∞} results in excessive error.

IV asenapine pharmacokinetic metrics, the raw data, and concentration vs. time plots on the untransformed and on the semi-log scale for study 41036 are shown in Table 60, Table 61, Figure 54, and Figure 55.

Table 60 Asenapine Pharmacokinetic Metrics after 0.5 mg over 1 hour IV – Study 41036

n	3
Tmax (h)	[0.98] 0.75 - 0.98
Cmax (ng/mL)	2.69 ± 0.8 (29.7) 1.79 - 3.32 [2.96]
dn - Cmax (ng/mL/mg)	5.38 ± 1.60
$AUC_{0 - tlast}$ ($ng/mL \times hr^{-1}$)	8.51 ± 1.80 (21.2) 6.58 - 10.2 [8.79]
dn - $AUC_{0 - tlast}$ ($ng/mL \times hr^{-1}$)	17.0 ± 3.61

Table 61 Asenapine Concentrations over Time when 0.5 mg is administered Intravenously over 1 hour – Study 41036

Sample no.	Time (hours)	Asenapine Concentration (ng/ml)		
		Subject 1	Subject 2	Subject 3
1	0	0	0	0
2	0.25	0.737	0.221	1.11
3	0.5	1.25	1.06	2.57
4	0.75	2.96	1.61	2.96
5	1.0	3.32	1.79	2.25
6	1.083	2.24	1.41	1.90
7	1.167	1.77	1.16	1.87
8	1.33	1.52	1.08	1.34
9	1.5	1.39	1.03	1.35
10	1.75	1.05	0.891	1.22
11	2	0.783	0.852	1.01
12	2.5	0.732	0.596	0.978
13	3	0.592	0.591	0.766
14	4	0.443	0.459	0.704
15	5	0.387	0.372	0.481
16	7	0.404	0.293	0.374
17	9	0.309	0.219	0.330
18	13	0.141	0.128	0.175
19	25	0.0506	0.0560	0.0623
20	37	0.0333	<0.0250	0.0286
21	49	<0.0250	<0.0250	<0.0250
22	61	<0.0250	<0.0250	<0.0250
23	73	<0.0250	<0.0250	<0.0250
AUCt		**9.0**	**6.92**	**10.33**
Estimated AUCextrap (Assuming t½ = 24 h)		**4.88**	**4.43**	**6.06**
% Extrapolated		**54.2**	**64.0**	**58.7**

Figure 54 Asenapine Concentration vs. Time Profiles after 0.5 mg IV over 1 hour – Study 41036

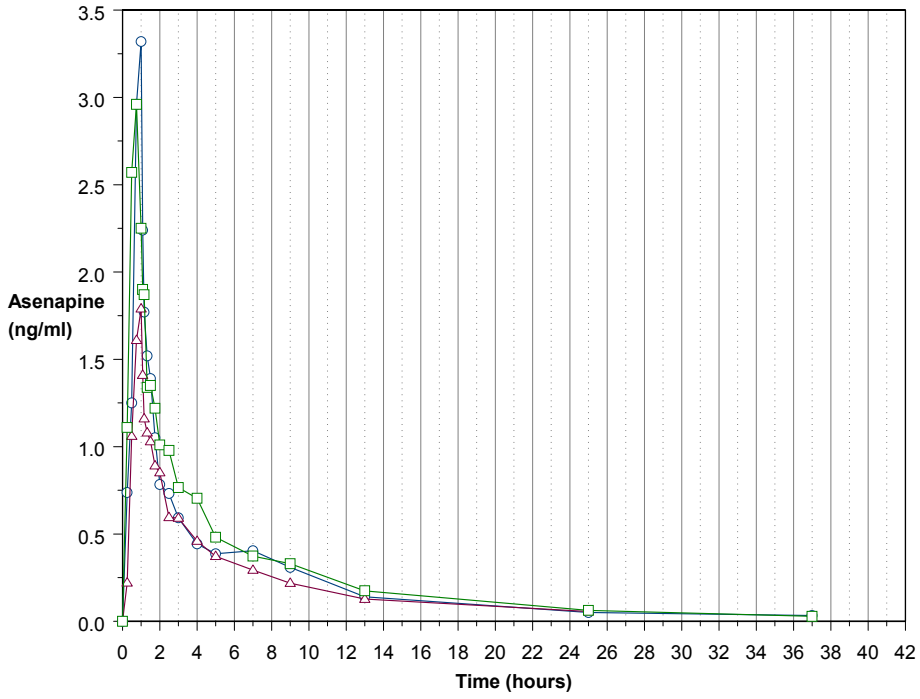
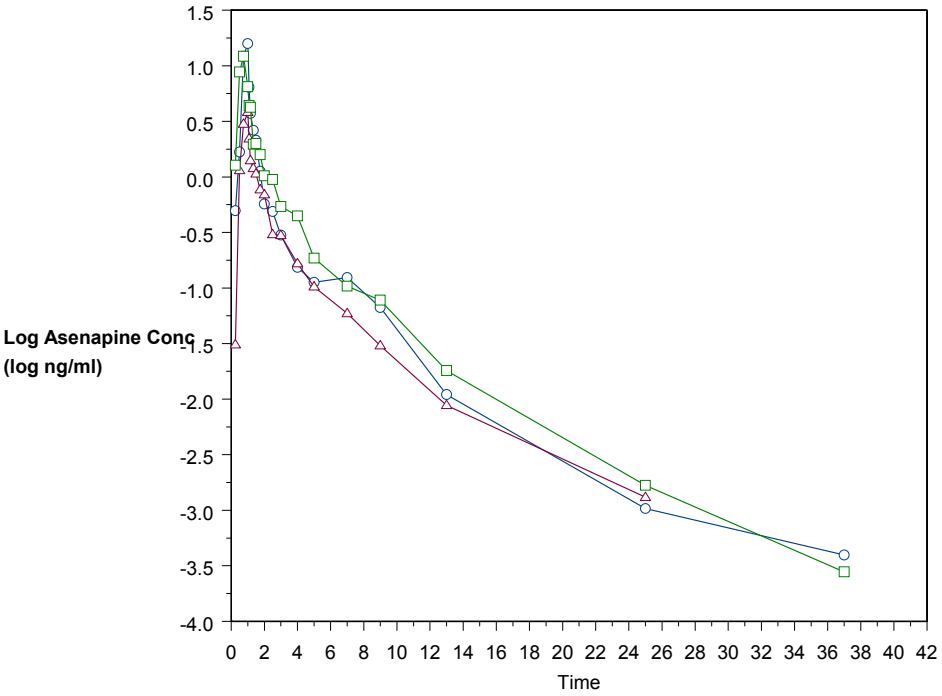


Figure 55 Asenapine Natural Log- Concentration vs. Time Profiles after 0.5 mg IV over 1 hour – Study 41036



5.5.4.1.3 Report INT00035825 – Absolute Bioavailability based on Studies 41036 and 25506

For report INT00035825, the pharmacokinetic results from intravenous administrations of asenapine from the failed absolute bioavailability study 41036 was combined with the IV data from study 25506. Both studies used doses of 0.5 mg, but study 41036 used an infusion duration of 1 hour and study 25506 a duration of 0.5 hours. Study 25506 was stopped because the intravenous dose was not well tolerated. See Table 62 for summary metrics.

An overall mean t½ from a series of PK trials, (see Table 63) was used to calculate the $AUC_{0-\infty,}^{IV}$s, for the IV data in Table 62. From these same trials, an overall estimate of $AUC_{0-\infty,}^{SL}$ was also determined in order to calculate the absolute bioavailability, (see Table 64).

The mean of 33.8 ng/mL*hr^{-1} was used as the overall $AUC_{0-\infty,}^{SL}$. Thus the overall dose normalized AUC (dn - $AUC_{0-\infty,}^{SL}$) was 6.76 ng/mL x hr^{-1} / mg.

F_{abs} was then calculated as follows:

$$F_{abs} = \frac{dn - AUC_{0-\infty,sl}}{dn - AUC_{0-\infty,iv}} \times 100\% = \frac{6.76}{19.4} \times 100\% = 34.8\%.$$

The sponsor's calculation of a 95% confidence interval for Fabs according to Fieller's theorem resulted in a 95% CI of 31.6% - 38.7%.

Table 62 Pharmacokinetic Metrics after Asenapine 0.5 mg IV Infusions by Study

Study	041036	25506	Overall
N	3	2	5
Infusion Duration	1 hour	0.5 hours	—
Tmax (h)	[0.98] 0.75 - 0.98	[0.55] 0.50 - 0.60	—
Cmax (ng/mL)	2.69 ± 0.8	2.58 ± 1.03	—
$AUC_{0 - tlast}$ (ng/mL* hr^{-1})	8.51 ± 1.80	6.55 ± 0.587	7.72 ± 1.69
$AUC_{0 - \infty, }^{IV}$ * (ng/mL* hr^{-1})	9.82 ± 1.33	9.55 ± 0.587	9.71 ± 0.997
dn - Cmax (ng/mL / mg)	5.38 ± 1.60	5.15 ± 2.05	—
dn - $AUC_{0 - tlast}$ (ng/mL* hr^{-1} / mg)	17.0 ± 3.61	13.1 ± 1.17	15.4 ± 3.39
dn - $AUC_{0 - \infty, }^{IV}$* (ng/mL* hr^{-1} / mg)	19.6 ± 2.66	19.1 ± 1.17	19.4 ± 1.99
CL (L/h)	51.6 ± 7.15	52.5 ± 3.22	51.9 ± 5.33
Vz (L)	1719 ± 238	1748 ± 107	1731 ± 178

* based on overall terminal t½ from Table 63

Table 63 Asenapine half-lives by Study after Single 5 mg SL Doses in Healthy Subjects

Metric (unit)	Study	n	Mean ± SD	Median t_{last} (h)	Group
$t_{½}$ (h)	041-029	26	22.4 ± 12.3	72	Fasting group
	041-030	32	20.2 ± 13.2	72	Sublingual group
	041-033	26	27.6 ± 17.1	72	Asenapine - only group
	25525	26	22.6 ± 9.52	72	Asenapine - only group
	25526	24	25.5 ± 15.3	72	Asenapine - only group
	25527	24	22.9 ± 8.66	72	Asenapine - only group
	25528	27	19.4 ± 9.96	72	Asenapine - only group
	25529	25	29.9 ± 18.1	72	Asenapine - only group
	25540	7	15.9 ± 5.04	60	Sublingual without charcoal group
	25545	24	17.1 ± 10.7	60	Non - smoking group
	25546	6	15.1 ± 8.01	48	Caucasian group
	A7501017	8	23.1 ± 5.68	72	Non - renally impaired group
	A7501018	8	39.2 ± 17.8	96	Non - hepatically impaired group
Overall (combined)*		263	23.1 ± 13.5		

* average of all individual values; equivalent to weighted mean

Table 64 Asenapine AUCs by Study after 5 mg SL Doses in Healthy Subjects

Metric (unit)	Study	n	Mean ± SD	Group
$AUC_{0-\infty}$ (ng/mL x hr^{-1})	041-029	26	38.5 ± 15.6	Fasting group
	041-030	32	25.6 ± 10.5	Sublingual group
	041-033	26	37.6 ± 12.9	Asenapine – only group
	25525	26	38.4 ± 11.7	Asenapine – only group
	25526	24	38.1 ± 11.2	Asenapine – only group
	25527	24	35.9 ± 10.7	Asenapine – only group
	25528	27	29.9 ± 8.67	Asenapine – only group
	25529	25	33.4 ± 10.3	Asenapine – only group
	25540	7	21.3 ± 6.11	Sublingual without charcoal group
	25545	24	24.3 ± 10.1	Non–smoking group
	25546	6	26.0 ± 10.7	Caucasian group
	A7501017	8	43.3 ± 10.9	Non-renally impaired group
	A7501018	8	55.0 ± 15.9	Non–hepatically impaired group
Overall (combined)*		263	33.8 ± 13.2	

* average of all individual values; equivalent to weighted mean

5.5.4.2 Relative Bioavailability

5.5.4.2.1 Relative Bioavailability – Oral vs. Sublingual

Study 25540 was a randomized, open label, placebo controlled, parallel design, single dose, fixed sequence study of the relative bioavailability of asenapine 5 mg administered sublingually and as an oral solution in two groups of 8 healthy adult males.

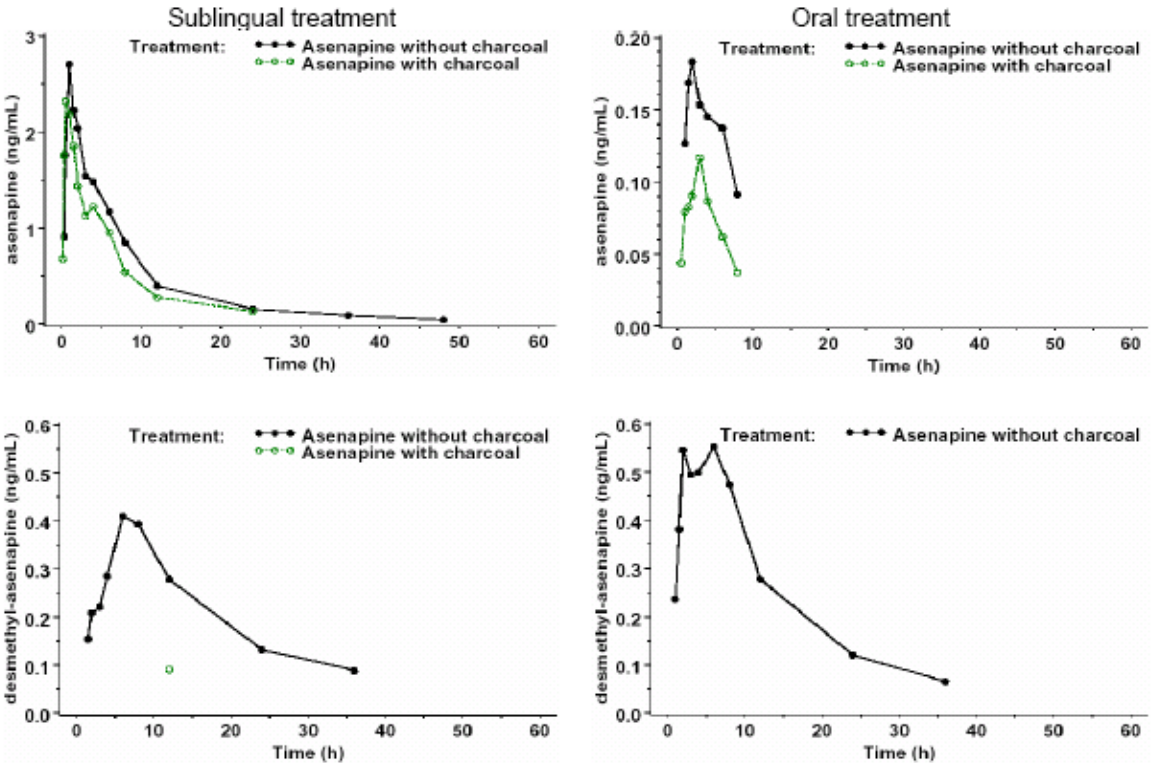
Subjects in Group 1 were administered asenapine sublingually and subjects in Group 2 were administered asenapine tablets orally dissolved in 150 ml of water. After an interperiod wash-out of 7 days subjects received the same asenapine treatment as previously, however it was administered 10 minutes after a 50 gm dose of activated charcoal in 400 ml of water.

Figure 56 shows the mean concentration-versus-time profiles for asenapine (upper panels) and desmethyl-asenapine (lower panels) after sublingual (left panels) and oral (right panels) asenapine treatment (5 mg single dose) with and without charcoal.

Based on Figure 56 the following conclusions may be drawn:

a) Asenapine peak concentrations after oral administration are approximately 1/15 (7%) those after sublingual administration
b) Desmethyl-asenapine peak concentrations are 40% higher after oral administration
c) Charcoal administration effects oral absorption more than sublingual absorption, with a decrease in asenapine exposure after oral administration of approximately 50% compared to a decrease in asenapine exposure of approximately 25% after sublingual administration.
d) The effect of charcoal administration on desmethyl-asenapine exposure is even greater than the effect on asenapine.
e) There is significant enterohepatic circulation of asenapine, but it is much greater for desmethyl-asenapine.

Figure 56 Mean Asenapine and Desmethyl-Asenapine Concentration vs. Time Profiles after Administration Sublingually and as an Oral Solution in the Absence and Presence of Activated Charcoal – Study 25540



Pharmacokinetic summary metrics are shown in Table 65. The values confirm the conclusions made from Figure 56.

Quantitatively the relative bioavailability of asenapine after oral administration compared to sublingual administration is approximately 7% with an estimated absolute oral bioavailability of around 3%.

In addition, the exposure to desmethyl-asenapine is only 4.6% lower after oral administration, however the rapid delivery results in a 60% higher peak desmethyl concentration after oral administration.

These results indicate that the first pass effect is not due to metabolism to desmethyl-asenapine but rather to a different elimination pathway. Based on Figure 56 it cannot be due to biliary excretion of asenapine and is unlikely due to glucuronidation because this tends to be a low affinity pathway. The most likely pathways responsible for the first pass effect are either N-oxidation or 11-hydroxylation. Depending upon which pathway it is, the clinical ramifications regarding labeling may vary greatly, as an N-oxide is likely much more toxic.

Table 65 Asenapine and Desmethyl-Asenapine Pharmacokinetic Metrics and Relative Bioavailability after Single 5 mg Oral vs. SL Doses in the Presence and Absence of Activated Charcoal - Study 25540

Route of Administration	Parameter (unit)	Asenapine		Desmethyl-Asenapine	
		with charcoal	without charcoal	with charcoal	without charcoal
Sublingual (n=7)	Tmax (h)	0.53 (0.33 - 2.0)	1.0 (0.5 - 2.0)	12.0 (8.00 - 12.0)	6.0 (4.0 - 8.0)
	Cmax (ng/mL)	2.58 ± 1.88	3.02 ± 1.38	0.096 ± 0.048	0.428 ± 0.210
	GeoMean Cmax	1.87	2.70	0.0838	0.371
	$AUC_{0\text{-tlast}}$ (ng·h/mL)	15.4 ± 12.0	20.3 ± 5.75	0.882 ± 0.981	7.59 ± 4.13
	$AUC_{0\text{-}\infty}$ (ng·h/mL)	16.2 ± 12.4	21.3 ± 6.11	—	10.3 ± 3.34 [b]
	GeoMean AUC_{∞}	12.4	20.4	—	9.86
	$t_{½}$ (h)	11.1 ± 5.46	15.9 ± 5.04	—	15.1 ± 4.32 [b]
Oral (n=8)	Tmax (h)	3.0 (1.0 - 4.0)	2.0 (1.5 - 4.0)	—	3.00 (1.98 - 8.07)
	Cmax (ng/mL)	0.138 ± 0.0627	0.204 ± 0.079	—	0.598 ± 0.117
	GeoMean Cmax	0.126	0.189	—	0.588
	$AUC_{0\text{-tlast}}$ (ng·h/mL)	0.612 ± 0.275	1.38 ± 0.621	—	8.38 ± 1.47
	$AUC_{0\text{-}\infty}$ (ng·h/mL)	0.868 ± 0.287 [a]	1.87 ± 0.768	—	9.56 ± 1.63
	GeoMean AUC_{∞}	0.824	1.75	—	9.41
	$t_{½}$ (h)	4.19 ± 0.671 [a]	6.75 ± 3.72	—	10.5 ± 2.72
Geometric Mean Ratios Oral : SL	Cmax	0.067	0.070	—	1.584
	AUC_{∞}	0.066	0.086	—	0.954
Estimated Absolute Oral Bioavailability			~ 3.0%	—	—

a n = 7
b n = 6

5.5.4.2.2 Relative Bioavailability – Supra-lingual and Buccal vs. Sublingual

Study 25512 was a 3-way 3-period crossover study of the relative bioavailability of asenapine 200 mcg, (2 x 100 mcg rapidly dissolving gelatin and mannitol tablets) administered via the supra-lingual and buccal routes as compared to sublingually in 23 healthy young males.

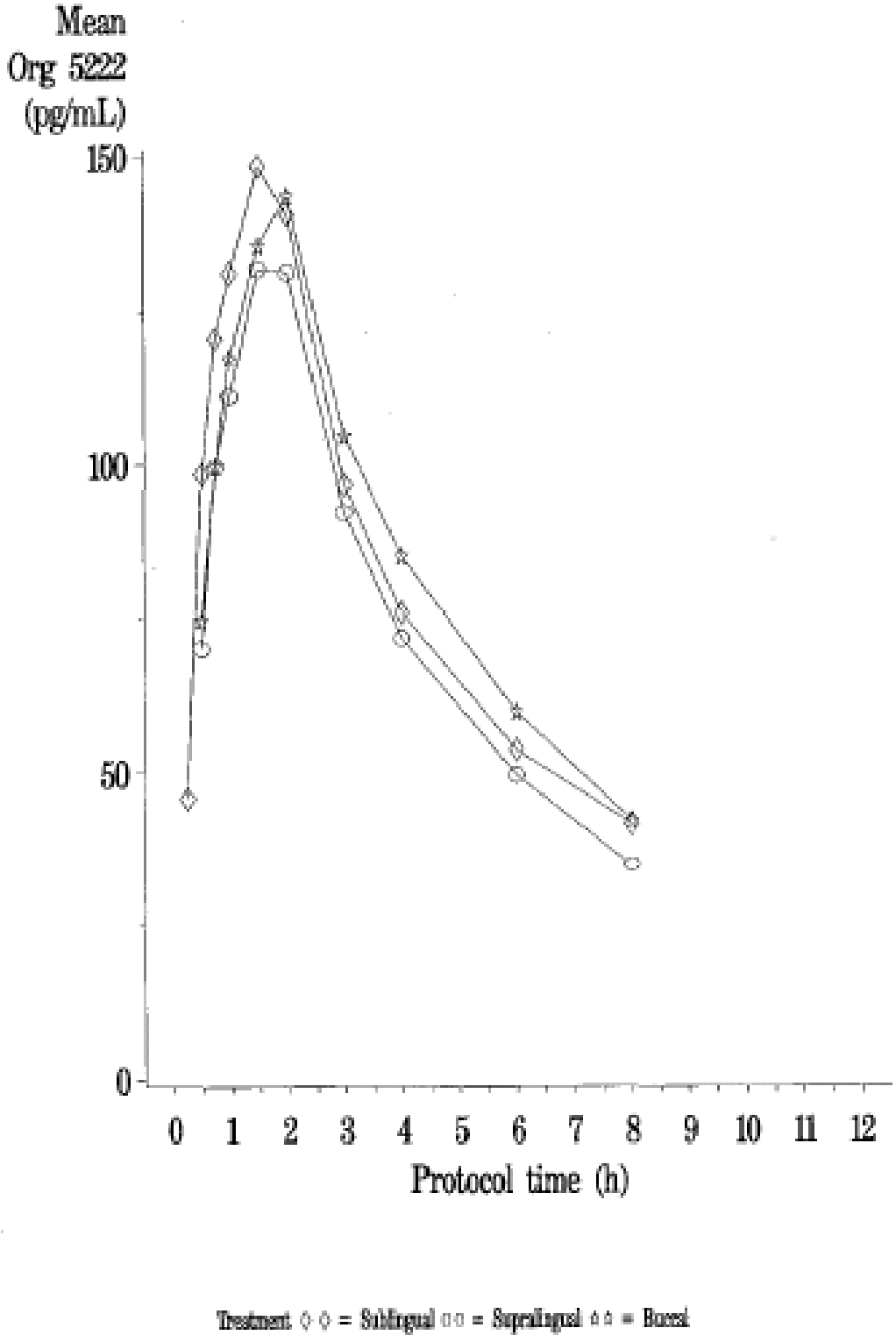
Both the lingual and buccal routes had lower Cmaxs, AUCs and delayed Tmaxs as compared to the sublingual route, with absorption via the supralingual route being less than the buccal route. The supralingual route was bioinequivalent to sublingual administration and although the buccal route met the criteria for bioequivalence, it barely did so, (see Table 66 and Figure 57). Since this formulation is different than the to-be-marketed formulation and since the dose used is in a range where bioavailability is greater than with clinical dosages no conclusions can be drawn regarding bioequivalence under clinical dosing conditions.

Table 66 Comparative Bioavailability of Asenapine 200 mcg after Supralingual, Buccal, and Sublingual Administration of a Development Formulation – Study 25512

	Summary Statistics			Geometric Means			Geometric Mean Ratios (90% CI)	
	Supralingual	Buccal	Sublingual	Supralingual	Buccal	Sublingual	Supralingual : Sublingual	Buccal : Sublingual
N	23a	23a	23a	—	—	—	—	—
Tmax	1.66 ± 0.32	2.1 ± 0.8	1.38 ± 0.35	—	—	—	—	—
Cmax	150.8 ± 63.5	152.2 ± 48.5	157.3 ± 43.2	135.85	143.2	151.42	0.90 (0.77 - 1.05)	0.95 (0.81 - 1.11)
AUC	864.2 ± 290.5	955.8 ± 212.6	966.8 ± 233.7	799.9	929.7	944.4	0.85 (0.75 - 0.96)	0.98 (0.87 - 1.12)
t½	4.31 ± 1.18	4.36 ± 0.89	4.88 ± 1.02	—	—	—	—	—

a n = 21 for t½

Figure 57 Comparison of Mean Asenapine Concentration vs. Time Profiles after Supralingual, Buccal, and Sublingual Administration of a Development Formulation – Study 25512



5.5.5 Bioequivalence

5.5.5.1 Pivotal BE Study (b) (4)) - Study A7501015

Study A7501015 examined the effect of different (b) (4) on the on the bioequivalence of asenapine 5 mg tablets.

This was a single-center, open-label, randomized, single dose, 3-treatment, 3-way crossover, bioequivalence study in healthy volunteers comparing the pharmacokinetic parameters following 3 treatments. Thirty-eight subjects Healthy male and/or female subjects between the ages of 18 and 55 years, inclusive were randomized to the study, and 32 completed the study.

On Study Days 1, 8, and 15, subjects received 1 of the 3 treatments indicated below in random order:

A: Reference: Asenapine 5 mg (b) (4)a
(clinical formulation).

B: Test 1: Asenapine 5 mg (b) (4)
(proposed commercial formulation).

C: Test 2: Asenapine 5 mg (b) (4)
(proposed commercial formulation)

In addition to bioequivalence the study assessed the organoleptic properties of the formulations through a taste test questionnaire.

Results are shown in Table 67, Figure 58, and Figure 59.

Table 67 Asenapine Pharmacokinetic Parameters Following Sublingual Administration of 5-mg Asenapine Tablets Manufactured With Gelatin Supplied by Croda (Reference) and With Gelatin Supplied by DGF in an Unflavored Formulation (Test 1) and a Raspberry Flavored Formulation (Test 2) - Study A7501015

(b) (4)	Least-Squares Mean Parameter Values[a]		Ratio	90% Confidence Interval
	(b) (4) (Test1)	(b) (4) (Reference)		
N	33	36		
Cmax, ng/mL	3.07	2.96	104	91.51 to 117.45
AUC(0-tlqc), ng*hr/mL	21.9	21.6	101	91.19 to 112.51
AUC(0-∞), ng*hr/mL	23.4	23.2	101	91.15 to 111.73
tmax, hr	1.00	1.06		Not Applicable
t½, hr	12.3	13.4		Not Applicable
	DGF Tablet Red Raspberry	**Croda Tablet**		
	(Test2)	**(Reference)**		
N	34	36		
Cmax, ng/mL	3.23	2.96	109	96.66 to 123.64
AUC(0-tlqc), ng*hr/mL	23.5	21.6	109	97.96 to 120.53
AUC(0-∞), ng*hr/mL	24.8a	23.2	107	96.79 to 118.55
tmax, hr	1.11	1.06		Not Applicable
t½, hr	13.0b	13.4		Not Applicable

Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference). 90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean.

a It's stated in the text of the clinical study report that these are geometric means

b N = 33 (t½ could not be determined for all subjects).

Figure 58 Individual Asenapine Cmax and AUCs by Treatment for (b) (4) in Pivotal BE Study A7501015

(b) (4)

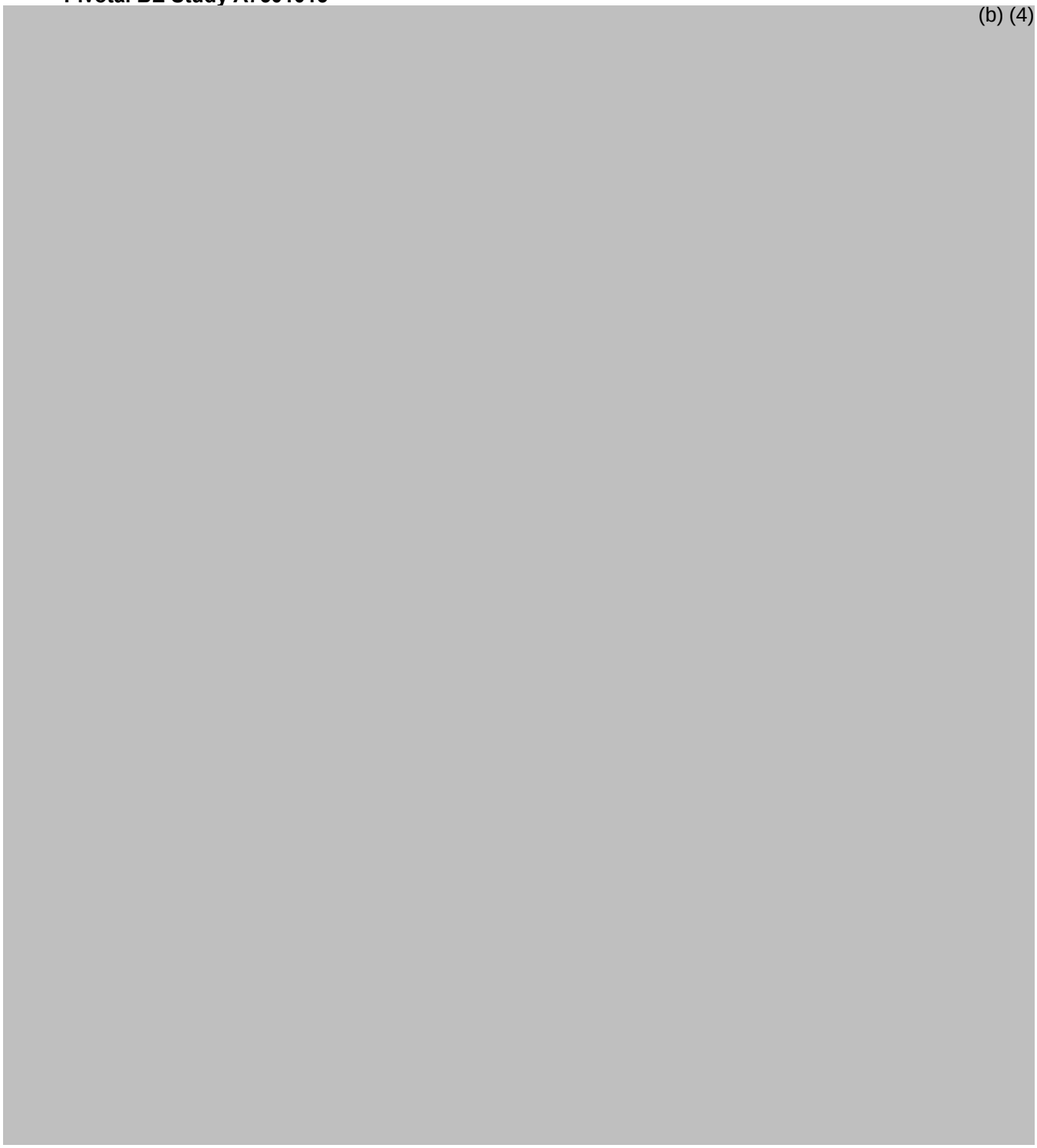
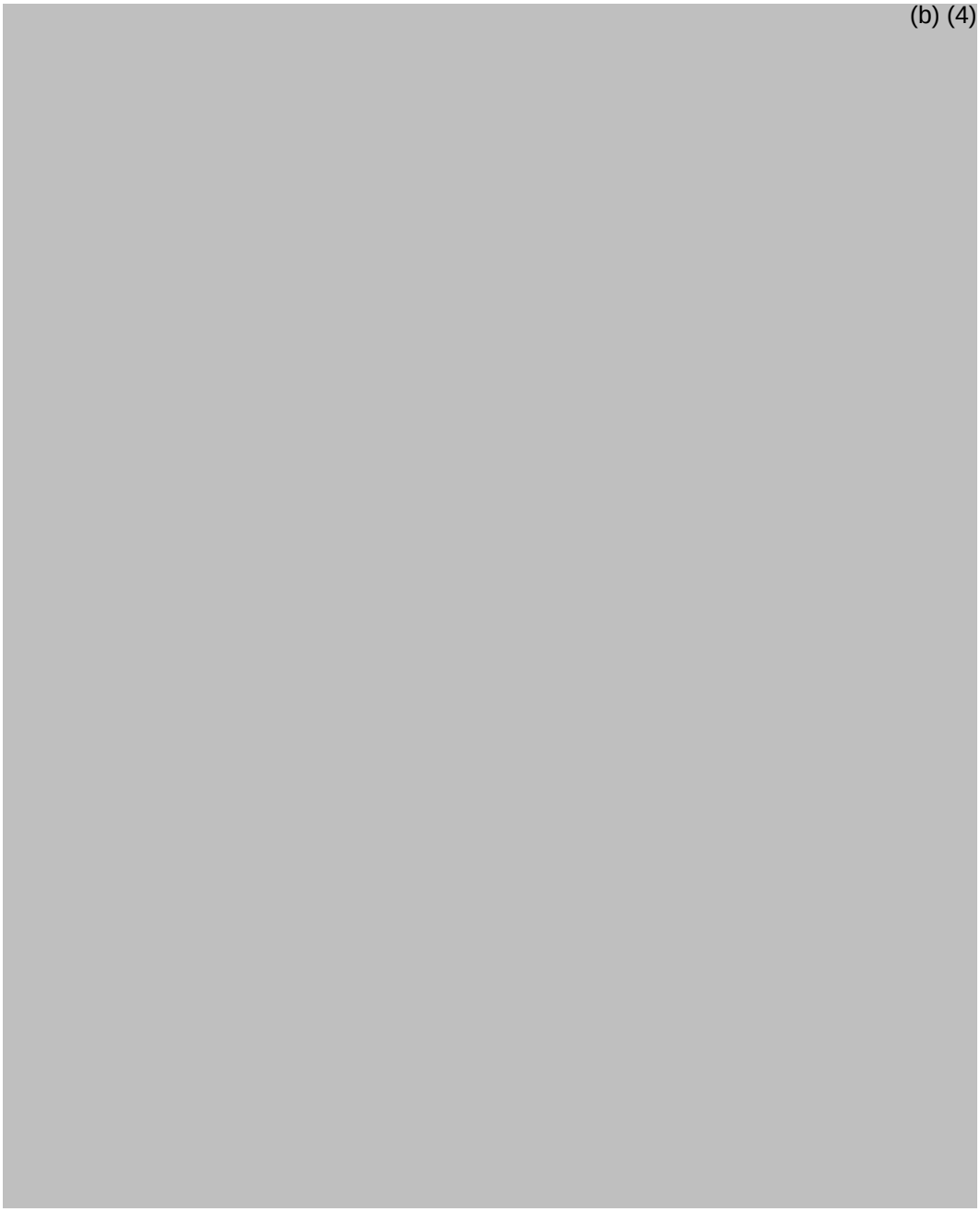


Figure 59 Individual Desmethyl-Asenapine Cmax and AUCs by Treatment for (b) (4) (b) (4) in Pivotal BE Study A7501015

Figure 4. Individual Desmethyl Asenapine Cmax (Upper Panel, ng/mL) and AUC(0-∞) (Lower Panel, ng·hr/mL) Values Following Sublingual Administration of 5-mg Asenapine Tablets Manufactured (b) (4) and (b) (4) (Test 1) and a (b) (4) (Test 2) (Study 7501015)



5.5.5.2 Pivotal BE Study (b) (4) - Study A7501016

Study A7501016 examined the effect of differen (b) (4) of asenapine maleate on the bioequivalence of asenapine 5 mg tablets. According to the sponsor the rationale is as follows:

'Asenapine is currently developed as a sublingual formulation, which quickly disintegrates in the saliva. Clinical supplies (b) (4) used in Phase 3 clinical trials have been manufactured with (b) (4) active pharmaceutical ingredient (API). Future drug supplies for the provisional market image of asenapine may be manufactured with (b) (4) API. The bioequivalence between the (b) (4) differences of these 2 formulations needs to be determined. Thus, this study was conducted to determine whether future commercial formulations could be manufactured with the (b) (4) API.'

However, based on information from study 41026, which is reported in the next section, the rationale for decreasing (b) (4) appears to be in order to mask the bitter taste of asenapine.

Study A7501016 was a randomized, open-label, single-dose, 2-way crossover study of single 5 mg sublingual doses administered a week apart in 36 healthy male and female volunteers between the ages of 18 and 55 years.

Treatments were as follows:

A = Asenapine 5 mg (b) (4) tablet (TBM formulation)
B = Asenapine 5 mg (b) (4) tablet (Phase 3 formulation; CTF).

Table 68 Summary of Asenapine Pharmacokinetic Parameter Values Following Administration of Asenapine 5 mg (b) (4) Tablets (Reference) and 5 mg (b) (4)d Tablets (Test) - Study A7501016

Parameter	Least-Squares Mean Parameter Values[c]		Ratio	90% Confidence Interval
	(b) (4) Tablet (Test)	(b) (4)d Tablet (Reference)		
N	35	34		
Cmax ng/mL	2.95	3.25	90.6	80.80 to 101.65
AUC(0-tlqc) ng*hr/mL	21.2	23.0	92.1	83.62 to 101.45
AUC(0-∞) ng*hr/mL	23.1a	25.1b	92.0	83.69 to 101.18
Tmax hr	1.13	1.12		Not Applicable
t½ hr	18.7a	19.1b		Not Applicable

a N=33;
b N = 32 (t½ could not be determined for all subjects)
Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference). 90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean.
c In the text of the study report it indicates that these are geometric means

This study was discovered while writing the pertinent CPB questions. Although the sponsor's conclusions are that the formulations are bioequivalent, the comparison is on the least square means and there is no mention of geometric means. In addition, the datafiles could not be opened and the basis of these calculations could not be verified. Thus bioequivalence cannot be assured presently and further verification is needed. Whether this is an internal or external issue is unknown.

Table 69 Summary of Desmethyl Asenapine Pharmacokinetic Parameter Values Following Administration of Asenapine 5 mg (b) (4) Tablets (Reference) and 5 mg (b) (4) Tablets (Test) - Study A7501016

Parameter	Least-Squares Mean Parameter Values[a]		Ratio	90% Confidence Interval
	(b) (4) Tablet (Test)	(b) (4) Tablet (Reference)		
N	35	34		
Cmax ng/mL	0.604	0.623	97.0	92.48 to 101.66
AUC(0-tlqc) ng*hr/mL	11.3	11.3	99.9	95.81 to 104.15
AUC(0-∞) ng*hr/mL	13.6	13.3a	102	96.94 to 107.10
Tmax hr	5.44	5.17		Not Applicable
t½ hr	15.6	14.7a		Not Applicable

Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference).
90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean.
a In the text of the study report it indicates that these are geometric means

A cursory review of the bioanalytic method indicates that the precision of the assay may be unacceptably high at the lower end and thus estimates of AUC and half-life may be off.

Table 70 Accuracy and Precision of Asenapine Quality Control Samples – Study A7501016

QC	A	B	C	D	E
Nominal Concentration	0.075	0.75	1.5	6.0	15.0
Measured Mean Concentraion	0.0753	0.82	1.55	6.53	16.20
SD	0.0137	0.079	0.201	0.246	0.581
%CV (Precision)	18.2	9.7	13.0	3.8	3.6
Accuracy	100.4	109.3	103.3	108.8	108.0
Bias	0.4	9.3	3.3	8.8	8.0

Figure 60 Mean Plasma Asenapine Concentration-Time Profiles Following Administration of Asenapine 5 mg (b) (4) Tablets (Filled Circles; Reference) and 5 mg (b) (4) Tablets (Open Circles, Test) (Study A7501016)

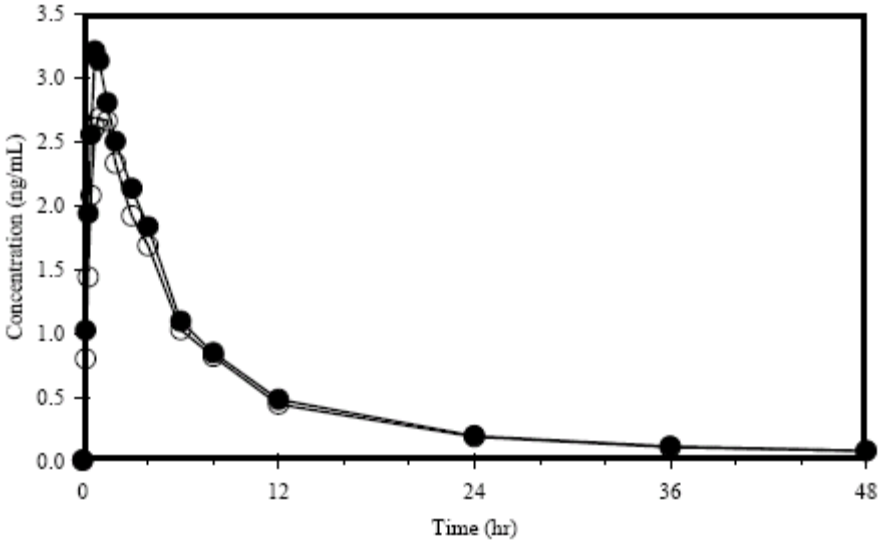


Figure 61 Mean Plasma Asenapine Concentration-Time Profiles Following Administration of Asenapine 5 mg (b) (4) Tablets (Filled Circles; Reference) and 5 mg (b) (4) Tablets (Open Circles, Test) (Study A7501016)

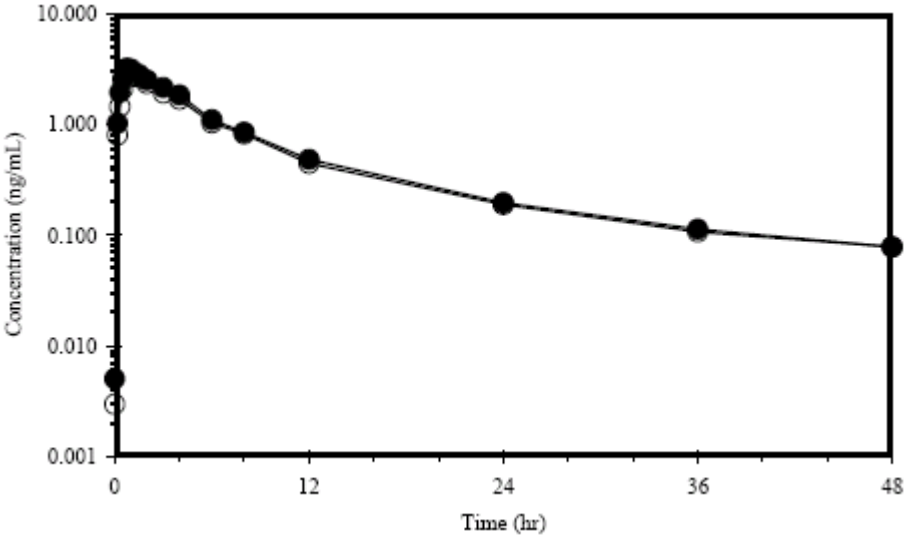
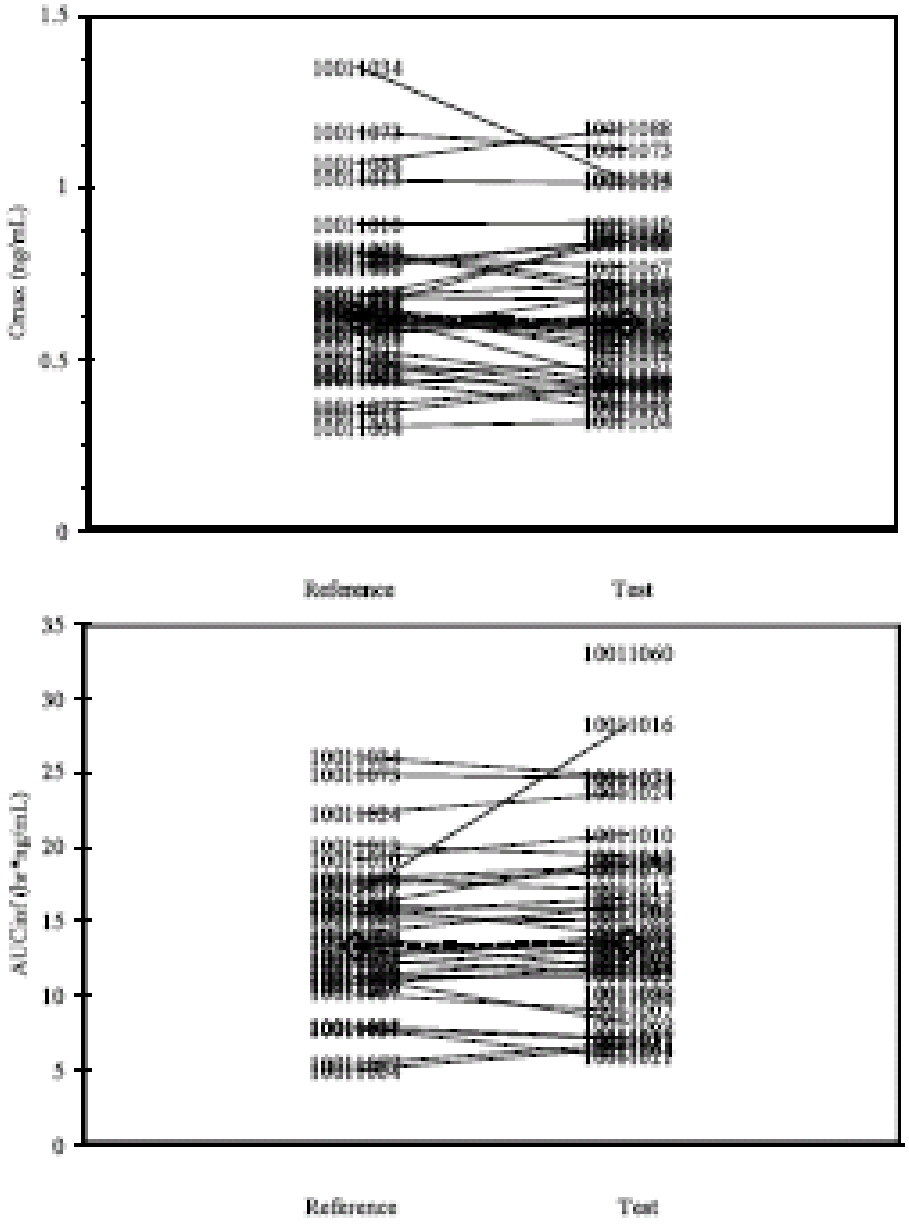


Figure 62 Asenapine Cmax Values Following Administration of Asenapine 5 mg (b) (4) Tablets (Reference) and 5 mg (b) (4) Tablets (Test) (Study A7501016)

Figure 63 Asenapine AUC(0-∞)Values Following Administration of Asenapine 5 mg (b) (4) Tablets (Reference) and 5 mg (b) (4) Tablets (Test) (Study A7501016)

Figure 64 Desmethyl- Asenapine Cmax (Upper Panel, ng/mL) and AUC(0-∞) (Lower Panel, ng·hr/mL) Values Following Administration of Asenapine 5 mg (b) (4) Tablets (Reference) and 5 mg (b) (4) Tablets (Test) (Study A7501016)

Figure 4. Desmethyl Asenapine Cmax (Upper Panel, ng/mL) and AUC(0-∞) (Lower Panel, ng·hr/mL) Values Following Administration of Asenapine 5 mg (b) (4) Tablets (Reference) and 5 mg (b) (4) Tablets (Test) (Study A7501016)



Individual subjects are identified by numbers; mean values are represented by diamonds.

According to the sponsor three subjects withdrew from the study during the treatment phase. Two subjects were withdrawn due to lack of compliance, and 1 withdrew consent. No subjects withdrew due to adverse events. All subjects were analyzed for safety.

During telemetry monitoring, 10 subjects experienced bradycardia; eight subjects experienced tachycardia; seven subjects experienced sinus pause, 3 subjects experienced junctional rhythm; and 1 subject experienced bradycardia with junctional rhythm (Appendix B9.3).

The central nervous system, gastrointestinal system, and cardiovascular systems were the body systems most frequently affected by adverse events in the milled tablet treatment group (Table 13.6.4). The most frequently reported adverse events were somnolence (35 subjects), oral hypoaesthesia (22 subjects), dizziness (11 subjects), bradycardia and tachycardia (7 subjects each), dysgeusia, oral paraesthesia and sinus arrest (5 subjects each), nausea (4 subjects), hypotension and nodal rhythm (3 subjects each), and oral paraesthesia and sinus arrest (5 subjects each), nausea (4 subjects each), headache (3 subjects each), and acne, headache, hypoaesthesia, and restless legs syndrome (2 subjects each) (Table 13.6.5).

All other adverse events were single occurrences.

Subject 1001026 was an alcoholic

Several subjects experienced potentially clinically significant increases in triglycerides and lipid values.

Subject 10011008 had a value of 245 mg/dL on Day 8. Values at Baseline and at the Follow-up visit on Day 15 were 128 mg/dL and 80 mg/dL, respectively.

Subject 10011017 had a value of 323 mg/dL on Day 8. Values at Baseline and at the Follow-up visit on Day 15 were 80 mg/dL and 61 mg/dL, respectively.

- Subject 10011024 had a value of 344 mg/dL on Day 8. Values at Baseline and at the Follow-up visit on Day 15 were 141 mg/dL and 149 mg/dL, respectively.

- Subject 10011026 had values of 243 mg/dL on Day 1 and 168 mg/dL on Day 12. The value at Baseline was 83 mg/dL.

Subject 10011046 had a value of 1573 mg/dL on Day 8. Values at Baseline and at the Follow-up visit on Day 15 were 55 mg/dL and 42 mg/dL, respectively.

AEs are shown on the following pages from this study. There are a disturbing number of cases of sinus arrest and other cardiac findings, with these single 5 mg doses in healthy volunteers.

Regimen	Asenapine 5mg sublingual tablet (b) (4)		Asenapine 5mg sublingual tablet (b) (4)	
Number of Subjects	(N=34)		(N=35)	
Adverse Event	Number	(%) of Subjects	Number	(%) of Subjects
--Somnolence	34	(100.0)	35	(100.0)
-- oral Hypoaesthesia	25	(73.5)	22	(62.9)
--Dizziness	13	(38.2)	11	(31.4)
--Bradycardia	4	(11.8)	7	(20.0)
--Tachycardia	10	(29.4)	7	(20.0)
--Dysgeusia	8	(23.5)	5	(14.3)
--Paraesthesia oral	5	(14.7)	5	(14.3)
--Sinus arrest	5	(14.7)	5	(14.3)
--Nausea	4	(11.8)	4	(11.4)
--Hypotension	6	(17.6)	3	(8.6)
--Nodal rhythm	1	(2.9)	3	(8.6)
--Acne	0	(0.0)	2	(5.7)
--Headache	3	(8.8)	2	(5.7)
--Hypoaesthesia	2	(5.9)	2	(5.7)
--Restless legs syndrome	0	(0.0)	2	(5.7)
--Anxiety	0	(0.0)	1	(2.9)
--Bradyphrenia	0	(0.0)	1	(2.9)
--Depilation	0	(0.0)	1	(2.9)

Regimen	Asenapine 5mg sublingual tablet (b) (4)	Asenapine 5mg sublingual tablet (b) (4)
Number of Subjects	(N=34)	(N=35)
Number (%) of subjects reporting TESS AEs	34 (100.0)	35 (100.0)
All TESS AEs	34 (100.0)	35 (100.0)
Associated TESS AEs		
Number (%) of subjects reporting TESS AEs by Maximum Intensity		
All TESS AEs	0 (0.0)	1 (2.9)
Mild	33 (97.1)	33 (94.3)
Moderate	1 (2.9)	1 (2.9)
Severe		
Mild	0 (0.0)	1 (2.9)
Moderate	33 (97.1)	33 (94.3)
Severe	1 (2.9)	1 (2.9)
Number of total TESS AE reports by intensity		
All TESS AEs	166	154
Mild	50	54
Moderate	114	99
Severe	2	1
Associated TESS AEs	154	142
Mild	42	47
Moderate	110	94
Severe	2	1
Number of: Withdrawals due to TESS Adverse Events		
Serious TESS AEs	0	0
Deaths	0	0

	Asenapine 5mg sublingual tablet	Asenapine 5mg sublingual tablet
Regimen	(b) (4)	(b) (4)
Number of Subjects	(N=34)	(N=35)
Body System/Adverse Event	Number (%) of Subjects	Number (%) of Subjects
Nervous system disorders	34 (100.0)	35 (100.0)
--Somnolence	34 (100.0)	35 (100.0)
--Dizziness	13 (38.2)	11 (31.4)
--Dysgeusia	8 (23.5)	5 (14.3)
--Paraesthesia oral	5 (14.7)	5 (14.3)
--Headache	3 (8.8)	2 (5.7)
--Hypoaesthesia	2 (5.9)	2 (5.7)
--Restless legs syndrome	0 (0.0)	2 (5.7)
--Dizziness postural	1 (2.9)	1 (2.9)
--Coordination abnormal	1 (2.9)	0 (0.0)
--Syncope	1 (2.9)	0 (0.0)
Gastrointestinal disorders	25 (73.5)	22 (62.9)
--Hypoaesthesia oral	25 (73.5)	22 (62.9)
--Nausea	4 (11.8)	4 (11.4)
--Oral discomfort	4 (11.8)	1 (2.9)

Table 13.6.4. Summary of TESS Adverse Events by Body System (Sorted by Body System and Decreasing Frequency) A PHASE 1, OPEN-LABEL, SINGLE-DOSE, BIOEQUIVALENCE STUDY OF THE (b) (4) FORMULATIONS OF (b) (4) AND (b) (4) ASENAPINE TABLETS (5 MG) IN HEALTHY VOLUNTEERS (Protocol A7501016)

Regimen	Asenapine 5mg sublingual tablet (b) (4)	Asenapine 5mg sublingual tablet (b) (4)
Number of Subjects	(N=34)	(N=35)
Body System/Adverse Event	Number (%) of Subjects	Number (%) of Subjects
Skin and subcutaneous tissue disorders (cont.)		
--Dermatitis allergic	0 (0.0)	1 (2.9)
--Dermatitis	1 (2.9)	0 (0.0)
--Dermatitis contact	1 (2.9)	0 (0.0)
--Erythema	1 (2.9)	0 (0.0)
--Rash	1 (2.9)	0 (0.0)
--Skin exfoliation	1 (2.9)	0 (0.0)
Psychiatric disorders	7 (20.6)	2 (5.7)
--Anxiety	0 (0.0)	1 (2.9)
--Bradyphrenia	0 (0.0)	1 (2.9)
--Restlessness	7 (20.6)	1 (2.9)
Respiratory, thoracic and mediastinal diso	2 (5.9)	2 (5.7)
--Nasal congestion	0 (0.0)	1 (2.9)
--Pharyngeal hypoaesthesia	0 (0.0)	1 (2.9)
--Dry throat	1 (2.9)	0 (0.0)
--Sneezing	1 (2.9)	0 (0.0)
Eye disorders	1 (2.9)	1 (2.9)

Table 13.6.4. Summary of TESS Adverse Events by Body System (Sorted by Body System and Decreasing Frequency) A PHASE 1, OPEN-LABEL, SINGLE-DOSE, BIOEQUIVALENCE STUDY OF THE (b) (4) FORMULATIONS OF (b) (4) AND M (b) (4) ASENAPINE TABLETS (5 MG) IN HEALTHY VOLUNTEERS (Protocol A7501016)

Regimen	Asenapine 5mg sublingual tablet (b) (4)	Asenapine 5mg sublingual tablet (b) (4)
Number of Subjects	(N=34)	(N=35)
Body System/Adverse Event	Number (%) of Subjects	Number (%) of Subjects
--Eyelid oedema	0 (0.0)	1 (2.9)
--Vision blurred	1 (2.9)	0 (0.0)
General disorders and administration site	0 (0.0)	1 (2.9)
--Feeling of relaxation	0 (0.0)	1 (2.9)
Investigations	1 (2.9)	1 (2.9)
--Heart rate decreased	0 (0.0)	1 (2.9)
--Blood pressure decreased	1 (2.9)	0 (0.0)
Surgical and medical procedures	0 (0.0)	1 (2.9)
--Depilation	0 (0.0)	1 (2.9)
Infections and infestations	1 (2.9)	0 (0.0)
--Upper respiratory tract infection	1 (2.9)	0 (0.0)
Injury, poisoning and procedural complica	2 (5.9)	0 (0.0)
--Incision site complication	1 (2.9)	0 (0.0)
--Sunburn	1 (2.9)	0 (0.0)
Musculoskeletal and connective tissue disorders	1 (2.9)	0 (0.0)
--Back pain	1 (2.9)	0 (0.0)

Information provided on the drug supplies are shown in Table 71.

Table 71 Reference and Test Batch Information Included in Study Report - Study A7501016

Test/Ref	Drug	Lot Number	FID Number	Strength	Formulation
Reference	Asenapine	05-024601	D0501645	5 mg	DGF (b) (4)
Test	Asenapine	05-024604	D0501720	5 mg	DGF (b) (4)

No information was provided on the actua (b) (4)s of comparison in the study report. Upon checking with the chemistry reviewer on April 14, 2008 he was unaware that the (b) (4) had changed. While looking for the (b) (4) with the chemistry reviewer we found that in amendment 007 an additional additional manufacturing site was proposed that used a (b) (4)

(b) (4)

In this review the stated particle size was listed as follows '***The typical particle size (D[v, 0.95]), of asenapine maleate drug substance varies between 6 μm and 14 μm',*** and apparently this was found by this reviewer under the drug product section of the submission. On April 14, 2008 upon further review it was found that the particle size specification was a D[v,0.95] of 30 μM and no particle size information was included in the batch analyses submitted.

The following was then also found in the original submission under the drug substance section:

(b) (4)

Tested from batch P onwards, results found ranging (b) (4)*. Batch AT had a* (b) (4) (b)*. A deviating* (b) (4) *was intentionally obtained to support manufacturability and bioavailability studies.*

(b) (4)

The (b) (4)*e distribution is determined* (b) (4)*.* (b) (4) (b) (4)

(b) (4)

The proposed acceptance criterion on (b) (4) *can therefore be fully justified both from a manufacturability and from a biopharmaceutical point of view.'*

In summary only this single batch used in the bioequivalence study has a (b) (4) (b), and all efficacy and safety data was generated with (b) (4) (b) (4)

Table 72 Subject Demographics Study - A7501016

Subject Number	Age at Day 1	Sex (Hormonal Status)	Race	Height (cm)	Weight (kg)	BMI (kg/m2)	Smoking Status	Alcohol Drinks per Week
10011002	25	Male	Caucasian	189.2	79.2	22.1	Never Smoked	5
10011004	22	Male	Caucasian	196.2	91.1	23.7	Never Smoked	0
10011005	20	Male	Caucasian	186.1	98.5	28.4	Never Smoked	0
10011007	20	Male	Caucasian	176.5	59.4	19.1	Never Smoked	0
10011008	19	Female (Premenopausal)	Caucasian	164.5	65.0	24.0	Never Smoked	0
10011009	23	Male	Other-HISPANIC	170.2	54.4	18.8	Never Smoked	0
10011010	38	Male	Caucasian	165.7	72.4	26.4	Past Smoker	2
10011011	22	Male	Caucasian	174.0	82.6	27.3	Current Smoker	4
10011013	19	Female (Premenopausal)	Caucasian	159.4	57.7	22.7	Never Smoked	0
10011016	19	Female (Premenopausal)	Caucasian	174.0	72.8	24.0	Never Smoked	0
10011017	19	Male	Caucasian	168.9	83.3	29.2	Past Smoker	0
10011018	25	Female (Premenopausal)	Caucasian	172.1	69.4	23.4	Current Smoker	2
10011021	33	Male	Caucasian	183.5	89.9	26.7	Current Smoker	1
10011022	24	Male	Caucasian	184.2	82.4	24.3	Never Smoked	0
10011024	43	Male	Caucasian	170.8	76.6	26.3	Never Smoked	0
10011026	24	Male	Caucasian	177.2	83.1	26.5	Current Smoker	10
10011027	18	Female (Premenopausal)	Black	170.8	70.8	24.3	Never Smoked	0
10011034	19	Female (Premenopausal)	Caucasian	166.4	59.2	21.4	Never Smoked	0
10011035	30	Male	Caucasian	171.5	68.2	23.2	Never Smoked	1
10011037	22	Female (Premenopausal)	Caucasian	170.2	60.6	20.9	Never Smoked	4
10011039	19	Male	Caucasian	191.1	80.7	22.1	Current Smoker	1
10011046	19	Male	Caucasian	196.2	90.7	23.6	Past Smoker	0
10011058	45	Female (Premenopausal)	Caucasian	161.3	67.8	26.1	Past Smoker	0
10011059	38	Female (Premenopausal)	Black	175.3	95.7	31.1	Never Smoked	2
10011060	50	Female (Premenopausal)	Caucasian	161.9	73.3	28.0	Never Smoked	0
10011066	45	Male	Caucasian	173.4	73.0	24.3	Never Smoked	1
10011067	27	Female (Premenopausal)	Caucasian	162.6	61.7	23.3	Current Smoker	3
10011069	20	Female (Premenopausal)	Black	162.6	75.3	28.5	Never Smoked	0
10011073	24	Female (Premenopausal)	Caucasian	163.8	65.1	24.3	Never Smoked	2
10011074	30	Female (Premenopausal)	Caucasian	170.2	71.9	24.8	Never Smoked	0
10011075	42	Male	Black	180.3	75.6	23.3	Current Smoker	2
10011077	32	Male	Caucasian	186.1	81.0	23.4	Never Smoked	3
10011079	24	Male	Caucasian	175.3	77.6	25.3	Past Smoker	1
10011080	20	Male	Caucasian	181.0	63.3	19.3	Never Smoked	0
10011086	26	Male	Caucasian	183.5	85.9	25.5	Past Smoker	0
10011088	20	Male	Caucasian	176.5	63.6	20.4	Never Smoked	0

5.5.5.3 BE Study- (b) (4) - Study 41026

This was an open label, randomized, two-way cross-over trial to assess the relative bioavailability of asenapine tablets made via (b) (4) versus (b) (4) techniques in 24 healthy male volunteers of at 18 - 45 years of age inclusive.

One asenapine tablet (5 mg; sublingual) was to be given on Days 1 and 8. A 48-hr pharmacokinetic profile was to be made after each asenapine dosing. A questionnaire was to be used to assess themouth feel and taste of the two asenapine formulations.

Results

Disintegration time after administration of the (b) (4) tablet was statistically significantly shorter (mean 01:36 mm:ss) compared to the disintegration time after administration of the (b) (4) tablet (mean 03:48 mm:ss).

Both tablets were reported to be generally acceptable. The time to dissolve was reported to be more acceptable after the (b) (4) tablet compared to the (b) (4). The taste of the (b) (4) tablets was reported to be more acceptable compared to the taste of the (b) (4) tablet.

The taste was generally described to be bitter.

Table 73 Bioequivalence Testing Comparing Asenapine Sublingual Tablets Manufactured by Freeze-Drying and Direct Compression – Study 41026

	Test	Ref	Geometric Mean Parameter		Conclusion
	(b) (4) (dc)	(b) (4) (fd)	Point estimate of μ(dc) / μ(fd)	90% confidence interval	
N	24	24			
Cmax (ng/mL)	4.32	5.02	0.86	0.78 -0.95	Not bioequivalent
AUC0-tlast (ng*h/mL)	27.5	32.4	0.85	0.78 - 0.91	Not bioequivalent
AUC0-∞ (ng*h/mL)	29.2	34.3	0.85	0.79 - 0.91	Not bioequivalent

5.5.6 Intrinsic Factors and Special Populations

5.5.6.1 Race and Ethnicity

As asenapine is a CYP2D6 substrate, and CYP2D6 activity is trimodally distributed with different frequencies by race and ethnicity, race and ethnicity would be expected to result in differences in metabolism. Specifically 7%- 10% of Caucasians are expected to be poor metabolizers and 17% of Ethiopians are expected to be extensive metabolizers.

5.5.6.1.1 Comparative Asenapine Pharmacokinetics in Caucasians and Japanese – Study 25546

Study 25546 was a double blind, randomized, placebo controlled, parallel group, two-period single and multiple dose study with asenapine in nonsmoking and light smoking healthy Japanese and Caucasian males 20 – 45 years old. In one treatment period asenapine was dosed as a single 1, 3, or 5 mg sublingual dose and in the other after a 1, 2, or 3 day titration 3, 5, or 10 mg was dosed BID for 6 days. There was an interperiod washout of at least 6 days.

Asenapine, desmethyl-asenapine, asenapine-glucuronide and N-oxide-asenapine concentrations were measured in plasma and urine at several time points. For the first three analytes, plasma and urine pharmacokinetic parameters were calculated.

For the metabolite asenapine 11-O-sulfate, concentrations in plasma were measured for the 5-mg single- and multiple-dose regimen and a limited set of PK parameters were calculated.

Neither genotyping nor phenotyping was performed although samples were obtained. Genotyping was only to be performed if the sponsor decided to do the analysis. This is troublesome as sponsors are required to perform provide all pertinent information for evaluation of safety.

Since the prevalence of CYP2D6 poor metabolizers in the Caucasian population is 7%-10% chances are good that not even a single CYP2D6 poor metabolizer was enrolled out of the 24 Caucasians studied. Even if there is one PM in just one group he is unlikely to disturb the mean by much and since the sponsor did not include information on genotype the implications would likely be overlooked. In the unlikely event that there is more than one poor metabolizer, the difference could easily be explained away by genotyping without mentioning the clinical implications.

Table 74 shows a summary of subject demographics by race and dose group.

Table 75 and Table 76 respectively show single and multiple dose pharmacokinetics for asenapine in Japanese and Causcasians. There are no obvious differences between the groups although there is a hint that bioavailability may be lower at the 5 mg dose.

Table 77 and Table 78 respectively show single and multiple dose pharmacokinetics for desmethyl-asenapine in Japanese and Causcasians. There is a significantly delayed Tmax in Caucasians as compared with Japanese on multiple dosing.

Table 79 and Table 80 respectively show single and multiple dose pharmacokinetics for asenapine glucuronide in Japanese and Causcasians.

Table 81 shows a comparison of geometric mean pharmacokinetic ratios of asenapine, desmethyl-asenapine, and asenapine glucuronide by race, with no clear differences by group. Table 82 shows the results of dose proportionality testing for asenapine. Table 83 and Table 84 a comparison of urinary excretion rates by dosage and race for asenapine, desmethyl-asenapine, and asenapine glucuronide.

Lastly Table 85 shows a comparison of the pharmacokinetics of asenapine-11-O-sulfate at a dose of 5 mg in Japanese and Caucasians.

For most of these metrics there is no clear difference between Japanese and Caucasians. However, exposure to asenapine 11-O-sulfate is lower in Japanese. However as variability is large any differences could be due to the small number of subjects employed.

Alhtough the the pharmacokinetics of the N-oxide metabolite was supposed to be determined in this study this reviewer could find no raw data. The only information was a statement to the effect that concentrations were so low as to preclude calculation of pharmacokinetic parameters. The available raw data will need to be obtained and reviewed.[6]

Due to the small sample size no firm conclusions can be drawn from this study.

Table 74 Summary of Subject Demographics by Race and Dose Group – Study 25546

	Caucasian			Japanese		
	Group 1	**Group 2**	**Group 3**	**Group 1**	**Group 2**	**Group 3**
Dosages	**1 mg SD**	**3 mg SD**	**5 mg SD**	**1 mg SD**	**3 mg SD**	**5 mg SD**
	3 mg BID	**5 mg BID**	**10 mg BID**	**3 mg BID**	**5 mg BID**	**10 mg BID**
n (%)	8 (100%)	8 (100%)	9 (100%)	8 (100%)	8 (100%)	8 (100%)
Age (years)	22.9 ± 2.2	23.9 ± 2.6	24.0 ± 3.2	22.9 ± 1.5	24.5 ± 2.7	28.5 ± 4.5
Weight (kg)	72.5 ± 8.1	71.7 ± 5.9	72.1 ± 5.4	63.2 ± 6.1	62.2 ± 8.7	64.3 ± 3.9
Height (cm)	176.5 ± 6.7	178.3 ± 4.4	179.3 ± 5.4	173.5 ± 5.8	170.6 ± 4.2	171.1 ± 3.8
BMI (kg/m^2)	23.2 ± 1.6	22.5 ± 1.5	22.4 ± 0.9	21.0 ± 1.7	21.3 ± 2.6	21.9 ± 1.2

[6] Potential comment for sponsor in followup meeting.

Table 75 Pharmacokinetic Metrics of Asenapine after Single Doses in Japanese & Caucasians – Study 25546

	Japanese			Caucasian		
	1 mg	3 mg	5 mg	1 mg	3 mg	5 mg
N	6	6	6	6	6	6
Tmax (h)	0.7 0.33 - 2.00	1.0 0.50 - 1.00	1.25 0.50 - 4.03	1.50 1.00 - 2.00	1.00 0.50 - 1.50	0.50 0.50 - 1.50
Cmax (ng/mL)	1.10 (36.1) 0.803 - 1.64	3.58 (44.4) 1.80 - 5.51	3.31 (51.7) 1.40 - 5.59	1.02 (15.4) 0.765 - 1.17	2.90 (36.8) 0.846 - 3.70	3.99 (44.9) 1.19 - 5.61
dn-Cmax (ng/mL/mg)	1.10 (36.1) 0.803 - 1.64	1.19 (44.4) 0.600 - 1.84	0.662 (51.7) 0.280 - 1.12	1.02 (15.4) 0.765 - 1.17	0.968 (36.8) 0.282 - 1.23	0.797 (44.9) 0.238 - 1.12
$AUC_{0-tlast}$ (ng/mL x hr^{-1})	7.78 (34.1) 4.87 - 11.3	22.0 (38.2) 11.3 - 28.6	25.0 (30.7) 15.4 - 33.6	6.81 (14.5) 5.14 - 8.24	19.3 (34.0) 6.77 - 25.3	24.9 (41.4) 7.91 - 34.4
dn-$AUC_{0-tlast}$ (ng/mL x hr^{-1} / mg)	7.78 (34.1) 4.87 - 11.3	7.34 (38.2) 3.77 - 9.53	5.00 (30.7) 3.08 - 6.71	6.81 (14.5) 5.14 - 8.24	6.45 (34.0) 2.26 - 8.45	4.98 (41.4) 1.58 - 6.87
AUC_{∞} (ng/mL x hr^{-1})	8.47 (34.8) 5.09 - 12.5	23.2 (37.6) 11.7 - 29.9	26.4 (30.1) 15.9 - 34.9	7.50 (17.9) 5.17 - 9.31	20.0 (33.1) 7.18 - 25.8	26.0 (41.0) 8.24 - 35.4
dn-AUC_{∞} (ng/mL x hr^{-1} / mg)	8.47 (34.8) 5.09 - 12.5	7.73 (37.6) 3.90 - 9.97	5.28 (30.1) 3.17 - 6.98	7.50 (17.9) 5.17 - 9.31	6.65 (33.1) 2.39 - 8.59	5.20 (41.0) 1.65 - 7.07

Table 76 Steady-State Pharmacokinetic Metrics of Asenapine in Japanese & Caucasians – Study 25546

	Japanese			Caucasian		
	3 mg BID	5 mg BID	10 mg BID	3 mg BID	5 mg BID	10 mg BID
N	6	6	5	6	6	4
Tmax (h)	0.50 0.50 - 1.50	0.50 0.50 - 1.50	1.00 0.33 - 1.50	0.50 0.50 - 2.00	1.50 0.50 - 2.00	0.75 0.33 - 3.00
Cmax,ss (ng/mL)	3.93 (23.6) 2.46 - 4.85	5.05 (51.0) 1.84 - 7.96	5.39 (46.2) 2.50 - 8.82	3.40 (22.3) 2.52 - 4.36	3.56 (51.0) 1.50 - 6.69	8.18 (66.2) 3.19 - 13.3
dn-Cmax,ss (ng/mL/mg)	1.31 (23.6) 0.820 - 1.62	1.01 (51.0) 0.368 - 1.59	0.539 (46.2) 0.250 - 0.882	1.13 (22.3) 0.840 - 1.45	0.712 (51.0) 0.300 - 1.34	0.818 (66.2) 0.319 - 1.33
AUCss,0-12 (ng/mL x hr^{-1})	24.3 (26.3) 13.9 - 32.5	29.4 (35.1) 14.2 - 40.5	37.5 (44.3) 19.6 - 61.2	21.9 (11.1) 18.0 - 24.4	22.1 (37.3) 10.7 - 34.0	41.7 (46.2) 23.6 - 64.5
dn-AUCss,0-12 (ng/mL x hr^{-1} / mg)	8.09 (26.3) 4.64 - 10.8	5.87 (35.1) 2.84 - 8.10	3.75 (44.3) 1.96 - 6.12	7.29 (11.1) 6.01 - 8.15	4.43 (37.3) 2.15 - 6.81	4.17 (46.2) 2.36 - 6.45
CLss/F (L/h)	133 (32.9) 92.2 - 215	195 (45.3) 124 - 352	312 (43.1) 163 - 509	139 (11.9) 123 - 166	259 (44.1) 147 - 465	283 (45.0) 155 - 423
wn-CLss/F (L/h/kg)	2.09 (38.1) 1.29 - 3.58	3.20 (57.0) 1.72 - 6.80	4.85 (42.5) 2.63 - 7.61	1.95 (25.8) 1.48 - 2.89	3.78 (52.4) 1.95 - 7.35	4.02 (42.0) 2.24 - 5.55
t½ (h)	38.3 (57.6) 22.8 - 79.5	35.5 (56.7) 17.3 - 74.2	27.8 (28.6) 17.4 - 37.0	28.9 (23.6) 18.3 - 37.1	25.7 (51.5) 16.7 - 51.6	34.1 (73.6) 13.2 - 68.0

Table 77 Pharmacokinetic Metrics of Desmethyl-Asenapine after Single Doses in Japanese & Caucasians – Study 25546

	Japanese			Caucasian		
	1 mg	3 mg	5 mg	1 mg	3 mg	5 mg
N	6	6	6	6	6	6
Tmax (h)	8.00 6.00-12.0	6.00 6.00-8.00	7.01 6.00-12.0	6.00 6.00-12.0	7.00 2.00-8.00	6.00 6.00-8.00
Cmax (ng/mL)	0.129 (25.7) 0.0805-0.172	0.306 (30.0) 0.186-0.450	0.524 (42.4) 0.133-0.802	0.0942 (46.1) 0.0583-0.175	0.269 (21.6) 0.165-0.315	0.599 (36.8) 0.403-1.03
dn-Cmax (ng/mL/mg)	0.129 (25.7) 0.0805-0.172	0.102 (30.0) 0.0620-0.150	0.105 (42.4) 0.0266-0.160	0.0942 (46.1) 0.0583-0.175	0.0898 (21.6) 0.0550-0.105	0.120 (36.8) 0.0806-0.206
$AUC_{0-tlast}$ ($ng/mL \times hr^{-1}$)	1.47 (23.6) 0.936-1.91	4.46 (41.2) 2.51-7.43	10.7 (51.9) 1.54-16.7	0.684 (65.0) 0.239-1.24	4.11 (29.8) 2.00-5.36	10.7 (47.1) 6.48-20.0
dn-$AUC_{0-tlast}$ ($ng/mL \times hr^{-1}$ / mg)	1.47 (23.6) 0.936-1.91	1.49 (41.2) 0.837-2.48	2.14 (51.9) 0.309-3.33	0.684 (65.0) 0.239-1.24	1.37 (29.8) 0.666-1.79	2.14 (47.1) 1.30-4.01
AUC_{∞} ($ng/mL \times hr^{-1}$)	6.59 (85.6) 2.49-17.8	5.77 (35.1) 3.32-8.56	12.7 (47.2) 2.56-19.2	6.79# (23.1) 5.68-7.89	5.27 (25.2) 3.22-6.68	13.5 (50.6) 7.75-25.9
dn-AUC_{∞} ($ng/mL \times hr^{-1}$ / mg)	6.59 (85.6) 2.49-17.8	1.92 (35.1) 1.11-2.85	2.55 (47.2) 0.511-3.83	6.79# (23.1) 5.68-7.89	1.76 (25.2) 1.07-2.23	2.70 (50.6) 1.55-5.19
t½ (h)	36.6 (68.8) 9.70-76.6	14.5 (44.7) 9.13-25.6	15.5 (21.9) 9.97-18.6	54.1# (78.3) 24.1-84.0	12.7 (21.0) 8.59-16.0	17.1 (42.4) 8.68-26.9

Table 78 Steady-State Pharmacokinetic Metrics of Desmethyl-Asenapine in Japanese & Caucasians – Study 25546

	Japanese			Caucasian		
	3 mg BID	5 mg BID	10 mg BID	3 mg BID	5 mg BID	10 mg BID
N	6	6	5	6	6	4
Tmax (h)	6.00 3.00-8.00	5.00 3.00-6.00	1.50 1.50 - 6.05	6.00 2.00-6.02	4.03 2.00-6.05	5.01 0.33-8.00
Cmax (ng/mL)	0.974 (22.8) 0.694-1.26	1.21 (37.3) 0.681-1.78	2.43 (66.9) 0.648-4.50	0.789 (34.0) 0.535-1.23	1.23 (27.5) 0.710-1.72	3.29 (65.2) 1.67-6.43
dn-Cmax (ng/mL/mg)	0.325 (22.8) 0.231-0.420	0.242 (37.3) 0.136-0.356	0.243 (66.9) 0.0648-0.450	0.263 (34.0) 0.178-0.410	0.245 (27.5) 0.142-0.344	0.329 (65.2) 0.167-0.643
AUC_{0-12} ($ng/mL \times hr^{-1}$)	9.74 (21.4) 7.25-12.8	11.5 (37.5) 5.91-16.4	23.1 (69.8) 5.95-45.4	7.61 (36.0) 4.38-11.4	11.8 (24.6) 6.93-14.8	27.7 (51.7) 14.0-47.6
dn-AUC_{0-12} ($ng/mL \times hr^{-1}$ / mg)	3.25 (21.4) 2.42-4.27	2.30 (37.5) 1.18-3.28	2.31 (69.8) 0.595-4.54	2.54 (36.0) 1.46-3.79	2.36 (24.6) 1.39-2.96	2.77 (51.7) 1.40-4.76
t½ (h)	15.8 (30.0) 8.48-22.5	21.8 (59.4) 9.00-46.6	18.7 (26.5) 14.2-27.0	16.5 (44.1) 8.82-27.7	19.0 (26.2) 10.4-23.7	17.2 (12.6) 14.7-20.0

Table 79 Pharmacokinetic Metrics of Asenapine Glucuronide after Single Doses in Japanese & Caucasians – Study 25546

	Japanese			Caucasian		
	1 mg	3 mg	5 mg	1 mg	3 mg	5 mg
N	6	6	6	6	6	6
Tmax (h)	6.00 4.00-6.00	5.00 4.00-8.00	6.00 4.00-6.02	6.00 4.00-6.00	6.00 4.00-6.00	4.00 4.00-8.00
Cmax (ng/mL)	1.70 (36.8) 1.05-2.69	4.16 (51.1) 1.27-7.65	8.90 (56.3) 2.16-15.3	1.49 (43.7) 0.978-2.69	4.41 (25.4) 2.68-5.90	6.53 (24.3) 4.88-9.31
dn-Cmax (ng/mL/mg)	1.70 (36.8) 1.05-2.69	1.39 (51.1) 0.423-2.55	1.78 (56.3) 0.432-3.06	1.49 (43.7) 0.978-2.69	1.47 (25.4) 0.893-1.97	1.31 (24.3) 0.976-1.86
$AUC_{0-tlast}$ (ng/mL x hr^{-1})	15.6 (40.1) 8.54-24.8	43.9 (43.8) 13.1-68.8	99.4 (51.8) 20.7-150	11.4 (46.7) 5.13-18.0	46.6 (26.9) 24.3-59.4	71.1 (36.6) 44.6-116
dn-$AUC_{0-tlast}$ (ng/mL x hr^{-1} / mg)	15.6 (40.1) 8.54-24.8	14.6 (43.8) 4.35-22.9	19.9 (51.8) 4.15-30.1	11.4 (46.7) 5.13-18.0	15.5 (26.9) 8.09-19.8	14.2 (36.6) 8.92-23.3
AUC_{∞} (ng/mL x hr^{-1})	19.2 (29.3) 11.7-27.5	49.5 (46.2) 15.7-79.9	107 (51.0) 26.0-155	15.1 (34.4) 10.7-21.9	52.1 (28.5) 27.1-66.8	77.2 (35.0) 49.3-121
dn-AUC_{∞} (ng/mL x hr^{-1} / mg)	19.2 (29.3) 11.7-27.5	16.5 (46.2) 5.22-26.6	21.4 (51.0) 5.21-30.9	15.1 (34.4) 10.7-21.9	17.4 (28.5) 9.03-22.3	15.4 (35.0) 9.85-24.2
t½ (h)	5.52 (19.3) 4.11-6.80	12.3 (82.9) 5.17-27.3	11.6 (74.9) 4.01-28.4	5.24 (27.1) 3.52-7.35	10.5 (79.2) 4.93-26.0	13.4 (74.3) 4.36-31.5

Table 80 Steady-State Pharmacokinetic Metrics of Asenapine-Glucuronide in Japanese & Caucasians – Study 25546

	Japanese			Caucasian		
	3 mg BID	5 mg BID	10 mg BID	3 mg BID	5 mg BID	10 mg BID
N	6	6	5	6	6	4
Tmax (h)	4.00 3.00-6.00	4.00 3.00-6.00	4.00 3.00- 6.05	4.00 3.00-4.00	4.00 3.00-4.00	3.50 3.00 - 4.00
Cmax (ng/mL)	9.77 (40.2) 6.04-15.3	15.7 (34.6) 10.3-25.6	35.5 (73.2) 2.48-58.9	9.40 (38.5) 6.33-15.2	16.5 (25.9) 10.7-23.0	33.7 (30.4) 23.7-47.8
dn-Cmax (ng/mL/mg)	3.26 (40.2) 2.01-5.10	3.14 (34.6) 2.06-5.12	3.55 (73.2) 0.248-5.89	3.13 (38.5) 2.11-5.07	3.29 (25.9) 2.14-4.60	3.37 (30.4) 2.37-4.78
AUC_{0-12} (ng/mL x hr^{-1})	81.9 (42.0) 49.2-131	124 (34.8) 90.7-207	282 (73.4) 26.1-496	76.8 (37.6) 53.8-117	129 (20.4) 87.1-166	261 (20.4) 193-323
dn-AUC_{0-12} (ng/mL x hr^{-1} / mg)	27.3 (42.0) 16.4-43.7	24.8 (34.8) 18.1-41.4	28.2 (73.4) 2.61-49.6	25.6 (37.6) 17.9-39.0	25.7 (20.4) 17.4-33.2	26.1 (20.4) 19.3-32.3
t½ (h)	15.7 (35.6) 8.50-22.5	18.8 (44.4) 10.6-33.7	12.7 (34.2) 8.56-19.1	13.6 (27.5) 9.57-18.9	15.8 (12.4) 13.8-19.2	18.6 (19.4) 14.9-23.1

Table 81 Comparison of Single Dose and Steady-State Dose Normalized Geometric Mean Pharmacokinetic Ratios of Asenapine, Desmethyl-Asenapine, and Asenapine Glucuronide by Race – Study 25546[a]

Dosing	Metric	Asenapine		Desmethyl - Asenapine		Asenapine - Glucuronide	
		μ(Jap.) : μ(Cauc.) Point Estimate	95% CI	μ(Jap.) : μ(Cauc.) Point Estimate	95% CI	μ(Jap.) : μ(Cauc.) Point Estimate	95% CI
Single Dose [a] (n=36)	dn-Cmax	1.02	0.74 - 1.42	1.09	0.84 - 1.42	1.04	0.76 - 1.43
	dn-AUC0-tlast	1.10	0.83 - 1.46	1.33	0.91 - 1.94	1.14	0.80 - 1.62
	dn-AUC0-inf	1.11	0.84 - 1.47	0.91#	0.60 - 1.37	1.11	0.81 - 1.53
	CL/F	0.90	0.68 - 1.19	—	—	—	—
	wn-CL/F	1.02	0.77 - 1.35	—	—	—	—
	Vz/F	1.15	0.77 - 1.71	—	—	—	—
	wn-Vz/F	1.30	0.87 - 1.96	—	—	—	—
	t½	1.27	0.84 - 1.94	0.88#	0.60 - 1.29	1.02	0.68 - 1.53
Steady State [a] (n=33)	dn-Cmax	1.05	0.74 - 1.50	0.93	0.66 - 1.30	0.87	0.56 - 1.34
	dn-AUC0-12	1.09	0.84 - 1.42	0.96	0.69 - 1.34	0.89	0.60 - 1.34
	CL/F	0.92	0.70 - 1.20	—	—	—	—
	wn-CL/F	1.02	0.76 - 1.37	—	—	—	—
	Vss,z/F	1.07	0.69 - 1.66	—	—	—	—
	wn-Vss,z/F	1.19	0.76 - 1.86	—	—	—	—
	t½	1.17	0.84 - 1.63	1.04	0.79 - 1.36	0.94	0.75 - 1.18

a metrics are grand means of dose normalzed values

Table 82 Results of Single Dose and Steady-State Dose Proportionality Testing for Asenapine in Caucasians and Japanese – Study 25546

Parameter	Point Estimate of μ(doseH)/ μ(doseL)	95% Confidence Interval	Point Estimate of μ(doseH)/ μ(doseL)	95% Confidence Interval
	Single dose (n=36)			
	Japanese, 5 mg/1 mg SD		Caucasian, 5 mg/1 mg SD	
dn-Cmax	0.56	0.32 - 0.98	0.70	0.40 - 1.23
dn-AUC0-tlast	0.65	0.40 - 1.05	0.66	0.41 - 1.08
dn-AUC0-inf	0.63	0.39 - 1.02	0.63	0.39 - 1.03
CL/F	1.59	0.98 - 2.58	1.58	0.97 - 2.57
wn-CL/F	1.60	0.99 - 2.61	1.56	0.96 - 2.53
t½	1.54	0.74 - 3.19	1.20	0.58 - 2.48
	Japanese, 5 mg/3 mg SD		Caucasian, 5 mg/3 mg SD	
dn-Cmax	0.54	0.30 - 0.95	0.80	0.45 - 1.41
dn-AUC0-tlast	0.71	0.43 - 1.15	0.75	0.46 - 1.22
dn-AUC0-inf	0.71	0.44 - 1.15	0.76	0.47 - 1.23
CL/F	1.41	0.87 - 2.30	1.32	0.81 - 2.15
wn-CL/F	1.39	0.85 - 2.26	1.26	0.78 - 2.05
t½	0.92	0.44 - 1.90	1.40	0.68 - 2.90
	Steady state (n=33)			
	Japanese, 10 mg/3 mg b.i.d. SS		Caucasian, 10 mg/3 mg b.i.d. SS	
dn-Cssmax	0.39	0.21 - 0.71	0.60	0.32 - 1.16
dn-AUCss0-12	0.44	0.28 - 0.70	0.53	0.33 - 0.86
CLss/F	2.26	1.43 - 3.56	1.89	1.16 - 3.07
wn-CLss/F	2.26	1.36 - 3.77	1.97	1.14 - 3.39
t½ss	0.78	0.44 - 1.38	0.98	0.53 - 1.80
	Japanese, 10 mg/5 mg b.i.d. SS		Caucasian, 10 mg/5 mg b.i.d. SS	
dn-Cssmax	0.56	0.30 - 1.03	1.05	0.55 - 2.01
dn-AUCss0-12	0.63	0.40 - 0.99	0.92	0.57 - 1.50
CLss/F	1.59	1.01 - 2.51	1.08	0.67 - 1.76
wn-CLss/F	1.55	0.93 - 2.58	1.09	0.64 - 1.88
t½ss	0.84	0.48 - 1.49	1.17	0.64 - 2.15

Table 83 Comparison of Urinary Excretion of Asenapine, Desmethyl-Asenapine, and Asenapine Glucuronide in Caucasians and Japanese – Study 25546

		Japanese			Caucasian		
	Dosage	**1 mg**	**3 mg**	**5 mg**	**1 mg**	**3 mg**	**5 mg**
	N	6	6	6	6	6	6
fe,u (%) SD	**Asenapine**	0.0167 (60.9)	0.0364 (104)	0.0292 (92.9)	0.00167 (245)	0.0169 (91.2)	0.0173 (128)
	Desmethyl-Asenapine	0.582 (47.9)	0.266 (30.0)	0.128 (39.0)	0.0935 (86.8)	0.0797 (75.5)	0.0991 (49.9)
	Asenapine Glucuronide	7.11 (35.2)	5.59 (28.1)	12.9 (41.1)	11.7 (31.9)	11.3 (30.3)	9.1 (34.7)
	Dosage	3 mg BID	5 mg BID	10 mg BID	3 mg BID	5 mg BID	10 mg BID
	N	6	6	5	6	6	4
fe,u (%) SS	**Asenapine**	0.0925 (38.2)	0.0648 (65.7)	0.0414 (91.1)	0.0655 (47.8)	0.0392 (60.1)	0.0434 (52.3)
	Desmethyl-Asenapine	0.179 (22.8)	0.106 (21.1)	0.0474 (34.5)	0.0939 (54.6)	0.0884 (19.6)	0.0724 (27.0)
	Asenapine Glucuronide	8.08 (42.0)	8.57 (13.6)	16.6 (71.0)	17.3 (33.2)	17.3 (15.5)	16.2 (22.5)

Table 84 Comparison of Pharmacokinetic Metrics for Urinary Excretion of Asenapine, Desmethyl-Asenapine, and Asenapine Glucuronide in Caucasians and Japanese – Study 25546

Parameter	**p-value for Race**		
	Asenapine	**Desmethyl - Asenapine**	**Asenapine - Glucuronide**
	Single dose (n=36)		
CL,R (L/h)	0.052	0.029	<0.0001
wn - CL,R (L/h/kg)	0.047	0.019	<0.0001
fe	0.018	<0.0001	0.038
	Steady state (n=33)		
CLss,R (L/h)	0.392	0.210	<0.0001
wn - CLss,R (L/h/kg)	0.197	0.044	<0.0001
fess	0.218	0.057	0.0002

Table 85 Single 5 mg and Multiple Dose 5 mg BID Steady-State Pharmacokinetic Metrics of Asenapine-11-O-Sulfate in Japanese & Caucasians– Study 25546

Parameter (unit)	Summary Statistics		Geometric Means		Geometric Mean Ratio Japanese : Caucasian (95% CI)
Race	Japanese	Caucasian	Japanese	Caucasian	
n	4	5	4	5	
	5 mg Single Dose				
Tmax (h)	4.00 2.00-6.00	3.02 1.50-4.03			
Cmax (ng/mL)	0.983 (78.8) 0.176-2.04	2.78 (66.0) 0.581-5.27	0.717	2.19	0.33 0.10 – 1.02
AUC_{tlast} (ng·h/mL)	9.17 (79.4) 1.42-18.8	17.7 (73.9) 4.49-39.1			
AUC_{0-inf} (ng·h/mL)	11.2 (72.4) 1.84-21.0	20.1 (62.9) 8.91-41.2	8.14	17.2	0.47 0.16 - 1.38
$t_{½}$ (h)	21.0 (81.7) 4.38-44.8	24.0 (86.3) 4.99-57.0			
	Steady-State 5 mg BID				
Tmax (h)	3.00 3.00-4.00	3.00 2.00-4.00			
Cmax (ng/mL)	3.23 (67.3) 0.747-5.96	2.96 (34.9) 1.75-4.25	1.93	1.92	1.01 0.32 - 3.15
$Cmax^{ss}_{corr}$ (ng/mL)	2.27 (50.6) 0.646-3.09	2.14 (51.7) 1.11-3.78			
$AUCss_{,0-12}$ (ng·h/mL)	19.8 (85.9) 4.08-42.9	17.0 (19.2) 12.0-20.6	14.2	16.7	0.85 0.29 - 2.50
$t_{½}$ (h)	21.1 (30.3) 14.6-27.2	26.7 (28.1) 15.7-35.1			

5.5.6.2 Gender

No specific gender study was performed. Since asenapine is a CYP1A2 substrate and drugs that are substrates of CYP1A2 tend to have higher exposures in women and the elderly, the effect of gender and age will need to be examined. In at least two PK studies, the elderly study and a pivotal BE study there may be sufficient numbers of women to allow for a comparison. However, for the BE study the availability of gender data was not realized until too late in the review cycle and the study in the elderly was hidden. By the time the reviewer realized that this data might be extractable there was insufficient time to extract the data and analyze it for the review.

5.5.6.3 Elderly

It was originally thought that no specific study in the elderly was performed. This was surprising since asenapine is a CYP1A2 substrate and drugs that are substrates of CYP1A2 tend to have higher exposures in women and the elderly and in particular elderly women. In addition cardiac toxicity and death is a known concern with using antipsychotics in the elderly. On May 5th, 2008 it was realized that summary statistics including ranges of pharmacokinetic metrics had been reported.

According to the interim report the first 33 elderly subjects greater than 65 years of age with psychosis enrolled in the study would have the pharmacokinetics and safety of asenapine assessed.

Subjects were dosed BID as per Figure 65.

Figure 65 BID Dosage Regimens for Asenapine in Elderly PK and S/T Study A7501021

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Days 7-42/EOT*
Group A (BID)	2 mg	2 mg	5 mg	5 mg	10 mg	10 mg	5-10 mg
Group B (BID)	5 mg	5 mg	5 mg	5 mg	10 mg	10 mg	5-10 mg

Subject demographics are shown in Table 86.

Table 86 Subject Demographics for Elderly PK and Safety / Tolerability Study A7501021

N	Age (yrs)	Gender M/F (%)	Race / Ethnicity Caucasian / Black / Palestinian
33	72.6 ± 5.43 65 - 85 [72]	12 / 21 (36.4 / 63.6)	22 / 10 / 66.7 / 30.3 / 3.03

For the interim analysis it was assumed that the asenapine dose administered at Day 4 was 5 mg and at Day 8 was 10 mg

Figure 66 shows the sponsor's comparison of PK parameters of elderly and adult schizophrenic patients indicating a 40% increase in exposure to asenapine and a doubling of exposure to desmethyl-asenapine.

Figure 66 Sponsor's Comparison of PK Parameters of Elderly and Adult Schizophrenic Patients – Study A7501021

Table 3 Comparison of PK parameters between elderly and adult schizophrenia patients

Parameter	Dose	Elderly patients	Adult patients	% difference Elderly vs Adult
Asenapine				
C_{max} (ng/mL)	5 mg BID	5.58 (70.2)	4.23 (45.3)	+32 %
	10 mg BID	8.51 (72.1)	6.56 (50.9)	+30 %
AUC_{0-12} (ng·h/mL)	5 mg BID	34.6 (58.9)	26.6 (38.4)	+30 %
	10 mg BID	61.2 (68.2)	43.4 (53.1)	+41%
N-desmethylasenapine				
C_{max} (ng/mL)	5 mg BID	1.89 (80.0)	1.02 (38.8)	+85%
	10 mg BID	4.30 (98.1)	2.21 (48.3)	+95%
AUC_{0-12} (ng·h/mL)	5 mg BID	16.2 (67.9)	9.65 (38.9)	+68%
	10 mg BID	38.0 (89.7)	19.6 (35.7)	+94%

Source: Appendix A, Table 4-1 and Table 4-2 and Clinical Trial Report A7501001, Table 48 and Table 49.

Table 87 shows the complete descriptive statistics of steady−state pharmacokinetic metrics for both asenapine and N−desmethylasenapine for the pharmacokineticallyevaluable group and it compares them to the range of exposures from the multiple-dose dose titration study 41012 the maximal asenapine exposure is nearly triple and the maximal N-desmethyl-asenapine exposure is 11 times higher and 3 times higher than seen in the healthy volunteer from the IV study who experienced asystole.

Although the data from study 41012 is only based on 2 subjects when the other doses are examined it still appears that maximal exposures in the elderly are 3 fold higher.What's especially troubling the combination of the large number of drop outs, the high maximum exposures seen in the elderly, the higher risk in the elderly, and the lack of and apparent hiding of the data. In addition without the raw data we are unable to determine if there is any relationship of age and / or gender and the high asenapine and desmethyl asenapine concentrations.

Table 87 Asenapine and N−Desmethyl-asenapine Steady−State Pharmacokinetic Metrics in the Elderly for the Pharmacokinetically Evaluable Group – Study A7501021 and Comparison to MD PK from Dose Titration Study 41012

Population	Asenapine Dose	Day	Metric	N	Summary Statistics	
					Asenapine	Desmethyl-asenapine
Elderly	5 mg BID	4	Tmax,ss (h)	32	2.33 ± 2.87 (123) 0.5 - 1.0 [12.0]	4.52 ± 3.8 (84.1) 0.5 - 12.0 [4.0]
			Cmax,ss (ng/mL)	32	5.58 ± 3.92 (70.2 0.296 - 4.06 [18.9]	1.89 ± 1.51 (80.0) 0.28 - 6.75 [1.28]
			AUCτ (ng*h/mL)	32	34.6 ± 20.4 (58.9) 2.21 - 30.0 [85.4]	16.2 ± 11.0 (67.9) 2.43 - 37.8 [10.5]
			Cmin,ss (ng/mL)	32	2.27 ± 1.87 (82.4) 0.106 - 1.72 [8.43]	1.12 ± 0.79 (70.7) 0.0525 - 2.9 [0.771]
	10 mg BID	8	Tmax,ss (h)	29	2.44 ± 2.48 (102) 0.5 - 8.0 [2.0]	4.37 ± 2.75 (62.9) 0.917 - 12.0 [4.0]
			Cmax,ss (ng/mL)	29	8.51 ± 6.14 (72.1) 1.89 - 27.0 [7.86]	4.3 ± 4.22 (98.1) 0.89 - 18.4 [3.02]
			AUCτ (ng*h/mL)	29	61.2 ± 41.8 (68.2) 13.5 - **144** [42.2]	38.0 ± 34.1 (89.7) 9.82 - **155** [23.2]
			Cmin,ss (ng/mL)	28	4.18 ± 3.41 (81.8) 1.01 - 12.9 [2.53]	2.36 ± 1.78 (75.7) 0.662 - 7.86 [1.78]
Young	Study 41012 Dose Titration Study 10 mg BID	10	Tmax,ss (h)	2	[1.25] 1.00 - 1.50	[4.00] 4.00 – 4.00
			Cmax,ss (ng/mL)		8.84 2.17 - 15.5	1.33 1.23 - 1.42
			AUCτ (ng*h/mL)		37.3 16.5 - **58.1**	12.7 11.0 - **14.4**
			Cmin,ss (ng/mL)		1.30 0.964 - 1.64	0.853 0.693 - 1.01

Figure 67 Mean Asenapine Steady-State Concentration vs. Time Profiles in the Elderly – Study A7501021

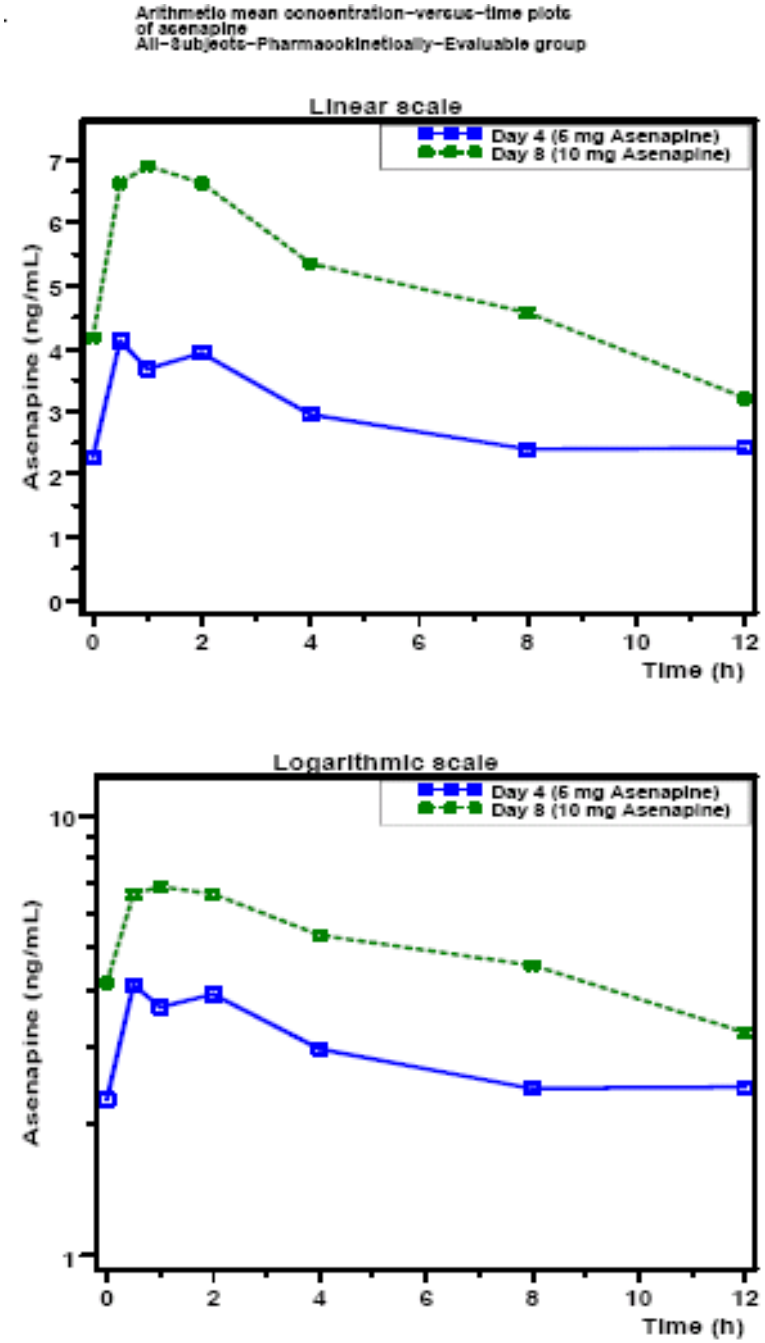
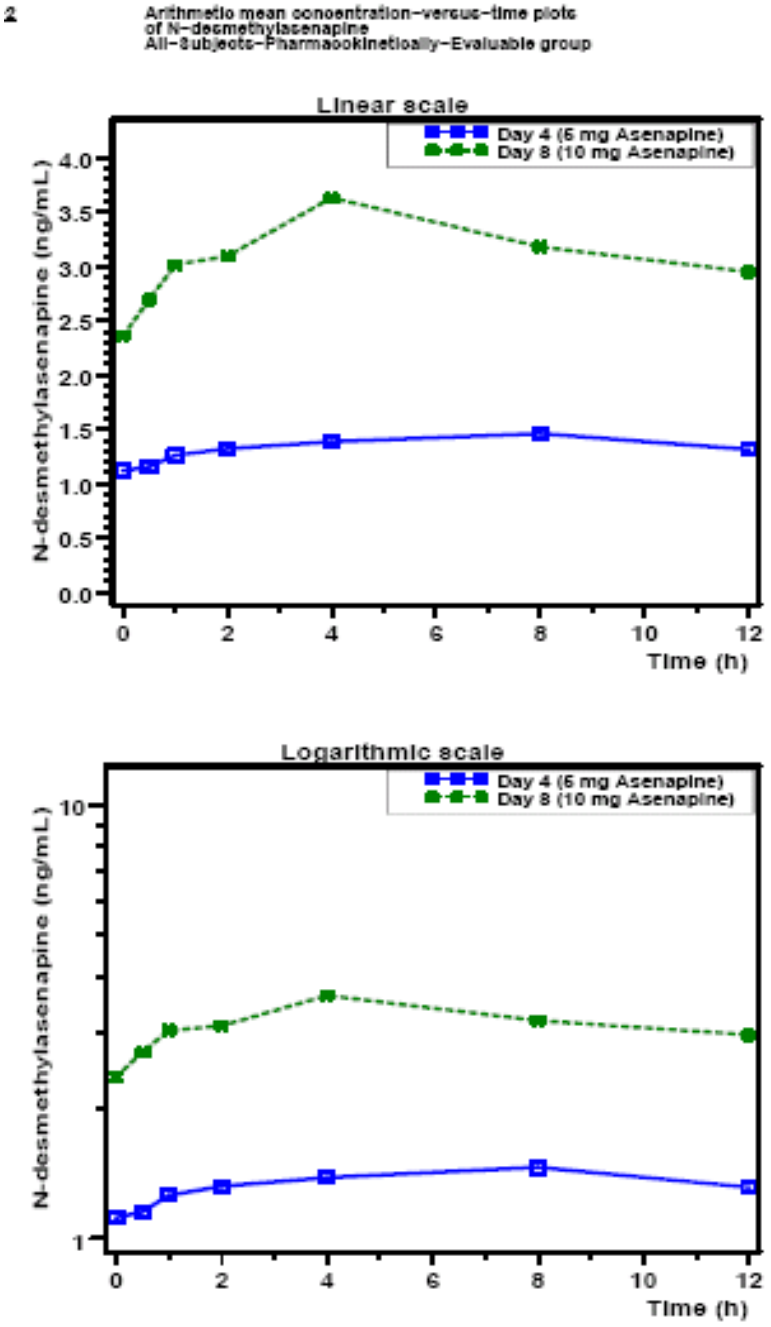


Figure 68 Mean Desmethyl-Asenapine Steady-State Concentration vs. Time Profiles in the Elderly – Study A7501021



5.5.6.4 Pediatrics - Adolescents - Study A7501022

Study A7501022 was a randomized, double-blind, placebo-controlled, 4-way parallel-group, multiple-dose study in 40 male and female adolescent patients 12 – 17 years of age. Asenapine at dosages ranging from 1 to 10 mg was administered BID sublingually for 10 days. Each group contained 10 subjects (8 active, 2 placebo).

Subjects had to have a documented history of schizophrenia, bipolar disorder, autism, conduct disorder, oppositional defiant disorder, or any condition for which the chronic use of antipsychotic medication (i.e., risperidone, olanzapine, haloperidol) was potentially warranted and/or administered.[7]

Maintenance medication was tapered and discontinued over a period of up to 3 days, placebo was administered on Day 0 and asenapine or placebo was administered over 10 - 11 days.

Treatment regimens were as follows.

Group	Regimen
1	Asenapine 1 mg SL BID x 10 days
2	Asenapine 3 mg SL BID x 10 days
3	Asenapine 5 mg SL BID x 10 days
4	Asenapine 5 mg SL BID on day 1 then 10 mg SL BID x 10 days

No raw pharmacokinetic data or metrics were supplied. It appears that many of the subjects were on Adderal® for ADHD and were also diagnosed with bipolar disorder or psychosis. There were a high percentage of blacks enrolled in this study. This raises the question whether this is simply due the recruiting area or to more black children being placed on antipsychotics for ADHD due to their socioeconomic circumstances, or whether it an intentional attempt to minimize Caucasians due the higher likelihood that they would be CYP2D6 poor metabolizers. In addition, since African American children are more likely to be at the upper end of the height and weight spectrum they would thus be more likely to have exposures that are more similar to adults and less likely to experience adverse effects.

A summary of the reported asenapine pharmacokinetic metrics by dose is shown in Table 88 and desmethyl-asenapine pharmacokinetic metrics in Table 89.

Examination of patient demographics revealed that 0 / 17 females and only 5 / 23 males had body weights of $\leq$ 45 kg, (see Table 90). This is significant as 45 kg is the median population weight in adolescents between 12 – 17 years of age.

This is shown graphically in Figure 69 where body mass in kg is plotted vs. age in years by gender and by race. Curves for population medians and 95% confidence intervals are also superimposed along with a cubic spline fit to the subjects data which demonstrates that the mean weights in this population tends to be closer to the 80th percentile. The data from this population thus likely underestimates the true exposure measured by AUC that would be expected in the actual treated population.

Thus unless further information is obtained, studies in adolescents are likely to result in excessively high concentrations in adolescents. Since, there appears to be a very narrow safety margin between therapeutic and potentially hepatotoxic doses this indicates that adolescents may be at higher risk for

[7] This raises ethical issues with this study as these are off-label uses and in spite of the off-label use of antipsychotics in practice there are questions as to whether off-label use for these conditions is even appropriate, i.e. has it been adequately studied and if so has the need and use been appropriately documented in these subjects. Since these subjects were largely on Adderall and had ADHD, the addition of an antipsychotic with a dopaminergic agent in and of itself is questionable. In addition analysis of the bipolar studies in this submission argues that this particular use is likely an inappropriate off-label use. All of these factors raise ethical issues whether some or all of this data is even usable to support an NDA for an appropriate use, i.e. should we refuse to use some or all of the data similar to the practice of refusing to use data obtained unethically such as from medical experiments conducted on holocaust victims.

hepatotoxicity if dosage is not adjusted. This is especially worrisome with off label use in even younger children as a sublingual formulaton would be a natural choice for prescribers to use off label, and the lack of appropriate dosage strengths might mean an even greater proportion of the dose would be swallowed as compared with adults and thereby increase the risk of hepatotoxicity.

Another concern with adolescents is the greater propensity for ingestion of high fat meals and the alterations in hepatic blood flow and increase in potentially hepatotoxic metabolites this might entail.

Table 88 Summary of Asenapine Pharmacokinetic Parameter Values following q12h Administration of Sublingual Tablet Doses to Adolescent Subjects receiving Antipsychotics - Study A7501022

Asenapine Dose	1 mg	3 mg	5 mg	10 mg
N (n)	8 (7)	8 (5)	8 (8)	8 (8)
Tmax (hr)	0.705 (0.25 - 1.5)	0.890 (0.0 - 1.5)	1.04 (0.0 - 2.8)	1.28 (0.0 - 3.0)
Cmax (ng/mL)	1.03 (49.6)	2.64 (55.6)	3.54 (47.9)	2.77 (81.8)
Cmin (ng/mL)	0.253 (53.8)	0.793 (49.8)	1.02 (41.9)	0.901 (55.8)
AUC(0-τ) (ng/mL x hr^{-1})	6.56 (60.8)	15.8 (49.5)	22.9 (47.5)	19.7 (54.0)
CL/F (L/min)	3.21 (43.5)	4.53 (83.5)	6.81 (138)	10.3 (42.8)
Vd/F (L)	7750 (64.4)	12100 (90.0)	14700 (79.5)	19700 (47.3)
t½ (hr)	29.3 (40.9)	25.6 (24.6)	32.3 (37.5)	22.6 (21.7)

N = Number of subjects.
n = Number of subjects where t½ and Vd/F were determined.

Table 89 Summary of Desmethyl-Asenapine Pharmacokinetic Parameter Values following q12h Administration of Sublingual Asenapine Tablet Doses to Adolescent Subjects receiving Antipsychotics - Study A7501022

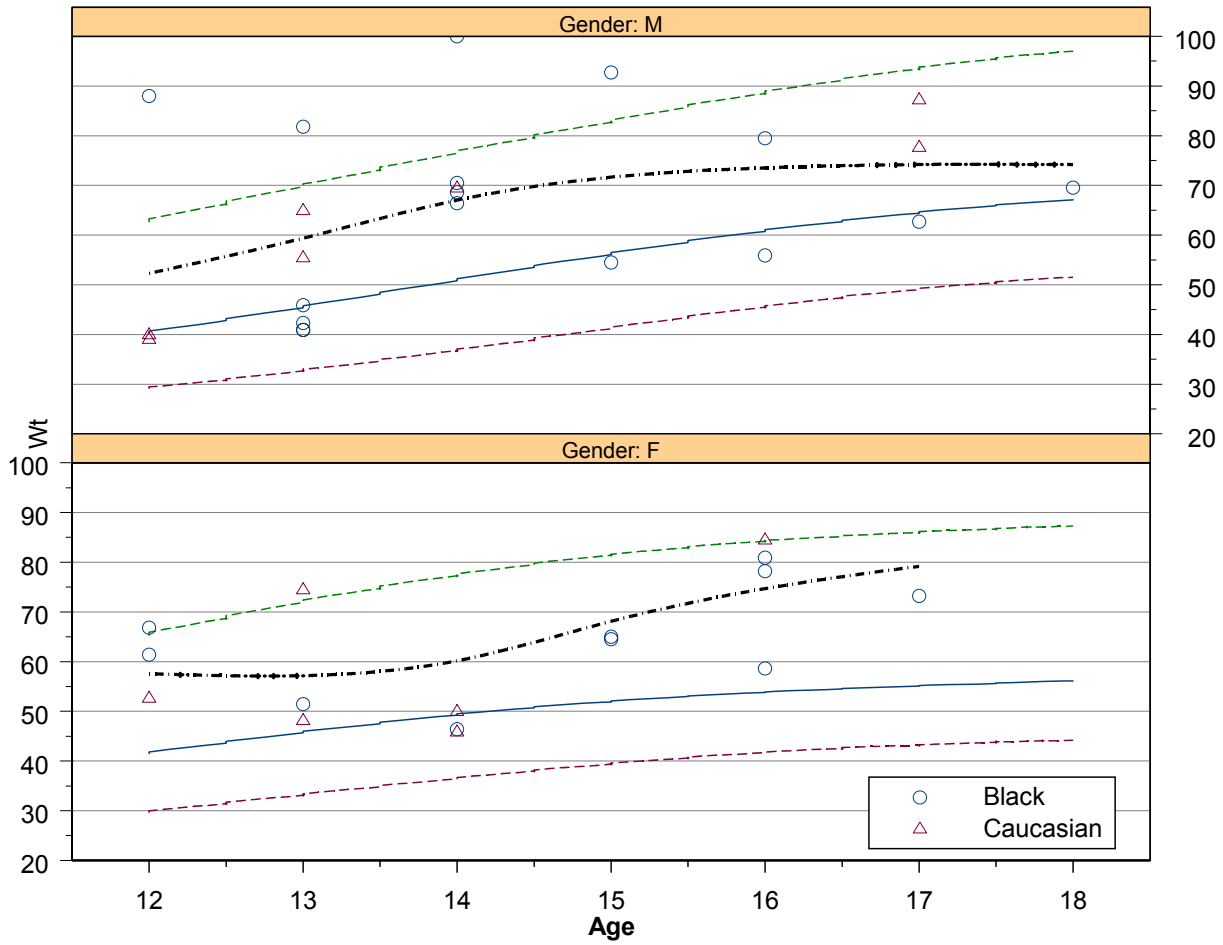
Asenapine Dose	1 mg	3 mg	5 mg	10 mg
N (n)	8 (5)	8 (5)	8 (8)	8 (6)
Tmax (hr)	3.04 (0.50 - 12)	1.82 (0.28 - 6.0)	4.00 (0.0 - 11)	3.59 (0.78 - 4.0)
Cmax (ng/mL)	0.430 (67.7)	1.04 (63.2)	1.40 (37.4)	2.96 (74.5)
Cmin (ng/mL)	0.219 (57.5)	0.621 (67.8)	0.800 (37.6)	1.07 (83.5)
AUC(0-τ) (ng/mL x hr^{-1})	4.03 (60.2)	10.1 (72.9)	13.3 (38.2)	25.8 (63.2)
t½ (hr)	23.0 (28.1)	31.2 (100.9)	21.1 (36.1)	15.2 (23.1)

N = Number of subjects.
n = Number of subjects where t½ was determined.

Table 90 Demographic Characteristics of Adolescent Subjects in Study - A7501022

Row	Site	Subject	Age (yrs)	Gender	Sexual Maturation	Race/Ethnicity	Height (cm)	Weight (kg)	BMI	Smoking Status	Weekly Alcohol Consumption (Units / week)
1	1002	10021010	12	Female		Caucasian	152.4	52.7	22.7	Never Smoked	
2	1001	10011010	12	Female		Black	154.9	61.4	25.6	Never Smoked	
3	1001	10012016	12	Female	Premenarchal	Black	160	66.8	26.1	Never Smoked	
4	1002	10021001	13	Female		Caucasian	145	48.2	22.9	Never Smoked	
5	1001	10011012	13	Female		Black	154.9	51.4	21.4	Never Smoked	
6	1002	10021012	13	Female		Caucasian	155	74.5	31	Current Smoker	6
7	1001	10012020	14	Female	Premenarchal	Caucasian	149	45.9	20.7	Never Smoked	
8	1001	10011009	14	Female		Black	157.5	46.4	18.7	Never Smoked	
9	1002	10021016	14	Female		Caucasian	157	50	20.3	Current Smoker	
10	1001	10011004	15	Female		Black	165.1	64.5	23.7	Never Smoked	
11	1001	10011002	15	Female		Black	162.6	65	24.6	Never Smoked	
12	1002	10021006	15	Female		Black	182.8	104.5	31.3	Never Smoked	
13	1002	10021007	16	Female	Premenarchal	Black	157.5	58.6	23.6	Never Smoked	
14	1001	10011001	16	Female		Black	165.1	78.2	28.7	Never Smoked	
15	1002	10021003	16	Female		Black	165.1	80.9	29.7	Never Smoked	
16	1002	10021005	16	Female		Caucasian	167.6	84.5	30.1	Never Smoked	
17	1001	10011006	17	Female		Black	157.5	73.2	29.5	Never Smoked	
18	1001	10011014	12	Male		Caucasian	143	39.1	19.1	Never Smoked	
19	1001	10011015	12	Male		Caucasian	146	40	18.8	Never Smoked	
20	1001	10012019	12	Male		Black	149.9	88	39.2	Never Smoked	
21	1001	10011013	13	Male		Black	152	40.9	17.7	Never Smoked	
22	1002	10022020	13	Male		Black	145	40.9	19.5	Never Smoked	
23	1002	10021015	13	Male		Black	152	42.3	18.3	Never Smoked	
24	1002	10021014	13	Male		Black	155	45.9	19.1	Never Smoked	
25	1002	10021009	13	Male		Caucasian	167.6	55.5	19.8	Never Smoked	
26	1002	10021011	13	Male		Caucasian	152	65	28.1	Never Smoked	
27	1002	10022017	13	Male		Black	178	81.8	25.8	Never Smoked	
28	1001	10012018	14	Male		Black	171	66.4	22.7	Never Smoked	
29	1001	10011011	14	Male		Black	157.5	68.6	27.7	Never Smoked	
30	1002	10021013	14	Male		Caucasian	170	69.5	24	Never Smoked	
31	1002	10022021	14	Male		Black	152	70.5	30.5	Never Smoked	
32	1001	10011003	14	Male		Black	182.9	100	29.9	Never Smoked	
33	1002	10022019	15	Male		Black	168	54.5	19.3	Never Smoked	
34	1001	10011007	15	Male		Black	177.8	92.7	29.3	Never Smoked	
35	1002	10022018	16	Male		Black	142	55.9	27.7	Never Smoked	
36	1001	10011008	16	Male		Black	167.6	79.5	28.3	Never Smoked	
37	1001	10012017	17	Male		Black	162.6	62.7	23.7	Never Smoked	
38	1002	10021002	17	Male		Caucasian	185.4	77.7	22.6	Past Smoker	1
39	1002	10021008	17	Male		Caucasian	162.6	87.3	33	Past Smoker	
40	1001	10011005	18	Male		Black	185.4	69.5	20.2	Never Smoked	

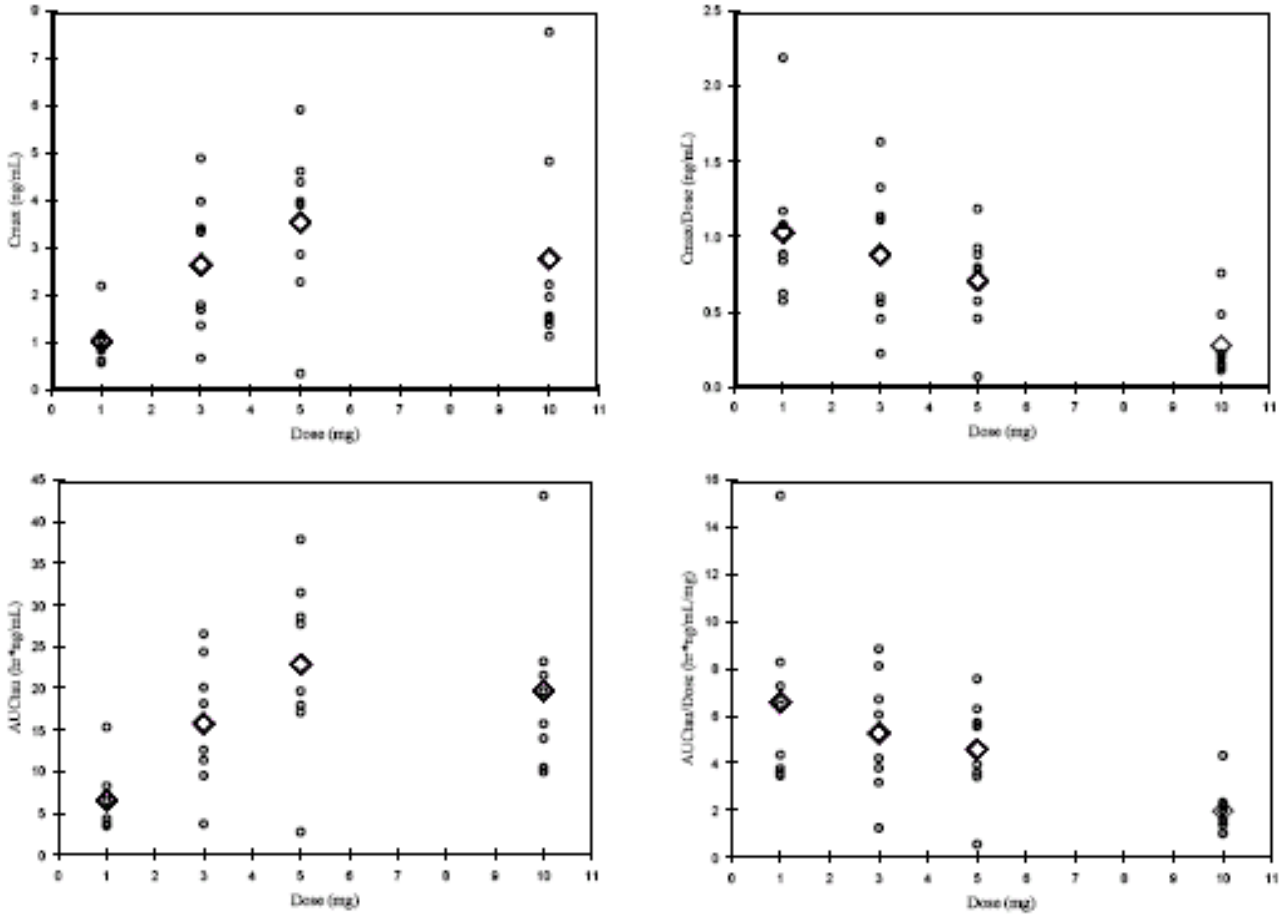
Figure 69 Adolescent Subjects Body Mass (kg) vs. Age (years) by Gender and Race, with Superimposed Curves for Population Medians and 95% Confidence Intervals along with a Cubic Spline Fit to the Subject's Data – Study A7501022



Plots of un-normalized and dose-normalized asenapine Cmax and AUCs by dose indicate that at least two subjects, (1 at 1 mg and 1 at 10 mg), were likely poor metabolizers. When dose and dose dependent bioavailability are considered, if an expected dose of 5 mg is used the mean and range of concentrations of Cmax and AUC seen with the 5 mg dose as shown in Figure 70 are similar to or slightly higher than exposures seen in adults at the same dosage in other studies, (see Table 53, and Table 76).

Figure 70 Unnormalized and Dose-normalized Asenapine Cmax and AUCs by Dose in Adolescent Subjects – Study A7501022

Figure 4. Asenapine Cmax (Upper Panel) and AUC(0-∞) (Lower Panel)Values Following q12h Administration of Sublingual Asenapine Tablet Doses to Adolescent Subjects With A Psychotic Disorder, Study A7501022



Left panels show observed values; right panels show dose-normalized values. Circles are individual subjects, diamonds are arithmetic means.

5.5.6.5 Hepatic Impairment

Two studies were conducted in subjects with hepatic impairment. The first study, study 25522, used a single 0.3 mg dose. Due to the low dose, desmethyl-asenapine could barely be detected in plasma and a second study, study A7501018 was conducted that used a single 5 mg SL dose. It appears that the sponsor used the 0.3 mg dose initially because they were concerned about the additive hepatotoxicity of asenapine.

Study 25522 only examined the effect of hepatic impairment on asenapine and desmethyl-asenapine, although the desmethyl-asenapine was largely unmeasurable due to the low dose. In contrast study A7501018, was able to examine the effect of hepatic impairment on asenapine, desmethyl-asenapine, asenapine glucuronide and unbound asenapine. Neither study examined the effects of hepatic impairment on the other primary pathway of asenapine 11-hydroxylation or on important secondary pathways.

The results of study A7501018 are more reliable due to the higher dose and longer sampling times.

In general after examination of both studies the following conclusions were reached.

- Average exposures to asenapine are increased by 2 – 5 fold in moderate and severe hepatic impairment, (see Table 93 and Table 99).

- On average there is little increase in exposure to asenapine in subjects with mild hepatic impairment, however in both studies there was 1 out of the 8 subjects with mild hepatic impairment who had an exposures two fold higher than the highest exposure in the normal group, (see Table 93 and Table 99).

- Similar results were seen with desmethyl-asenapine exposures, (see Table 100).

- There was an increase in free fraction with the degree of hepatic impairment, (see Table 96, Figure 75 and Table 102).

- The effect of hepatic impairment on exposure to unbound asenapine was even greater than the effect on total asenapine exposure, and is likely due to a greater decrease in intrinsic clearance with hepatic impairment than due to increases in free fraction. Exposures to free asenapine were almost twice as high in subjects with mild impairment compared to in normals in study A7501018, and the subject with mild impairment with the greatest exposure had exposures triple the highest expsore in the normal group, (see Table 102).

- There were indications of potentially worrisome effects of asenapine on the liver and QTc in these studies, (see Table 94 and Table 95).

- The use of only a single dose and exclusion of subjects who are more likely to be sensitive to drug induced hepatotoxicity, (additive or otherwise), biases these studies to show greater safety than would be expected in the hepatically impaired population under conditions of actual use.

- The narrow therapeutic index based on other studies for asenapine induced hepatic impairment along with the findings in the present studies argues against the use of asenapine in subjects with any degree of hepatic impairment.

5.5.6.5.1 Hepatic Impairment – Study 25522

Study 25522 was an open label, single dose study of the effects of chronic hepatic impairment on the pharmacokinetics of asenapine and its metabolite desmethyl-asenapine in 16 male and 16 female Caucasian subjects with a mild, moderate, severe, or no hepatic impairment as classified by Child-Pugh

score aged 35-52 years of age. There were 4 male and 4 female subjects per degree of hepatic impairment, and each subject was administered a single 0.3 mg dose of asenapine sublingually.

The Child-Pugh classification system is shown in Table 91.

Table 91 Child-Pugh Classification System

Class A: 5-6		Class B: 7-9	Class C: 10-15	
Measure	**1 point**	**2 points**	**3 points**	**units**
Bilirubin (total)	<34 (<2)	34-50 (2-3)	>50 (>3)	µmol/l (mg/dL)
Serum albumin	>35	28-35	<28	g/L
INR	<1.7	1.71-2.20	> 2.20	*no unit*
Ascites	None	Suppressed with medication	Refractory	*no unit*
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)	*no unit*

Exclusion criteria were as follows:

- Arterial hypertension (> 190/105 mmHg), chronic heart failure (CHF) nonstabilized (NYHA class III and IV);
- Hepatocarcinoma;
- Hepatic encephalopathy grade 3;
- Sepsis or spontaneous bacterial peritonitis;
- Gastrointestinal bleeding within one month before the study;
- Diabetes mellitus of any type requiring drug administration;
- Acute liver failure of any etiology, (surgical) portocaval shunt (primary biliary cirrhosis is allowed);
- Acute viral, toxic, or drug induced hepatitis;
- Current use of any drug intake with potentially hepatotoxicity;
- Change in used medication (prescribed by a physician and/or OTC medication) other than for liver insufficiency within 7 days prior to Org 5222 administration (for Child Pugh C patients, exceptions can be made if medically justified);
- Chronic drug induced hepatitis;
- Presence of alcohol abuse (alcohol consumption > 40 g/day)

Intake of alcohol was not allowed from 24 hours prior to dosing until the last PK blood sample. Smoking was not allowed during the entire hospitalization period. Food and drinks containing caffeine and other methylxanthines (e.g. coffee, tea, cola or chocolate) were not allowed from 48 hours prior to dosing until after the last PK blood sample. Grapefruit containing products were not allowed from 1 week prior to dosing until after the last PK blood sample

Strenuous physical exercise (including competitive sports) had to be avoided from 48 hours prior to dosing until the last PK blood sample.

Meals and snacks during hospitalization were to be provided according to the rules of Pharm PlanNet Contract Research-Ukraine.

Comments

Demographic characteristics demonstrate that subjects groups were relatively well matched with the possible exception of weight. Subjects were generally middle-aged, (see Table 92).

Exposures of asenapine assessed by AUCs were increased by over 2 fold in subjects with moderate and severe hepatic impairment, Cmax was lower and Tmax was delayed. Although the geometric mean AUC in subjects with mild impairment was 90% of the geometric mean AUC in healthy controls, the 90% confidence interval was 55% - 149% indicating that some individuals may have either exceptionally high or low exposures. In fact although the mean exposures were similar in the mild and healthy groups the subject with the largest AUCinf in the mild group had an AUC that was over twice the mean for the healthy group (see Table 93). Even more troubling however is the fact that the sampling in subjects with mild hepatic impairment was truncated and the mean concentration vs. time profiles indicate if sampling was continued, that the AUC ratio in subjects with mild impairment could be much higher, (see Figure 71).

Most demethyl-asenapine concentration values were below LLOQ. Consequently, for desmethyl-asenapine, the sponsor claims that no mean concentration values could be calculated at any time point and thus no curves were presented by the sponsor.

In the severely impaired group, (Child Pugh C), there was one case of severe jaundice in Subject 37. Subject 37 also had increases in liver function tests with a pattern that is suggestive of an acute hepatocellular injury, (see Table 94). This subject also had the 2nd highest free fraction of any subject at 2.2%.

Table 95 shows a table of adverse events as reported by the sponsor in the clinical study report. This table is included as it shows that the increase in LFTs in the patient with jaundice was not reported in this table. In addition it shows a fair number of increases in LFTs in the moderate impairment group and a case of QTc prolongation in each group of hepatically impaired subjects. Due to a lack of review time this was not pursued by this reviewer, however this should be examined more in depth by the safety reviewer.

The plasma bound asenapine fraction unbound in the Child-Pugh B and C groups (both 1.7%) was significantly higher than that in healthy subjects (1.3 %). Although no significant difference in binding was found between healthy subjects and the Child-Pugh A group (1.4%), this was not the case in study A7501018, (see Table 96 and Table 99).

According to the sponsor *'Regression analysis showed a significant positive correlation between AUC$_{0\text{-}tlast}$ and the Child-Pugh score. An even stronger (negative) correlation was found between AUC$_{0\text{-}tlast}$ and the albumin concentration which can be explained by the fact that the total Child-Pugh score is mainly determined by the albumin concentration at screening in the present study'*. This is true and can be seen by simple inspection of Figure 72, although an even clearer relationship can be seen between fraction unbound and AUCinf, (see Figure 73).

However, as a high intrinsic clearance drug this does not make sense. Instead we would expect that as free fraction increases that total AUC decreases while AUCunbound stays the same. This is clarified by examinating of AUCinf and unbound AUCinf vs. degree of hepatic impairment. From Figure 74 and Figure 75 we see a pattern that indicates that although the fraction unbound is changing the decrease in intrinsic clearance appears to be even greater in some subjects.

Blood samples were collected for genotyping however the decision whether genotyping took place was made by the sponsor. No data on genotype could be found and it is presumed that genotyping was not performed.

The exclusion criteria on the previous page demonstrate that the subjects used will likely provide a biased assessment of asenapine's safety in patients with hepatic impairment:

Virtually all of the categories of subjects who are excluded are those whose underlying cause of hepatic insufficiency indicates that they may be genetically predisposed to drug induced hepatotoxicity or whose hepatic injury is likely to be exascerbated in the face of a hepatotoxic drug.

It is this reviewer's opinion that while this may protect the small number of subjects in a particular study, the danger to the overall population of individuals with hepatic insufficiency once a drug is approved outweighs the risk from exposure to a single dose of drug in a carefully monitored population.

Table 92 Hepatic Impairment Study Subject Demographic Summary Statistics – Study 25522

	Gender	N	Healthy	Mild	Moderate	Severe	Total
Age (years)	**Female**	4/16	45.3 ± 7.27 (16.0) 35 - 52 [47.0]	46.0 ± 9.02 (19.6) 33 - 53 [49.0]	48.5 ± 10.34 (21.3) 33 - 54 [53.5]	51.0 ± 6.06 (11.9) 42 - 55 [53.5]	47.7 ± 7.81 (16.4) 33 - 55 [51.5]
	Male	4/16	46.8 ± 6.55 (14.0) 37 - 51 [49.5]	52.8 ± 7.27 (13.8) 46 - 60 [52.5]	46.8 ± 7.59 (16.2) 36 - 53 [49.0]	47.0 ± 7.12 (15.1) 39 - 53 [48.0]	48.3 ± 6.92 (14.3) 36 - 60 [49.5]
	Total	8/32	46.0 ± 6.46 (14.0) 35 - 52 [48.5]	49.4 ± 8.40 (17.0) 33 - 60 [49.0]	47.6 ± 8.45 (17.8) 33 - 54 [52.0]	49.0 ± 6.48 (13.2) 39 - 55 [53.0]	48.0 ± 7.26 (15.1) 33 - 60 [50.5]
Height (cm)	**Female**	4/16	162.3 ± 6.60 (4.1) 155 - 170 [162.0]	162.3 ± 9.84 (6.1) 154 - 175 [160.0]	166.0 ± 4.55 (2.7) 161 - 172 [165.5]	153.5 ± 4.73 (3.1) 150 - 160 [152.0]	161.0 ± 7.69 (4.8) 150 - 175 [160.5]
	Male	4/16	171.3 ± 1.50 (0.9) 170 - 173 [171.0]	173.8 ± 4.79 (2.8) 167 - 178 [175.0]	178.3 ± 2.06 (1.2) 176 - 180 [178.5]	172.5 ± 2.38 (1.4) 170 - 175 [172.5]	173.9 ± 3.80 (2.2) 167 - 180 [174.0]
	Total	8/32	166.8 ± 6.54 (3.9) 155 - 173 [170.0]	168.0 ± 9.44 (5.6) 154 - 178 [170.5]	172.1 ± 7.32 (4.3) 161 - 180 [174.0]	163.0 ± 10.73 (6.6) 150 - 175 [165.0]	167.5 ± 8.88 (5.3) 150 - 180 [170.0]
Weight (kg)	**Female**	4/16	63.80 ± 5.59 (8.8) 58.1 - 71.0 [63.05]	62.10 ± 2.85 (4.6) 60.0 - 66.1 [61.15]	71.82 ± 11.13 (15.5) 60.1 - 84.1 [71.55]	56.83 ± 4.69 (8.3) 50.1 - 60.1 [58.55]	63.64 ± 8.24 (12.9) 50.1 - 84.1 [60.55]
	Male	4/16	77.75 ± 7.41 (9.5) 71.0 - 88.0 [76.00]	73.28 ± 7.42 (10.1) 62.3 - 78.1 [76.35]	82.55 ± 6.55 (7.9) 75.1 - 88.1 [83.50]	84.28 ± 6.43 (7.6) 78.0 - 92.0 [83.55]	79.46 ± 7.65 (9.6) 62.3 - 92.0 [78.05]
	Total	8/32	70.78 ± 9.62 (13.6) 58.1 - 88.0 [71.00]	67.69 ± 7.92 (11.7) 60.0 - 78.1 [64.20]	77.19 ± 10.21 (13.2) 60.1 - 88.1 [78.50]	70.55 ± 15.57 (22.1) 50.1 - 92.0 [69.05]	71.55 ± 11.22 (15.7) 50.1 - 92.0 [72.50]
BMI (kg/m^2)	**Female**	4/16	24.20 ± 0.29 (1.2) 23.9 - 24.6 [24.15]	23.73 ± 2.229 (9.4) 21.6 - 26.2 [23.55]	26.00 ± 3.299 (12.7) 23.2 - 30.5 [25.15]	24.15 ± 1.857 (7.7) 22.3 - 26.7 [23.80]	24.52 ± 2.167 (8.8) 21.6 - 30.5 [24.10]
	Male	4/16	26.53 ± 2.734 (10.3) 24.0 - 30.4 [25.85]	24.33 ± 2.945 (12.1) 20.6 - 27.8 [24.45]	26.00 ± 2.286 (8.8) 23.2 - 28.4 [26.20]	28.40 ± 2.859 (10.1) 25.5 - 31.5 [28.30]	26.31 ± 2.86 (10.9) 20.6 - 31.5 [25.85]
	Total	8/32	25.36 ± 2.19 (8.6) 23.9 - 30.4 [24.40]	24.03 ± 2.439 (10.1) 20.6 - 27.8 [24.45]	26.00 ± 2.628 (10.1) 23.2 - 30.5 [25.80]	26.28 ± 3.185 (12.1) 22.3 - 31.5 [26.00]	25.42 ± 2.66 (10.4) 20.6 - 31.5 [24.80]

Table 93 Effect of Hepatic Impairment on Pharmacokinetics of Asenapine – Study 25522

Parameter	Summary Statistics				Geometric Means				Geometric Mean Ratios (90% CI)		
Group	Healthy Subjs	Child−Pugh A	Child−Pugh B	Child−Pugh C	HS	A	B	C	A:HS	B:HS	C:HS
N	8	8	8	8	—	—	—	—	—	—	—
Tmax (h)	1.75 (0.75 - 4.00)	1.50 (0.75 - 3.00)	3.00 (1.00 - 4.02)	1.75 (0.75 - 4.00)	—	—	—	—	—	—	—
Cmax (ng/mL)	0.284 ± 0.104 (36.7) 0.13 - 0.41 [0.26]	0.196 ± 0.053 (27.1) 0.13 - 0.275 [0.193]	0.187 ± 0.088 (47.2) 0.109 - 0.396 [161]	0.226 ± 0.074 (32.9) 0.171 - 0.390 [0.196]	0.266	0.190	0.174	0.217	0.71 0.53 - 0.95	0.66 0.49 - 0.87	0.82 0.61 - 1.09
AUC0−tlast (ng/mL x hr^{-1})	2.03 ± 0.531 (26.2) 1.16 - 3.00 [2.09]	2.14 ± 1.08 (50.6) 1.10 - 3.90 [1.68]	3.27 ± 0.686 (21.0) 2.52 - 4.43 [3.02]	3.68 ± 1.48 (40.2) 1.52 - 5.49 [3.91]	1.96	1.93	3.21	3.35	0.98 0.71 - 1.36	1.63 1.18 - 2.26	1.7 1.23 - 2.36
AUC∞ (ng*h/mL)	2.97 ± 0.865 (29.1) 1.94 - 4.51 [2.77]	2.99 ± 1.93 (64.5) 1.42 - 7.19 [2.46]	7.26 ± 4.05 [a] (55.8) 3.81 - 14.6 [4.90]	7.86 ± 5.82 (74.0) 1.73 - 17.4 [6.76]	2.87	2.58	6.43	5.96	0.90 0.55 - 1.49	2.24 1.34 - 3.77	2.08 1.26 - 3.43
AUCextrap (%)	29.8 ± 15.2 (51.0) 8.49 - 57.7 [28.4]	24.3 ± 11.9 (49.2) 11.2 - 45.8 [23.2]	44.7 ± 23.0 [a] (51.4) 9.34 - 79.0 [39.3]	39.3 ± 22.7 (57.7) 11.8 - 75.0 [36.5]	26.1	21.8	38.0	33.2	—	—	—
Tlast (h)	25.5 ± 6.21 (24.4) 12.0 - 30.0 [27.0]	29.3 ± 13.8 (47.1) 12.0 - 48.0 [27.0]	46.5 ± 4.24 (9.12) 36.0 - 48.0 [48.0]	42.0 ± 11.6 (27.5) 18.0 - 48.0 [48.0]	24.6	26.3	46.3	40.0	—	—	—
Clapp (L/h)	109 ± 30.9 (28.5) 66.6 - 155 [108]	131 ± 61.3 (46.9) 41.7 - 211 [123]	51.8 ± 23.1 [a] (44.6) 20.6 - 78.8 [61.2]	69.0 ± 60.3 (87.3) 17.2 - 174 [44.4]	105	116	46.6	50.3	1.11 0.61 - 2.03	0.45 0.24 - 0.83	0.48 0.26 - 0.88
wn−CLapp (L/h) / kg	1.55 ± 0.432 (28.0) 1.02 - 2.10 [1.55]	1.95 ± 0.899 (46.1) 0.538 - 3.19 [1.76]	0.696 ± 0.335 [a] (48.2) 0.263 - 1.16 [0.695]	1.15 ± 1.20 (105) 0.219 - 3.47 [0.631]	1.49	1.73	0.618	0.729	1.16 0.58 - 2.30	0.41 0.20 - 0.84	0.49 0.25 - 0.97
Vz,app (L)	3120 ± 1403 (45.0) 905 - 5239 [3006]	2565 ± 1063 (41.4) 1077 - 4362 [2528]	3536 ± 1251 [a] (35.4) 1003 - 4917 [3752]	2537 ± 769 (30.3) 1450 - 3358 [2674]	2792	2363	3225	2419	0.85 0.52 - 1.37	1.15 0.70 - 1.91	0.87 0.53 - 1.41
wn - Vz,app (L/kg)	—	—	—	—	39.8	35.1	42.7	35.0	0.88 0.54 - 1.45	1.07 0.64 - 1.79	0.88 0.54 - 1.45
t½ (h)	22.7 ± 13.1 (57.6) 4.06-42.8 [20.8]	19.1 ± 17.5 (91.6) 3.73-58.9 [15.45]	64.2 ± 52.7 (82.2) 11.3 – 166.0 [41.7]	48.7 ± 42.7 (87.7) 5.78 – 135.0 [38.15]	18.5	14.1	47.9	33.3	0.76 0.31 - 1.86	2.59 1.03 - 6.54	1.80 0.74 - 4.40

Figure 71 Mean Asenapine Concentration-vs.-Time Profiles after a 0.3 mg Sublingual Dose in Subjects with Various Degrees of Hepatic Function – Study 25522

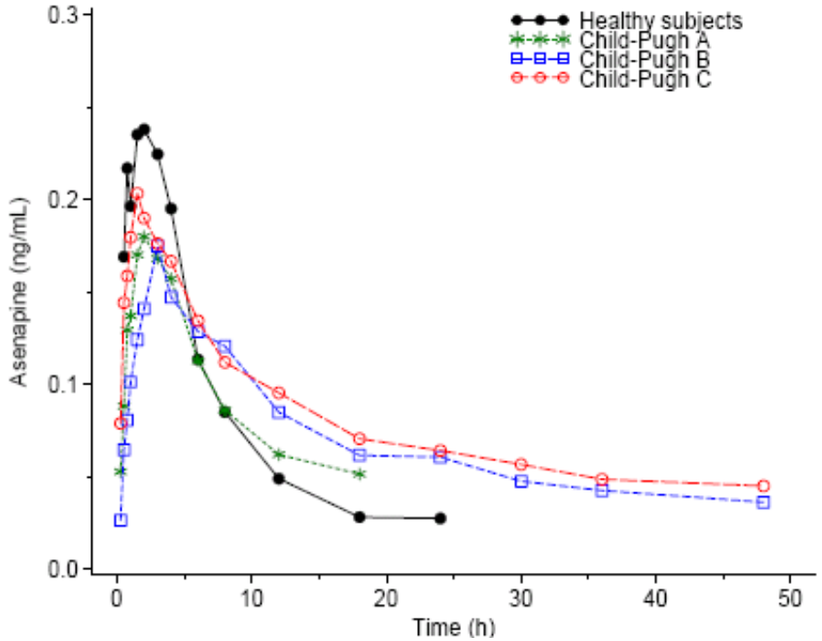


Table 94 Selected Laboratory Values in Subject 37- Study 25522

Group	Subject	Visit	Sample date	Sample time	total Bilirubin [umol/L]	Conjug Bili [umol/L]	Unconjug Bili [umol/L]	Triglycerides (TG) [mmol/L]	total Cholesterol [mmol/L]	total Protein [mmol/L]	Urea [g/L]	Albumin [g/L]	ALAT /SGPT [U/L]	ASAT /SGOT [U/L]	GGT [U/L]	AlkPhos [U/L]	LDH [U/L]	Lactate	GLDH	OCT
4	37*	Screening	22DEC2003	9:15	269.8 RH	96.2 RH	173.6 RH	6.0	0.69	2.0 RL	89 AH	23 RL	63 RH	51 RH	217 RH	265	804 RH	NR	NR	NR
		Follow-Up	26DEC2003	8:05	454.5 RH	124.0 RH	330.5 RH	5.9	0.61	1.2 RL	81	21 RL	36	123 RH	121 RH	180	762 RH	NR	NR	NR
Observed Increases						↑	↑↑							↑						
Pattern expected with Acute Hepatocellular Injury							↑						↑	↑			↑			
Pattern associated with hepatobiliary toxicity					↑										↑	↑				
Pattern expected with Mitochondrial based injury																		↑	↑	↑

* H/H at screening and followup were 90/36 abd 96/37 respectively.

Table 95 Number and Percent of Subjects with Adverse Events by MedDRA System Organ Class and Preferred Term as reported in Sponsor's Table in Clinical Study Report – Study 25522

Body system Preferred term	Group A (N = 8)	Group B (N = 8)	Group C (N = 8)	Group D (N = 8)	Total (N = 32)
Any Body System	4 (50%)	7 (88%)	5 (63%)	7 (88%)	23 (72%)
Cardiac disorders					
Sinus bradycardia	1 (13%)		1 (13%)		2 (6%)
Sinus tachycardia	1 (13%)	1 (13%)		1 (13%)	3 (9%)
Tachycardia				1 (13%)	1 (3%)
Gastrointestinal disorders					
Hypoaesthesia oral	2 (25%)				2 (6%)
General disorders and administration site conditions					
Injection site haemorrhage	1 (13%)	4 (50%)			5 (16%)
Hepatobiliary disorders					
Jaundice				1 (13%)	1 (3%)
Investigations					
Alanine aminotransferase increased			1 (13%)		1 (3%)
Aspartate aminotransferase increased			1 (13%)		1 (3%)
Blood albumin decreased		1 (13%)	1 (13%)		2 (6%)
Blood cholesterol decreased		1 (13%)			1 (3%)
Blood lactate dehydrogenase increased			1 (13%)	2 (25%)	3 (9%)
Electrocardiogram QRS complex prolonged	1 (13%)	1 (13%)			2 (6%)
Electrocardiogram QT corrected interval prolonged		1 (13%)	1 (13%)	1 (13%)	3 (9%)
Haematocrit decreased			1 (13%)		1 (3%)
Haemoglobin decreased		2 (25%)			2 (6%)
Protein urine present			1 (13%)	2 (25%)	3 (9%)
Red blood cell count decreased			1 (13%)		1 (3%)
Red blood cells urine positive			1 (13%)		1 (3%)
Urine bilirubin increased				2 (25%)	2 (6%)
White blood cells urine positive			1 (13%)	1 (13%)	2 (6%)
Nervous system disorders					
Headache	1 (13%)				1 (3%)
Respiratory, thoracic and mediastinal disorders					
Throat irritation				1 (13%)	1 (3%)

Table 96 Asenapine Fraction Bound to Plasma Proteins at 1.5 and 12 Hours Post-Dose – Study 25522

Sampling Time (hours)		Summary Statistics				Geometric Means			
		Normal	Child−Pugh Classification			Normal	Child−Pugh Classification		
			A (mild)	B (moderate)	C (severe)		A	B	C
1.5 hours	N	8	7	8	8	8	7	8	8
	Stats	98.7 ± 0.12 (0.120) 98.6 - 98.9 [98.7]	98.6 ± 0.15 (0.153) 98.4 - 98.8 [98.7]	98.3 ± 0.26 (0.269) 98.0 - 98.7 [98.4]	98.3 ± 0.32 (0.326) 97.9 - 98.9 [98.4]	98.7	98.6	98.3	98.3
12 hours	N	8	7	8	7	8	7	8	7
	Stats	98.7 ± 0.20 (0.203) 98.3 - 99.0 [98.7]	98.6 ± 0.15 (0.152) 98.3 - 98.8 [98.6]	98.3 ± 0.35 (0.353) 97.6 - 98.7 [98.3]	98.2 ± 0.24 (0.248) 97.8 - 98.6 [98.2]	98.6	98.6	98.2	98.2

Figure 72 Asenapine AUCinf vs. Albumin by Degree of Hepatic Impairment – Study 25522

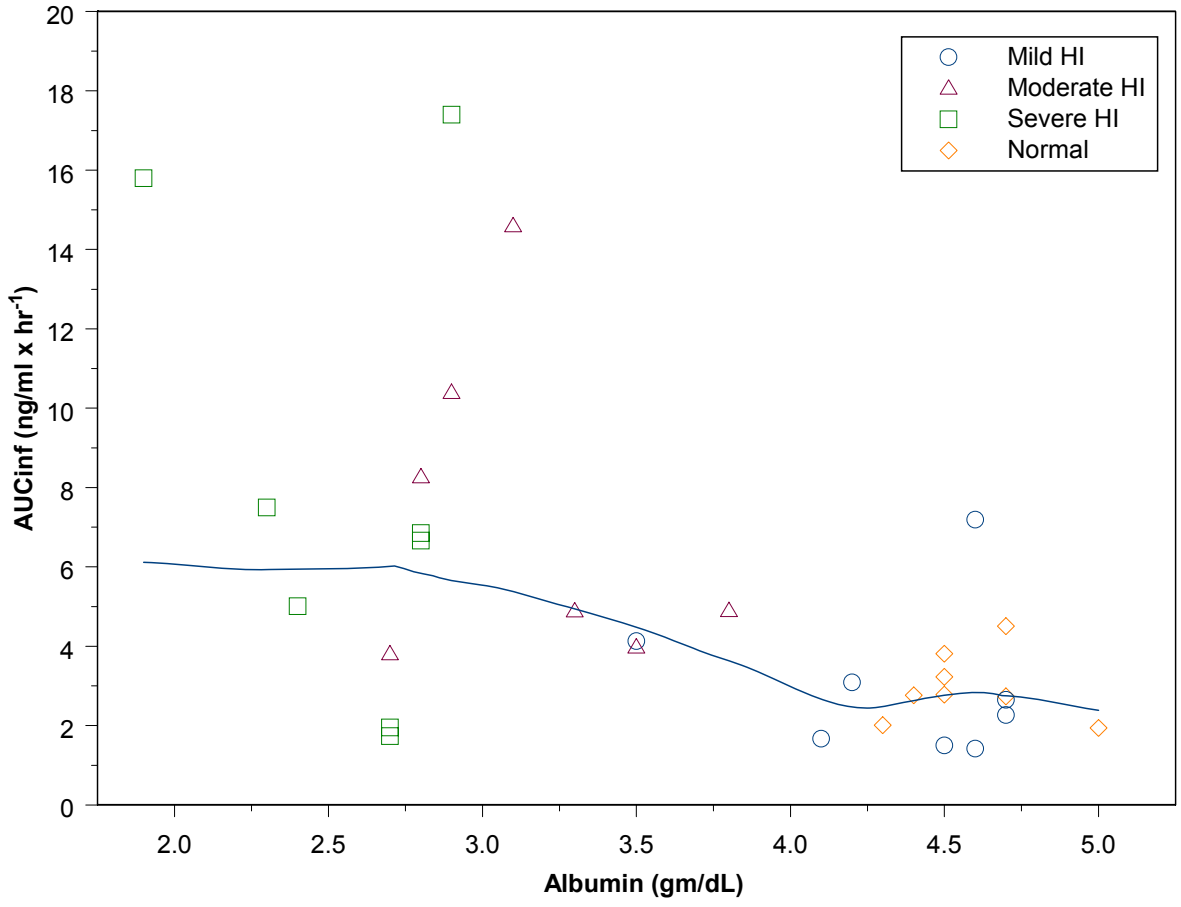


Figure 73 Asenapine AUCinf vs. Fraction Unbound (%) – Study 25522

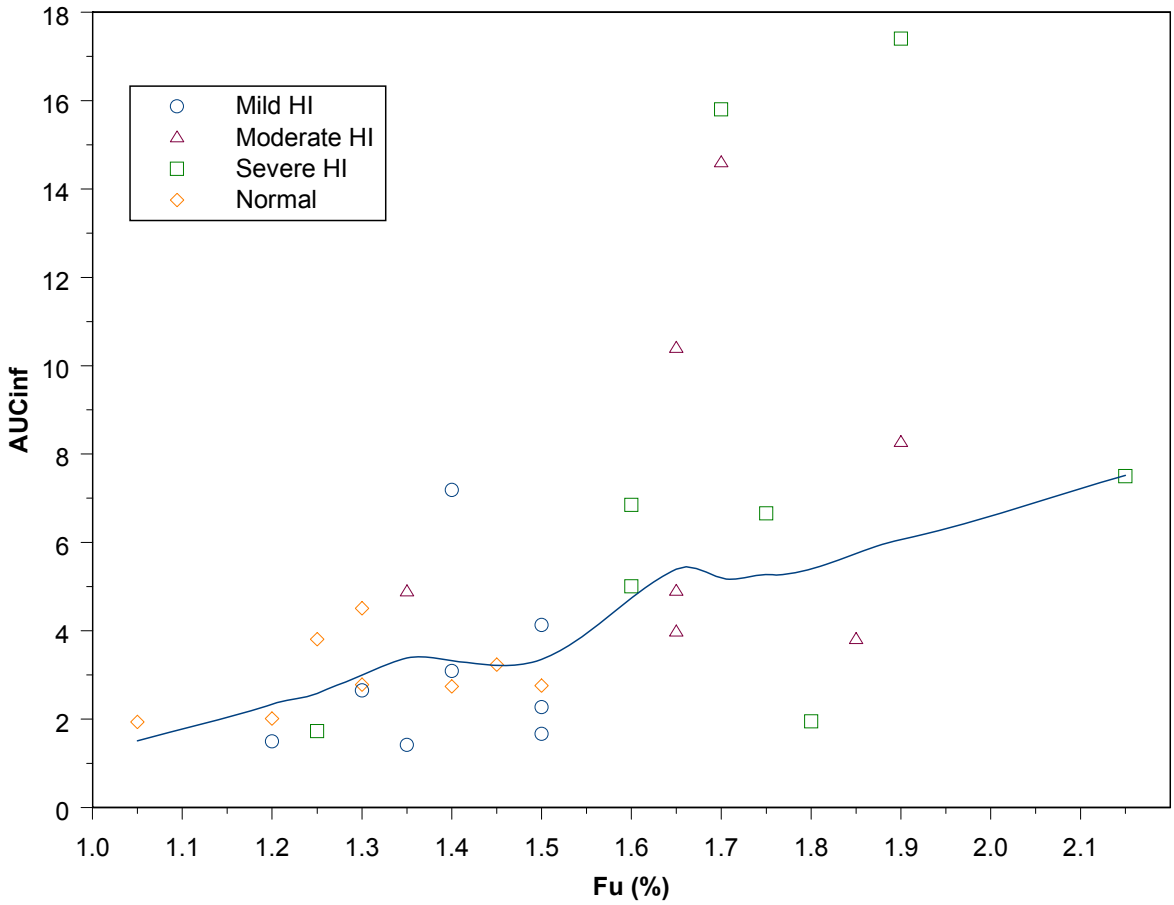


Figure 74 Asenapine AUCinf vs. Degree of Hepatic Impairment – Study 25522

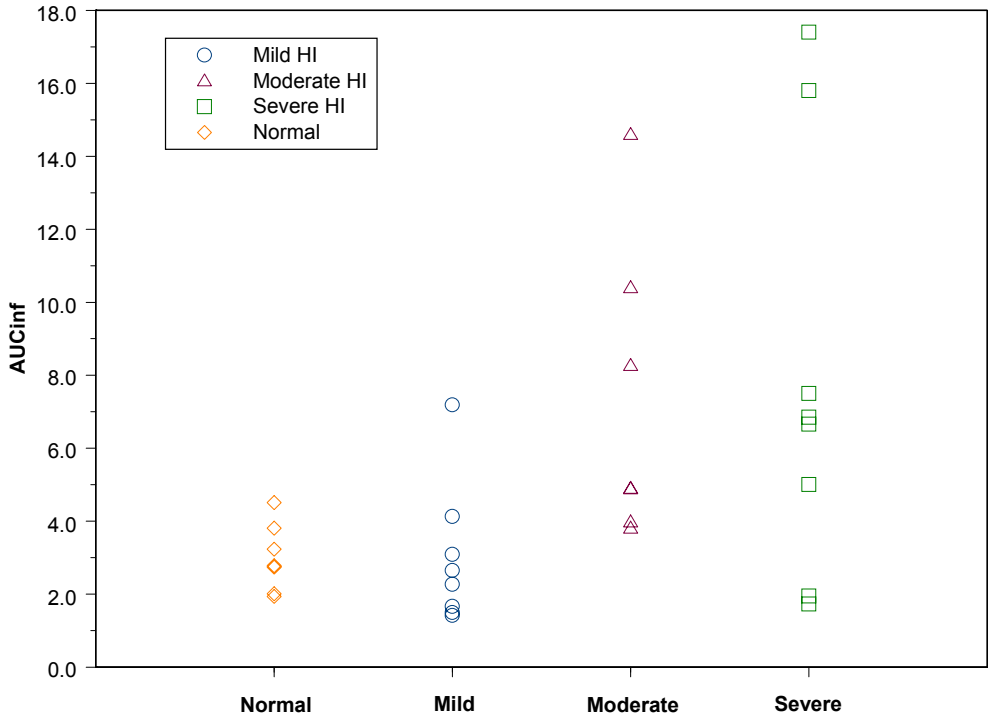
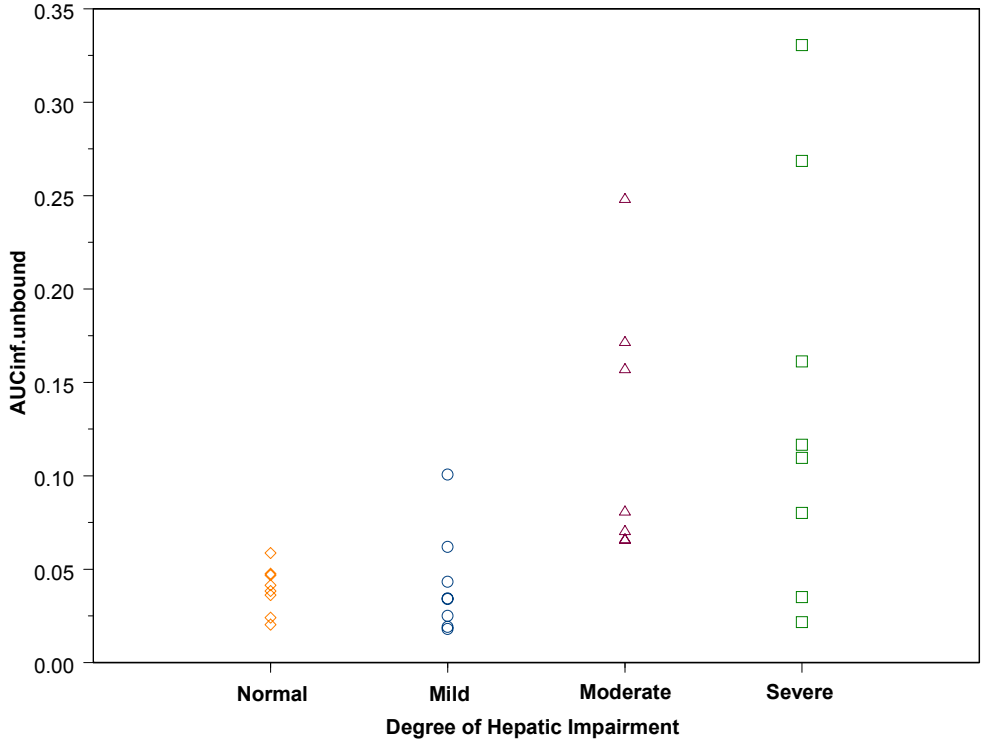


Figure 75 Asenapine Unbound AUCinf vs. Degree of Hepatic Impairment – Study 25522



5.5.6.5.2 Hepatic Impairment – Study A7501018

Study A7501018 was a single-center, open-label, single-dose study that examined the effect of varying degrees of hepatic impairment on the pharmacokinetics of asenapine, desmethyl-asenapine, and asenapine N-glucoronide.

Thirty subjects were enrolled (8 each in the normal hepatic function and Child-Pugh A and B groups, and 6 in the Child-Pugh C group). The study population included 20 men and 10 women with a mean age of 55.7 years (range 46 - 72 years) and a mean BMI of 28.4 kg/m^2 (range 18.1 - 32.7 kg/m^2). One subject was black and 29 were white, (see Table 97).

Each subject received a single dose of asenapine 5 mg sublingually (Phase III formulation), and pharmacokinetic samples were obtained up to 96-hours postdose in Groups 1 and 2, and up to 240-hours postdose in Groups 3 and 4.

Comparison of demographics by degree severity reveals that the healthy group contained the lowest proportion of women, males in the mild hepatic impairment group weighed more, and the mild and especially the moderate group had a high proportion of smokers, (see Table 98). It's this reviewer's impression from other NDAs that women and the elderly are likely to have higher exposures with CYP1A2 substrates. In addition it is well documented that smokers are likely to have lower exposures due to induction of CYP1A2.

When exposures to asenapine are compared there is a mean 5.5 fold increase in severe hepatic impairment with an upper 90% CI of 8.6. Even more concerning is that exposures to unbound asenapine are 8 fold higher. There's only a 1.12 fold mean increase in exposure to bound asenapline in moderate and mild impairment however, the 90% confidence intervals are quite wide going up to 1.68 and 1.71 fold in the mild and moderate groups respectively, (see Table 99).

Similar results are seen with the N-desmethyl metabolite, but with much lower Cmaxs in all groups, (see Table 100). For asenapine glucuronide there are increases in all three groups of hepatic impairment, (see Table 101).

The results in the moderate group are inconsistent with what was seen in study 25522 where exposures in the moderate group were double those in the healthy controls, (see Table 93). However, most troubling of all is that when unbound asenapine exposures are compared the mean exposure is nearly doubled in the mild group with some individuals having exposures 3 fold higher than any of the healthy subjects and this is in spite of free fractions being much higher, (see Table 102). This is in contrast to study 25522, (see §5.5.6.5.1), however the present study uses a higher dose and sampling is longer than in study 25522 thus the results of the present study should be considered more reliable.

Thus, it appears that some patients with mild hepatic impairment may have much higher exposures to asenapine and this is confirmed by comparing plots of individual exposures as compared with mean exposures, (see Figure 76 to Figure 81), although the subject with high exposure to asenapine (subject 1001006 in Figure 79) also has much higher exposure to the N-desmethyl-metabolite (Figure 81). Possibly indicating that this subject is a CYP2D6 poor metabolizer, this may not be a mitigating factor and could actually increase the risk, as the exposure to free drug in this subject is much higher, (see Figure 82). Since only slightly higher than the likely clinical doses appear to be associated with hepatotoxicity, the presence of even 1 or 2 individuals in the mild hepatic impairment groups with much higher total exposures and others with normal total exposures and much higher free exposures leaves no margin of safety. Thus even if the risk : benefit ratio turns out to be acceptable for patients with normal hepatic function, it is unlikely to be acceptable for patients with even mild degrees of hepatic function.

Safety and laboratory data was not closely inspected but even in passing it's noteworthy that several subjects had acute changes in lab tests, e.g. BUN, LFTs, as well as possibly significant AEs. A more detailed review will be needed and will need to be documented if there is any discussion on whether subjects with mild hepatic impairment should be allowed to take asenapine.

Table 97 Subject Demographics for Hepatic Impairment Study – Study A7501018

Site	Subj No.	Age	Gender	Menopausal Status	Race	Ht (cm)	Wt (kg)	BMI ($kg/m^{2)}$	Smoking Status	EtOH (U/wk)	Group
1001	10011009	56	Male		Caucasian	167.6	80.0	28.5	NS	0	Group 1
1001	10011010	66	Male		Caucasian	177.8	82.7	26.2	NS	0	Group 1
1001	10011011	60	Male		Caucasian	170.2	82.7	28.5	Current Smoker	0	Group 1
1001	10011012	53	Female	(Postmenopausal)	Black	157.5	70.5	28.4	Current Smoker	0	Group 1
1002	10021008	63	Female	(Postmenopausal)	Caucasian	168.0	73.8	26.1	Past Smoker	4	Group 1
1002	10021014	54	Male		Caucasian	170.0	80.0	27.7	NS	9	Group 1
1002	10021015	52	Male		Caucasian	165.0	87.7	32.2	Past Smoker	0	Group 1
1002	10021016	46	Male		Caucasian	171.5	95.7	32.5	NS	10	Group 1
1001	10011005	55	Female	(Postmenopausal)	Caucasian	172.7	54.1	18.1	Current Smoker	0	Group 2
1001	10011006	57	Female	(Postmenopausal)	Caucasian	160.0	70.5	27.5	Current Smoker	0	Group 2
1001	10011007	56	Male		Caucasian	182.9	88.2	26.4	Current Smoker	0	Group 2
1001	10011008	53	Male		Caucasian	177.8	91.8	29	NS	0	Group 2
1002	10021009	47	Male		Caucasian	182.0	92.3	27.9	NS	0	Group 2
1002	10021010	64	Female	(Postmenopausal)	Caucasian	161.0	76.4	29.5	Past Smoker	0	Group 2
1002	10021012	51	Male		Caucasian	183.5	99.1	29.4	NS	0	Group 2
1002	10021013	52	Male		Caucasian	175.0	88.8	29	NS	0	Group 2
1001	10011001	52	Male		Caucasian	165.1	75.5	27.7	NS	0	Group 3
1001	10011002	72	Female	(Postmenopausal)	Caucasian	162.6	86.4	32.7	NS	0	Group 3
1001	10011003	65	Male		Caucasian	162.6	84.5	32	Current Smoker	0	Group 3
1001	10011004	55	Male		Caucasian	175.3	98.2	32	Current Smoker	0	Group 3
1002	10021002	63	Female	(Postmenopausal)	Caucasian	165.5	78.2	28.6	NS	0	Group 3
1002	10021003	48	Female	(Postmenopausal)	Caucasian	157.0	71.8	29.1	Current Smoker	0	Group 3
1002	10021004	50	Male		Caucasian	188.5	94.1	26.5	Past Smoker	0	Group 3
1002	10021005	53	Male		Caucasian	169.0	84.5	29.6	Current Smoker	0	Group 3
1001	10011013	46	Female	(Postmenopausal)	Caucasian	167.6	80.9	28.8	NS	0	Group 4
1001	10011014	54	Male		Caucasian	182.9	88.2	26.4	NS	0	Group 4
1002	10021006	51	Male		Caucasian	169.0	79.1	27.7	NS	0	Group 4
1002	10021007	66	Male		Caucasian	176.0	98.2	31.7	NS	0	Group 4
1002	10021011	48	Male		Caucasian	175.2	92.6	30.2	NS	0	Group 4
1002	10021017	46	Female	(Premenopausal)	Caucasian	168.0	60.9	21.6	Current Smoker	0	Group 4

Table 98 Summary Statistics for Subject Demographics by Degree of Hepatic Impairment and Gender – Study A7501018

Group	Gender	Menopausal Status	N	Race W/B/A/H/NA	Age	Ht (cm)	Wt (kg)	BMI (kg/m$^{2)}$	Smoking Status Current/Past/NS	EtOH (U/wk)
1 Normal	Female	Post	2	1/1	58 ± 7.1 (12.2) 53 - 63 [58]	162.75 ± 7.4 (4.6) 157.5 - 168 [162.75]	72.15 ± 2.3 (3.2) 70.5 - 73.8 [72.15]	27.25 ± 1.6 (6.0) 26.1 - 28.4 [27.25]	1/1/0	0/4
	Male		6		55.7 ± 6.9 (12.3) 46 - 66 [55]	170.4 ± 4.3 (2.5) 165 - 177.8 [170.1]	84.8 ± 6.0 (7.1) 80 - 95.7 [82.7]	29.3 ± 2.5 (8.7) 26.2 - 32.5 [28.5]	1/1/4	4x0/9/10
2 Mild	Female	Post	3		58.7 ± 4.7 (8.1) 55 - 64 [57]	164.6 ± 7.1 (4.3) 160 - 172.7 [161]	67.0 ± 11.6 (17.2) 54.1 - 76.4 [70.5]	25.0 ± 6.1 (24.3) 18.1 - 29.5 [27.5]	2/1/0	0
	Male		5	5/	51.8 ± 3.3 (6.3) 47 - 56 [52]	180.2 ± 3.7 (2.0) 175 - 183.5 [182]	92.0 ± 4.3 (4.7) 88.2 - 99.1 [91.8]	28.3 ± 1.2 (4.3) 26.4 - 29.4 [29]	1/0/4	0
3 Moderate	Female	Post	3	3/	61 ± 12.1 (19.9) 48 - 72 [63]	161.7 ± 4.3 (2.7) 157 - 165.5 [162.6]	78.8 ± 7.3 (9.3) 71.8 - 86.4 [78.2]	30.1 ± 2.2 (7.4) 28.6 - 32.7 [29.1]	1/0/2	0
	Male		5	5/	55.0 ± 5.9 10.7 50 - 65 53	172.1 ± 10.3 6.0 162.6 - 188.5 169	87.4 ± 8.9 10.2 75.5 - 98.2 84.5	29.6 ± 2.5 8.4 26.5 - 32 29.6	3/1/1	0
4 Severe	Female	1 Pre 1 Post	2	2/	46 ± 0.0 0.0 46 - 46 [46]	167.8 ± 0.3 0.2 167.6 - 168 [167.8]	70.9 ± 14.1 19.9 60.9 - 80.9 [70.9]	25.2 ± 5.1 20.2 21.6 - 28.8 [25.2]	1/0/1	0
	Male		4	4	54.8 ± 7.9 (14.4) 48 - 66 [52.5]	175.8 ± 5.7 (3.2) 169 - 182.9 [175.6]	89.5 ± 8.1 (9.0) 79.1 - 98.2 [90.4]	29.0 ± 2.4 (8.30 26.4 - 31.7 [28.95]	0/0/4	0

Table 99 Asenapine Pharmacokinetic Summary Metrics with Varying Degrees of Hepatic Impairment Values – Study A7501018

	Summary Statistics				Geometric Means				Geometric Mean Ratios (90% CI)		
	Normal	Mild	Moderate	Severe	Normal	Mild	Moderate	Severe	Mild : NI	Mod : NI	Severe : NI
N	8	8	8	6							
Tmax (hr)	0.94 ± 0.66 (70.9) 0.50 - 2.0 [0.625]	1.09 ± 0.38 (34.4) 0.50 - 1.5 [1.00]	2.09 ± 1.13 (54.1) 0.75 - 4.0 [1.75]	2.21 ± 1.90 (86.0) 0.75 - 6.0 [1.50]							
Cmax (ng/mL)	6.85 ± 2.51 (36.6) 4.06 - 11.6 [5.92]	6.12 ± 1.78 (29.2) 3.44 - 8.59 [6.30]	4.06 ± 1.79 (44.1) 2.17 - 6.60 [4.24]	7.50 ± 4.58 (61.1) 3.60 - 16.6 [6.21]	6.49	5.87	3.71	6.67	0.904 0.641 – 1.28	0.571 0.405 – 0.806	1.03 0.708 – 1.49
AUC(0-tlast) (ng/mL x hr^{-1})	50.9 ± 15.3 (30.0) 31.7 - 71.6 [46.7]	58.2 ± 27.2 (46.7) 25.3 - 105 [53.3]	63.1 ± 34.2 (54.2) 20.4 - 115 [49.2]	247 ± 55.3 (22.4) 156 - 304 [260]	49.0	52.8	54.8	241	1.08 0.742 – 1.56	1.12 0.771 – 1.63	4.92 3.29 – 7.37
AUC∞ (ng/mL x hr^{-1})	55.0 ± 15.9 (28.9) 33.6 - 75.9 [51.3]	68.4 ± 39.6 (57.9) 26.9 - 130 [56.4]	68.9 ± 37.3 [a] (54.1) 22.0 - 121 [55.7]	304 ± 85.0 (27.9) 164 - 412 [319]	52.9	59.2	59.5	293	1.12 0.744 – 1.68	1.12 0.736 – 1.71	5.53 3.56 – 8.59
%extrap (%)	7.42 ± 3.45 (46.5) 3.96 - 13.6 [6.15]	10.4 ± 10.2 (98.6) 2.12 - 31.8 [6.98]	4.76 ± 1.53 [a] (32.1) 3.15 - 7.46 [4.78]	17.0 ± 11.1 (65.2) 4.48 - 32.3 [16.8]							
CL/F (mL/min)	1640 ± 490 (29.9) 1100 - 2480 [1630]	1610 ± 856 (53.1) 642 - 3100 [1510]	1660 ± 1090 [a] (65.7) 690 - 3780 [1500]	299 ± 110 (37.0) 202 - 509 [261]	1570	1410	1400	285	0.894 0.594 – 1.34	0.89 0.583 – 1.36	0.181 0.116 – 0.281
Vd/F (L)	5470 ± 3010 (55.0) 2670 - 12000 [4570]	4900 ± 2220 (45.3) 2920 - 9750 [4350]	6440 ± 2930 [a] (45.5) 3600 - 12000 [5740]	2240 ± 442 (19.8) 1670 - 2760 [2160]							
t½ (hr)	39.1 ± 17.8 (45.5) 16.7 - 76.4 [37.1]	39.9 ± 16.6 (41.6) 22.8 - 72.4 [33.9]	49.8 ± 9.53 [a] (19.1) 36.6 - 60.4 [48.1]	94.3 ± 31.7 (33.6) 51.6 - 124 [105]							

a n = 7

Table 100 Desmethyl-Asenapine Pharmacokinetic Metrics with Varying Degrees of Hepatic Impairment Values - Study A7501018

	Summary Statistics				Geometric Means				Geometric Mean Ratios (90% CI)		
	Nl	**Mild**	**Moderate**	**Severe**	**Nl**	**Mild**	**Moderate**	Severe	**Mild : Nl**	**Mod : Nl**	**Severe : Nl**
N	8a	8a	8	6b							
Tmax (hr)	7.25 ± 2.38 (32.8) 4 - 12 [7]	13 ± 11.2 (85.9) 6 - 36 [7]	13.3 ± 11.1 (83.3) 6 - 36.2 [8]	40 ± 29.1 (72.6) 12 - 96 [36]							
Cmax (ng/mL)	0.537 ± 0.163 (30.4) 0.299 - 0.782 [0.569]	0.399 ± 0.186 (46.6) 0.153 - 0.696 [0.343]	0.365 ± 0.131 (35.9) 0.167 - 0.564 [0.352]	0.179 ± 0.066 (37.2) 0.101 - 0.267 [0.176]	0.513	0.360	0.342	0.168	0.702 0.495 - 0.995	0.667 0.471 - 0.946	0.327 0.225 - 0.477
AUC(0-tlast) (ng/mL x hr^{-1})	12 ± 5.5 (45.6) 4.03 - 22.3 [12.1]	13.5 ± 5.21 (38.6) 6.35 - 24.4 [13.9]	15.5 ± 11.3 (72.8) 4.95 - 38.8 [12]	20.3 ± 8.73 (42.9) 5.89 - 31.8 [21.4]	10.9	12.7	12.5	18.1	1.17 0.727 – 1.87	1.15 0.718 – 1.85	1.67 1.00 – 2.78
AUC∞ (ng/mL x hr^{-1})	15.3 ± 6.22 [a] (40.7) 4.83 - 24.6 [15.4]	16.8 ± 7.36 [a] (43.8) 8.07 - 32 [15.7]	18.4 ± 12.2 (66.5) 6.27 - 43.6 [15.2]	47.8 ± 20.5 [b] (43) 29.5 - 70 [43.9]	13.9	15.6	15.4	44.9	1.13 0.693 – 1.83	1.11 0.695 – 1.78	3.24 1.73 – 6.06
%extrap (%)	19.8 ± 7.03 [a] (35.5) 9.63 - 30.2 [17.7]	17.3 ± 6.65 [a] (38.5) 6.08 - 25 [16]	18.5 ± 7.64 (41.2) 10.7 - 28.8 [17.4]	53.5 ± 16.5 [b] (30.8) 34.6 - 64.7 [61.2]							
t½ (hr)	21.1 ± 7.82 [a] (37.1) 7.67 - 31.4 [20.4]	24.8 ± 12.2 [a] (49.1) 11.3 - 44.6 [24.3]	31.5 ± 17.7 (56.3) 14.4 - 63.9 [23.5]	252 ± 147 [b] (58.2) 90.4 - 377 [289]							

a n = 7
b n = 3

Table 101 Asenapine Glucuronide Pharmacokinetic Metrics with Varying Degrees of Hepatic Impairment Values – Study A7501018

	Summary Statistics				Geometric Means				Geometric Mean Ratios (90% CI)		
	Normal	Mild	Moderate	Severe	Normal	Mild	Moderate	Severe	Mild : NI	Mod : NI	Severe : NI
	8	8	8	6							
Tmax (hr)	4.75 ± 1.39 (29.2) 3 - 6 [5]	4.38 ± 1.51 (34.4) 2 - 6 [4]	4.63 ± 1.6 (34.6) 2 - 6 [5]	7.15 ± 3.01 (42.1) 3 - 12 [7]							
Cmax (ng/mL)	8.19 ± 3.84 (46.8) 1.11 - 13.5 [8.32]	13.8 ± 17.8 (130) 2.26 - 56.7 [9.23]	8.04 ± 4.88 (60.7) 2.71 - 17.2 [5.64]	3.84 ± 1.54 (40.1) 2.47 - 6.42 [3.36]	6.84	8.28	6.87	3.61	1.21 0.635 – 23.1	1.01 0.527 – 1.92	0.528 0.263 – 1.06
AUC(0-tlast) (ng/mL x hr^{-1})	103 ± 46 (44.7) 8.06 - 153 [113]	210 ± 307 (146) 18.5 - 951 [108]	109 ± 83.4 (76.5) 20.8 - 227 [87]	119 ± 63.2 (53.1) 47.7 - 225 [111]	81.5	111	79.6	105	1.36 0.612 – 3.03	0.97.6 0.438 – 2.17	1.29 0.544 - .307
AUC∞ (ng/mL x hr^{-1})	105 ± 51.1 [a] (48.5) 9.3 - 159 [114]	232 ± 341 (147) 24.3 - 1060 [114]	119 ± 91 (76.8) 22.9 - 253 [95.5]	198 ± 131 [b] (66.2) 50.6 - 348 [196]	82.0	127	86.6	157	1.55 0.650 – 3.68	1.06 0.444 – 2.51	1.92 0.672 – 5.49
%extrap (%)	6.13 ± 3.84 [a] (62.7) 2.27 - 13.4 [5.11]	12 ± 8.69 (72.2) 4.43 - 26 [8.18]	8.08 ± 3.66 (45.3) 2.59 - 14.2 [8.18]	29 ± 16.3 [b] (56.1) 5.75 - 43.4 [33.4]							
t½ (hr)	7.44 ± 3.37 [a] (45.3) 3.07 - 13.1 [7.51]	20.8 ± 14.4 (69.1) 5.05 - 42 [19]	15 ± 18.8 (125) 2.23 - 58.6 [6.46]	90.7 ± 84.4 [b] (93) 5.91 - 207 [74.8]							

a n = 7
b n = 4

Table 102 Effect of Hepatic Impairment on the Pharmacokinetics of Unbound Asenapine – Study A7501018

	Normal	Mild	Moderate	Severe
N	8	8	8/7	6
Cmaxu (ng/mL)	0.317 ± 0.105 (33.1) 0.217-0.487 [0.278]	0.364 ± 0.148 (40.6) 0.206 - 0.659 [0.336]	0.229 ± 0.0948 (41.4) 0.119 - 0.347 [0.238]	0.524 ± 0.419 (80.1) 0.248 - 1.36 [0.353]
AUCu(0 - tlqc) (ng/mL x hr^{-1})	2.38 ± 0.686 (28.8) 1.55-3.17 [2.38]	3.65 ± 2.45 (67.1) 1.52 - 8.38 [2.78]	3.64 ± 2.16 (59.5) 1.20 - 7.69 [3.00]	16.5 ± 5.06 (30.7) 8.44 - 22.5 [16.4]
AUCu(0-∞) (ng/mL x hr^{-1})	2.57 ± 0.717 (27.9) 1.65-3.42 [2.61]	4.38 ± 3.44 (78.6) 1.61 - 10.4 [2.93]	3.93 ± 2.41 (61.2) 1.30 - 8.09 [3.34]	20.6 ± 7.71 (37.5) 8.83 - 28.4 [22.1]
CL/Fu (mL/min)	35000 ± 10400 (29.9) 24300-50600 [32200]	29400 ± 16900 (57.3) 8020 - 51600 [28600]	29900 ± 18900 (63.2) 10300 - 64100 [25000]	4790 ± 2480 (51.9) 2930 - 9430 [3860]
fu (%)	0.047 ± 0.005 0.040 - 0.057	0.059 ± 0.012 0.046 - 0.080	0.057 ± 0.007 0.046 - 0.067	0.066 ± 0.013 0.053 - 0.082

Figure 76 Linear and Semi-log Plots of Asenapine Concentration vs. Time Profiles for a Single 5 mg Sublingual Dose by Degree of Hepatic Impairment – Study A7501018

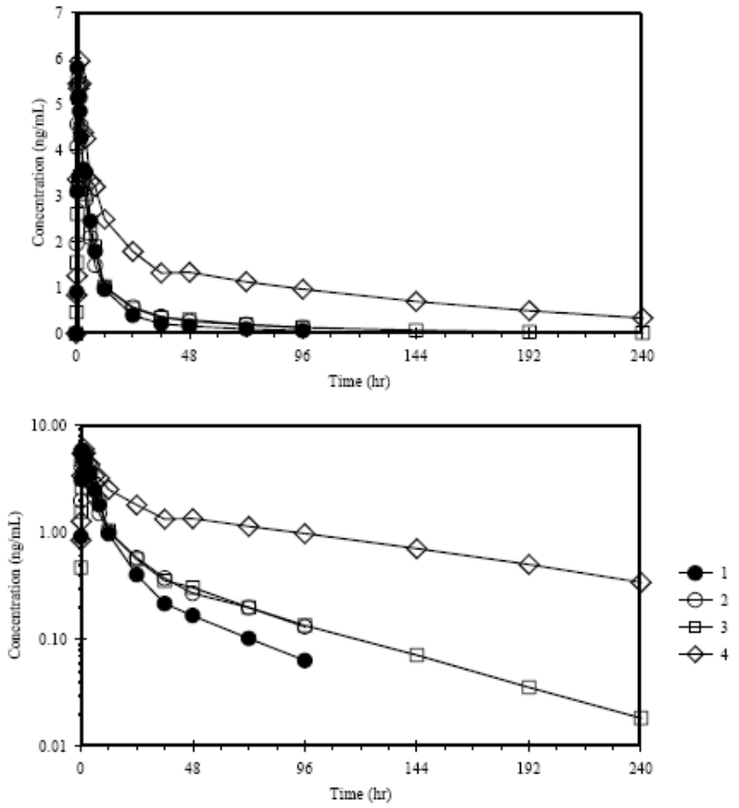


Figure 77 Linear and Semi-log Plots of Asenapine Glucuronide Concentration vs. Time Profiles for a Single 5 mg Sublingual Dose by Degree of Hepatic Impairment – Study A7501018

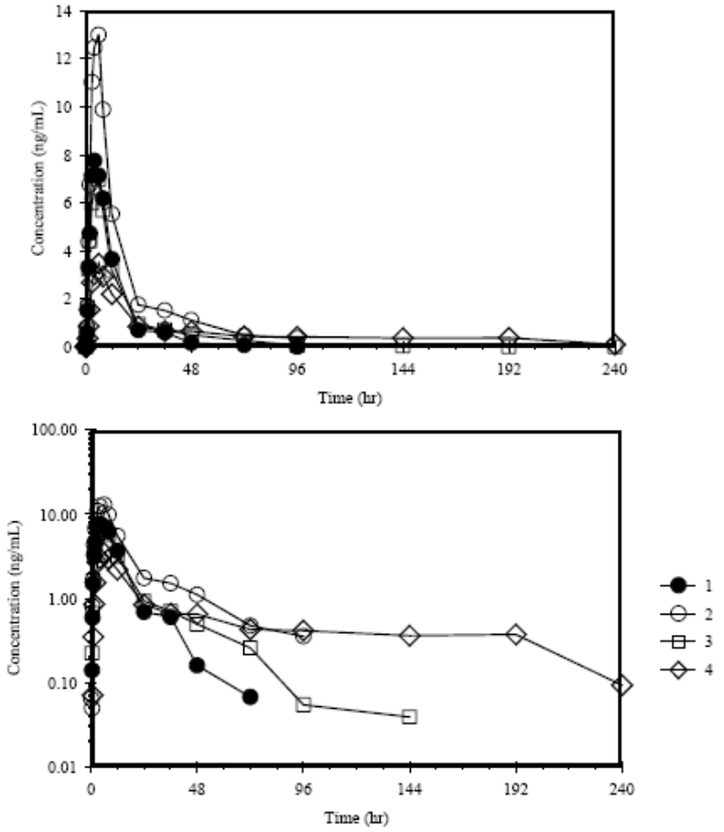


Figure 78 Linear and Semi-log Plots of Desmethyl-Asenapine Concentration vs. Time Profiles for a Single 5 mg Sublingual Dose by Degree of Hepatic Impairment – Study A7501018

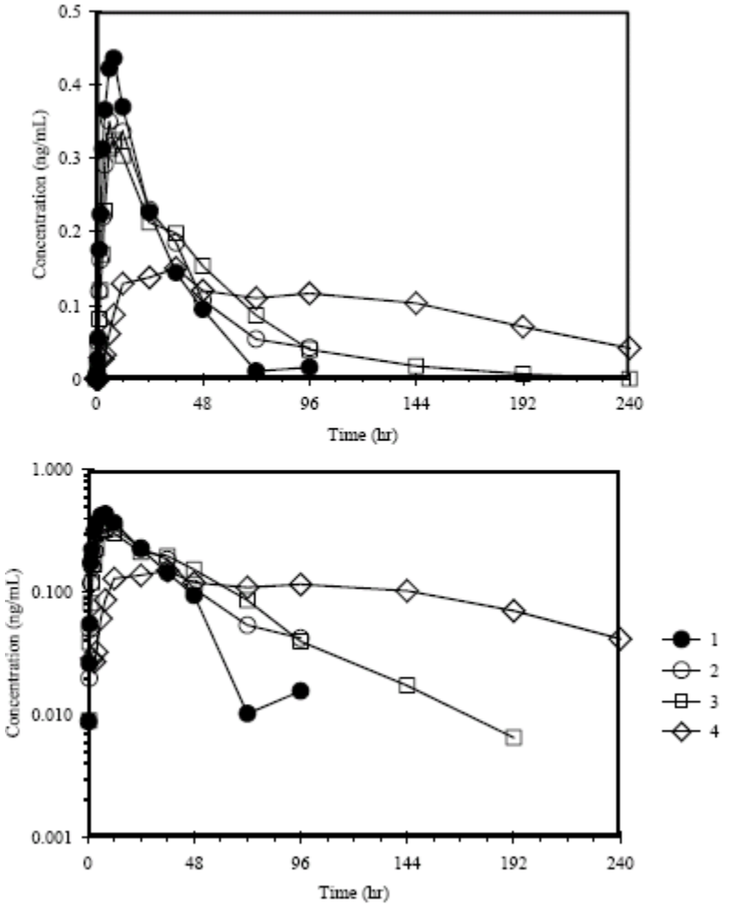


Figure 79 Individual Asenapine Cmax and AUC∞ following Single 5-mg Sublingual Doses in Subjects with Various Degrees of Liver Impairment - Study A7501018

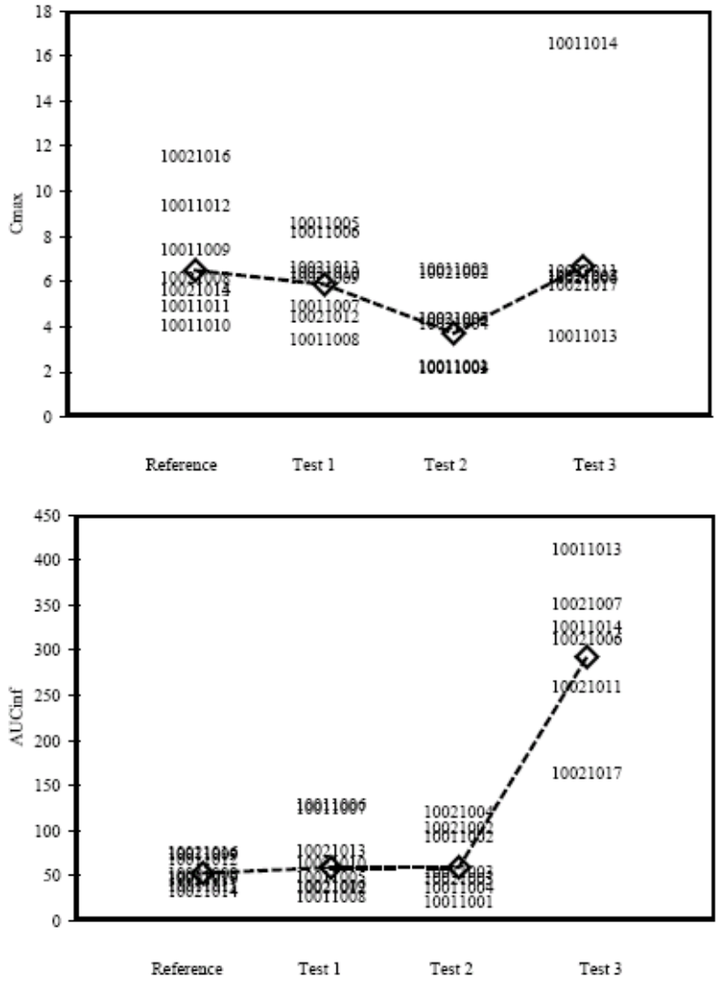


Figure 80 Individual Asenapine Glucuronide Cmax and AUC∞ following Single 5-mg Sublingual Doses in Subjects with Various Degrees of Liver Impairment - Study A7501018

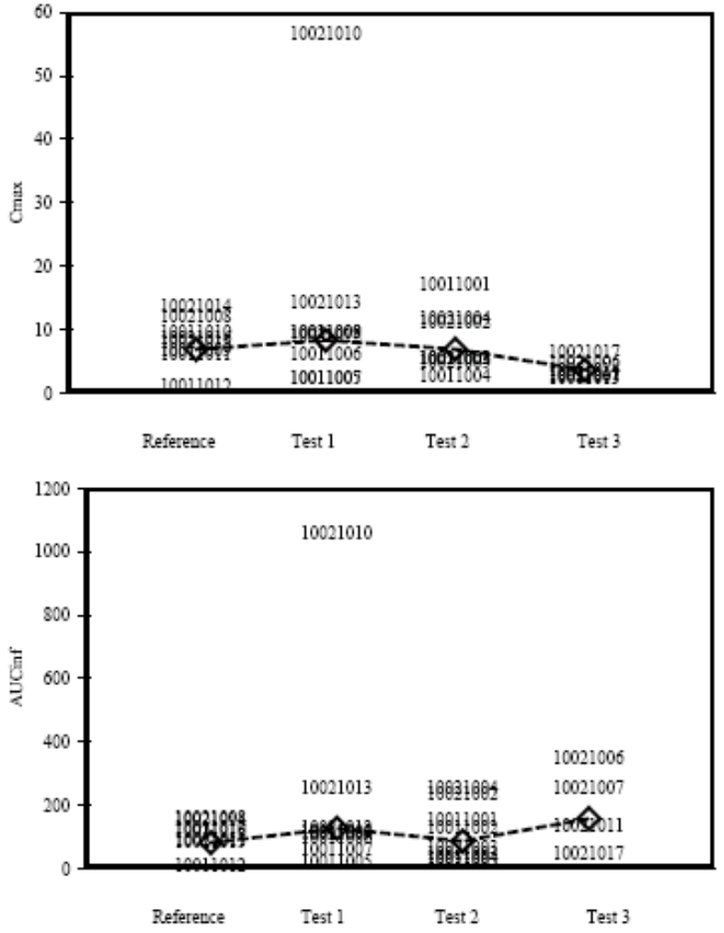


Figure 81 Individual Desmethyl-Asenapine Cmax and AUC∞ following Single 5-mg Sublingual Doses in Subjects with Various Degrees of Liver Impairment - Study A7501018

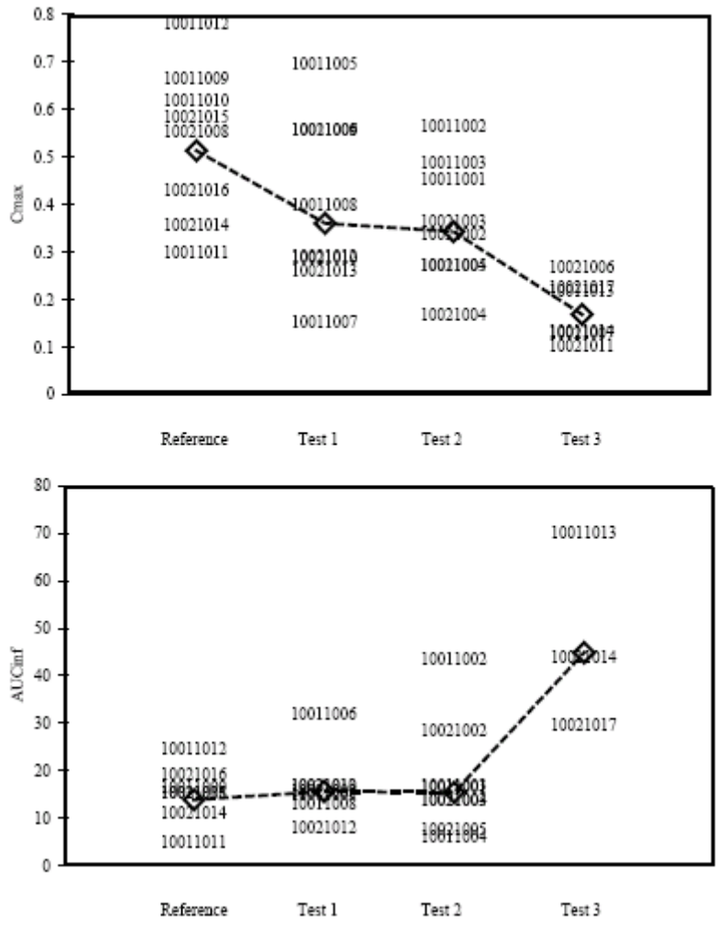
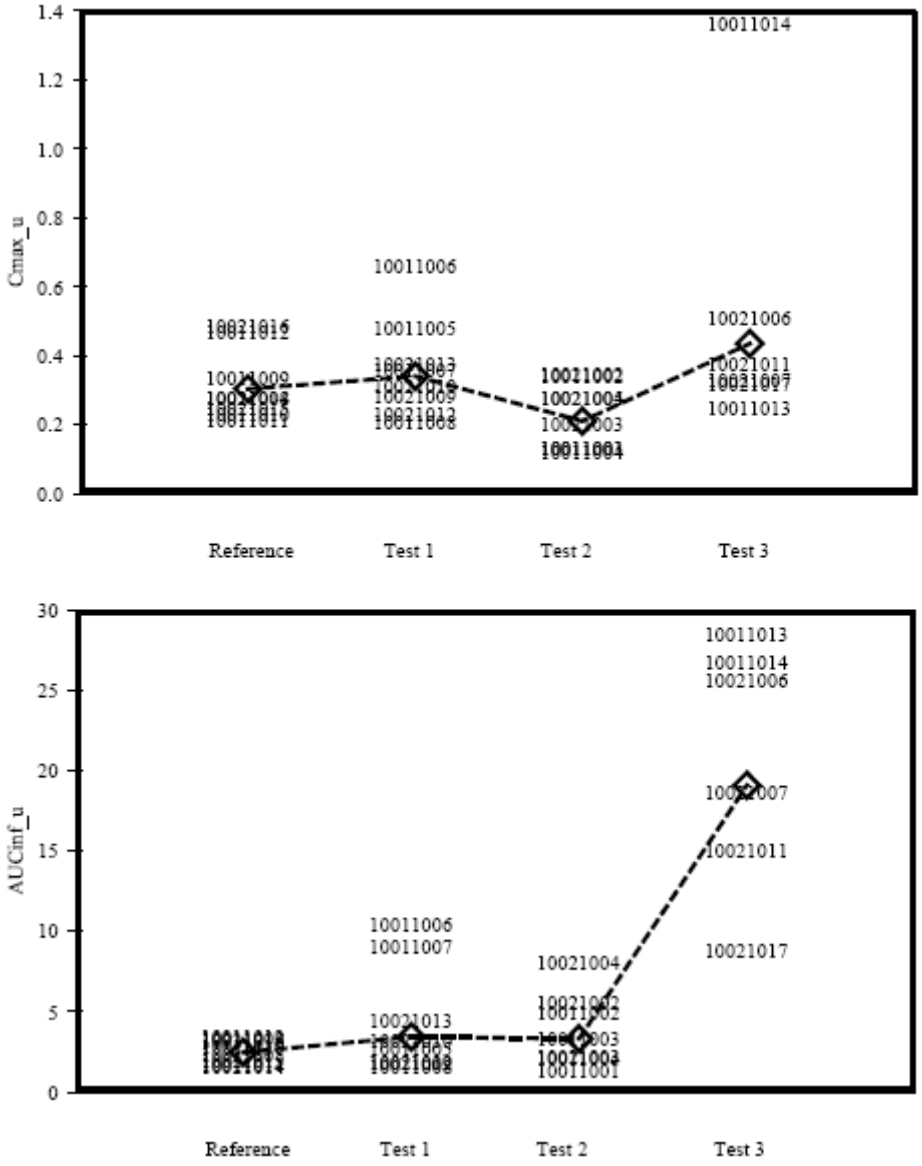


Figure 82 Individual Unbound Asenapine Cmax,u and AUCu∞ following Single 5-mg Sublingual Doses in Subjects with Various Degrees of Liver Impairment - Study A7501018



5.5.6.6 Renal Impairment

Two studies were conducted on the effects of renal impairment on the pharmacokinetics of asenapine and desmethyl-asenapine. The only finding was that desmethyl-asenapine exposures were lower in moderate and severe renal insufficiency, possibly indicating a decreased formation of desmethyl-asenapine.

Other metabolites such as the derivatives of the 11-hydroxy-asenapine and N-glucuronides were not assessed so the alterations in other major active metabolites cannot be assessed.

5.5.6.6.1 Renal Impairment – Study 25521

Study 25521 was a single dose, open label study to assess the effect of varying degrees of renal impairment on the pharmacokinetics of asenapine and desmethyl-asenapine following a 0.3 mg sublingual dose in 16 male and 16 female Caucasian subjects with varying levels of renal function aged 25 - 65 years old.

Renal function was assessed at screening by a 24 hour creatinine clearance, and subjects were grouped per degree of impaiment as follows:

- Normal renal function — Clcr ≥ 82.0 mL/min/1.73 m^2 — n = 8
- Mild renal insufficiency — Clcr ≥ 52.0 and < 78.0 mL/min/1.73 m^2 — n = 8
- Moderate renal insufficiency — Clcr ≥ 32.0 and < 48.0 mL/min/1.73 m^2 — n = 8
- Severe renal insufficiency — Clcr < 28.0 mL/min/1.73 m^2 — n = 8

Mean concentration vs. Time profiles are shown in Figure 83, AUCt vs. Clcr in Figure 84, and weight normalized Clapp vs. Clcr in Figure 85.

Due to the low dosage used desmethyl-asenapine was largely unmeasurable. This as well as differences in subject weight by group may also account for the truncated concentration vs. time profiles in Figure 83. The low body weight of subjects in the severe renal impairment group might account for higher exposures in this group, however low exposures in the mild group argues against this, (see Table 104, Figure 83, and Table 105). Another possibility is that severe renal insufficiency inhibits metabolism of asenapine. This is known to occur with CYP2D6.

AUCt and Cmax were largely independent of renal function although there were two individuals with higher Cmax's in the moderate and severe renal insufficiency groups although the reason for this is unclear, (see Figure 86 and Table 106).

Free fraction was unchanged with renal impairment, (see Table 107).

Figure 83 Asenapine Mean Concentration vs. Time Profiles for Various Degrees of Renal Function - Study 25521

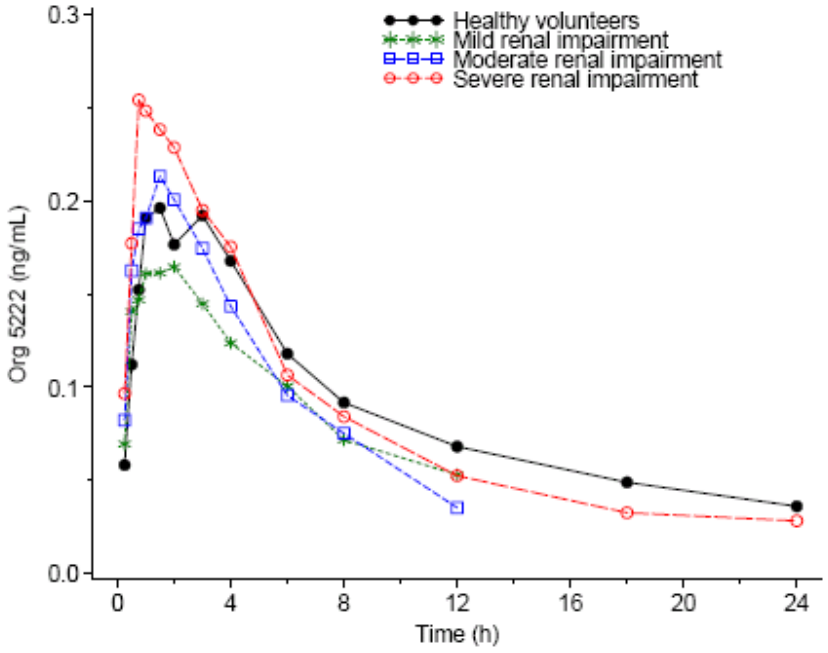


Figure 84 Asenapine AUCt vs. Creatinine Clearance - Study 25521

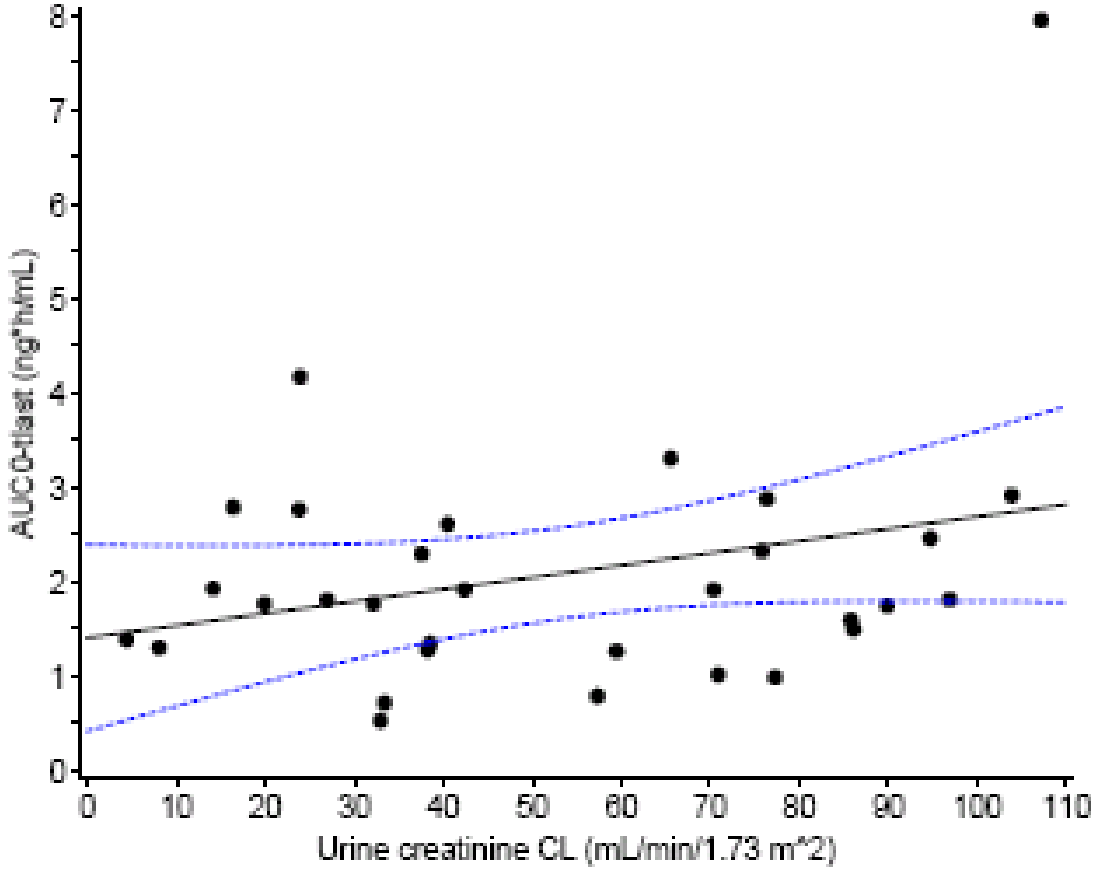


Figure 85 Asenapine Weight Normalized Apparent Clearance vs. Creatinine Clearance – Renal Impairment Study 25521

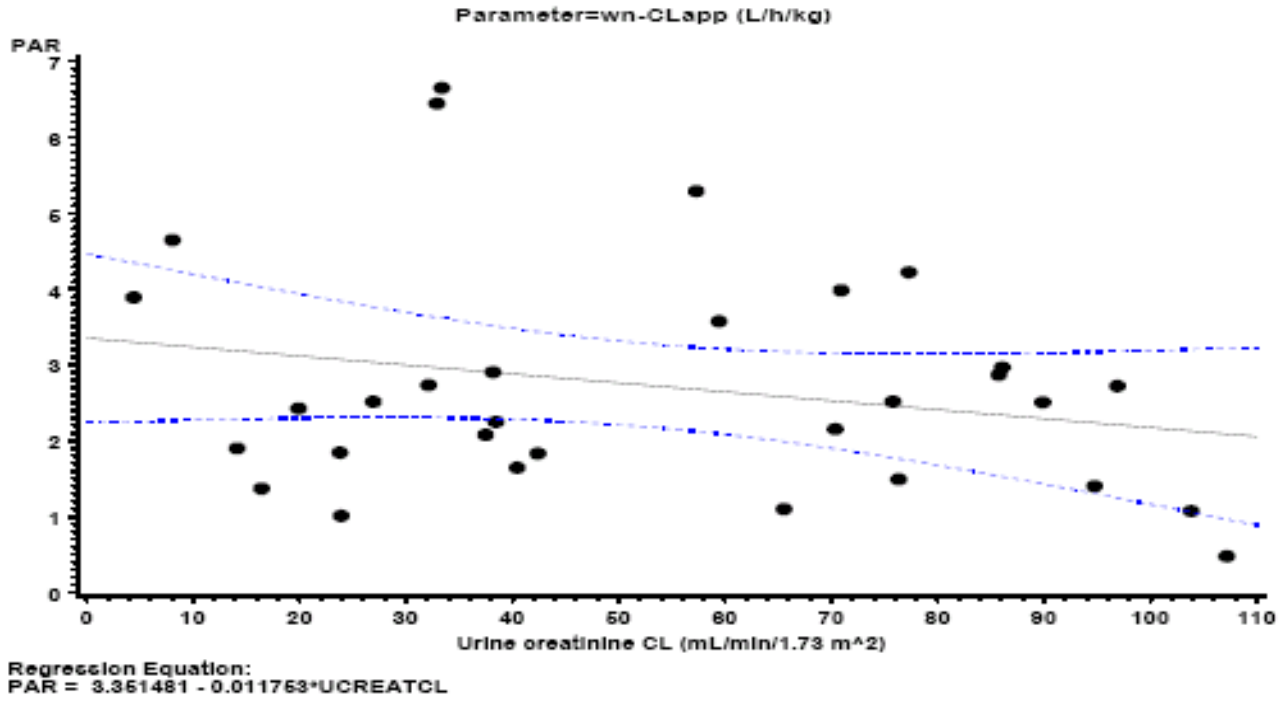


Table 103 Renal Impairment Study Individual Subject Demographic Characteristics- Study 25521

Group	Subj	Sex	Race	Age	Ht	Wt	BMI	BSA	Smoker?
Normal Renal Function CIcr ≥ 82.0 mL/min/1.73 m^2	1	Female	Caucasian	49	155	58.0	24.1	1.60	YES
	2	Female	Caucasian	50	158	68.1	27.3	1.78	NO
	3	Male	Caucasian	52	167	66.0	23.7	1.75	YES
	4	Female	Caucasian	43	156	61.2	25.1	1.65	NO
	5	Female	Caucasian	43	161	69.0	26.6	1.78	YES
	6	Male	Caucasian	48	185	96.0	28.0	2.23	YES
	7	Male	Caucasian	49	185	78.8	23.0	2.03	NO
	8	Male	Caucasian	50	176	87.1	28.1	2.06	NO
Mild Renal Impairment CLcr ≥ 52.0 and <78.0 mL/min/1.73 m^2	11	Male	Caucasian	26	183	70.0	20.9	1.93	NO
	12	Male	Caucasian	45	171	82.6	28.2	1.99	NO
	13	Male	Caucasian	43	172	75.0	25.4	1.88	NO
	14	Female	Caucasian	54	165	73.0	26.8	1.86	NO
	15	Female	Caucasian	49	163	51.4	19.3	1.52	YES
	16	Male	Caucasian	65	170	73.0	25.3	1.88	NO
	17	Female	Caucasian	31	165	67.0	24.6	1.75	YES
	18	Female	Caucasian	42	167	73.0	26.2	1.86	YES
Moderate Renal Impairment CLcr ≥ 32.0 and <48.0 mL/min/1.73 m^2	21	Male	Caucasian	38	183	100.0	29.9	2.28	NO
	22	Male	Caucasian	54	177	86.0	27.5	2.06	NO
	23	Female	Caucasian	63	153	70.0	29.9	1.76	NO
	24	Female	Caucasian	62	145	62.5	29.7	1.64	NO
	25	Male	Caucasian	27	177	81.5	26.0	2.01	NO
	26	Male	Caucasian	33	182	90.0	27.2	2.13	NO
	27	Female	Caucasian	57	166	63.0	22.9	1.70	NO
	28	Female	Caucasian	28	164	63.8	23.7	1.70	NO
Severe Renal Impairment CLcr < 28.0 mL/min/1.73 m^2	31	Female	Caucasian	61	155	50.0	20.8	1.48	NO
	32	Female	Caucasian	56	164	71.2	26.5	1.81	YES
	33	Female	Caucasian	41	160	58.9	23.0	1.62	NO
	34	Female	Caucasian	54	151	56.0	24.6	1.58	YES
	35	Male	Caucasian	55	169	78.6	27.5	1.94	NO
	36	Male	Caucasian	47	178	82.2	25.9	2.04	NO
	37	Male	Caucasian	31	172	66.5	22.5	1.78	YES
	38	Male	Caucasian	54	169	70.5	24.7	1.83	YES

Table 104 Demographic Summary Statistics by Degree of Renal Impairment - Study 25521

Degree of Renal Impairment	Gender	n	Age (yr)	Height (cm)	Weight (kg)	BMI (kg/m^2)	BSA (m^2)
Normal Renal Function CLcr ≥ 82.0 mL/min/1.73 m^2	Female	4	46.3 ±3.77 43 - 50 [46.0]	158 ±2.65 155 - 161 [157]	64.1 ±5.34 58.0 - 69.0 [64.7]	25.8 ±1.42 24.1 - 27.3 [25.9]	1.70 ±0.0918 1.60 - 1.78 [1.72]
	Male	4	49.8 ±1.71 48 - 52 [49.5]	178 ±8.62 167 - 185 [181]	82.0 ±12.8 66.0 - 96.0 [83.0]	25.7 ±2.75 23.0 - 28.1 [25.9]	2.02 ±0.199 1.75 - 2.23 [2.05]
	Total	8	48.0 ±3.30 43 - 52 [49.0]	168 ±12.6 155 - 185 [164]	73.0 ±13.2 58.0 - 96.0 [68.6]	25.8 ±2.03 23.0 - 28.1 [25.9]	1.86 ±0.221 1.60 - 2.23 [1.78]
Mild Renal Impairment CLcr ≥ 52.0 and <78.0 mL/min/1.73 m^2	Female	4	44.0 ± 9.97 31 - 54 [45.5]	165 ± 1.63 163 - 167 [165]	66.1 ± 10.2 51.4 - 73.0 [70.0]	24.2 ± 3.39 19.3 - 25.4 [26.8]	1.75 ± 0.160 1.52 - 1.81 [1.86]
	Male	4	44.8 ± 16.0 26 - 65 [44.0]	174 ± 6.06 170 - 183 [172]	75.2 ± 5.37 70.0 - 82.6 [74.0]	24.9 ± 3.03 20.9 - 28.2 [25.3]	1.92 ± 0.0523 1.88 - 1.99 [1.91]
	Total	8	44.4 ± 12.3 26 - 65 [44.0]	170 ± 6.32 163 - 183 [169]	70.6 ± 8.96 51.4 - 82.6 [73.0]	24.6 ± 3.00 19.3 - 28.2 [25.3]	1.83 ± 0.144 1.52 - 1.87 [1.99]
Moderate Renal Impairment CLcr ≥ 32.0 and <48.0 mL/min/1.73 m^2	Female	4	52.5 ± 16.5 28 - 63 [59.5]	157 ± 9.83 145 - 166 [159]	64.8 ± 3.49 62.5 - 70.0 [63.4]	26.6 ± 3.78 22.9 - 29.9 [26.7]	1.70 ± 0.0490 1.64 - 1.76 [1.70]
	Male	4	38.0 ± 11.6 27 - 54 [35.5]	180 ± 3.20 177 - 183 [180]	89.4 ± 7.89 81.5 - 100 [88.0]	27.6 ± 1.62 26.0 - 29.9 [27.3]	2.12 ± 0.117 2.01 - 2.28 [2.10]
	Total	8	45.3 ± 15.3 27 - 63 [46.0]	168 ± 13.9 145 - 183 [172]	77.1 ± 14.3 62.5 - 100 [75.8]	27.1 ± 2.75 22.9 - 29.9 [27.3]	1.91 ± 0.239 1.64 - 2.28 [1.89]
Severe Renal Impairment CLcr < 28.0 mL/min/1.73 m^2	Female	4	53.0 ± 8.52 41 - 61 [55.0]	158 ± 5.69 151 - 164 [158]	59.0 ± 8.92 50.0 - 71.2 [57.5]	23.7 ± 2.40 20.8 - 26.5 [23.8]	1.62 ± 0.138 1.48 - 1.81 [1.60]
	Male	4	46.8 ± 11.1 31 - 55 [50.5]	172 ± 4.24 169 - 178 [171]	74.5 ± 7.21 66.5 - 82.2 [74.6]	25.2 ± 2.13 22.5 - 27.5 [25.3]	1.90 ± 0.116 1.78 - 2.04 [1.89]
	Total	8	49.9 ± 9.75 31 - 61 [54.0]	165 ± 9.04 151 - 178 [167]	66.7 ± 11.2 50.0 - 82.2 [68.5]	24.4 ± 2.24 20.8 - 27.5 [24.6]	1.76 ± 0.189 1.48 - 2.04 [1.80]

Table 105 Asenapine Pharmacokinetic Metric Summary Statistics in Various Degrees of Renal Insufficiency – Study 25521

Degree of Renal Impairment	Summary Statistics				Geometric Means				Geometric Mean Ratio (90% CI)		
	Normal	Mild	Moderate	Severe	NI	Mild	Mod	Sev	Mild : NI	Mod : NI	Sev : NI
Clcr (ml/min / 1.73 m^2)	**≥ 82.0**	**≥ 52.0 + <78.0**	**≥ 32.0 + <48.0**	**< 28.0**							
n	8/7 [a]	8	8	8							
Tmax (h)	2.25 ± 1.13 (50.4) 1.00 - 4 [2.25]	1.56 ± 0.50 (31.7) 0.5 - 2 [1.50]	1.53 ± 0.81 (52.7) 0.50 - 3.00 [1.50]	1.56 ± 1.08 (69.0) 0.75 - 4.00 [1.23]	1.99	1.46	1.34	1.33			
Cmax (ng/mL)	0.224 ± 0.069 (30.80 0.161 - 0.363 [0.193]	0.189 ± 0.043 (22.9) 0.112 - 0.233 [0.196]	0.259 ± 0.120 (46.2) 0.129 - 0.497 [0.245]	0.309 ± 0.167 (54.2) 0.123 - 0.675 [0.292]	0.216	0.184	0.237	0.276	0.85 0.61 - 1.18	1.09 0.79 - 1.52	1.28 0.92 - 1.77
AUC0−12h (ng*h/mL)	1.51 ± 0.45 (29.6) 1.14 - 2.48 [1.40]	1.20 ± 0.35 (29.3) 0.716 - 1.68 [1.24]	1.31 ± 0.51 (38.7) 0.639 - 2.05 [1.30]	1.54 ± 0.33 (21.2) 0.959 - 1.98 [1.52]	1.47	1.15	1.22	1.51	0.79 0.60 - 1.03	0.83 0.63 - 1.09	1.03 0.78 - 1.35
CLapp (L/h)	142 ± 58 (40.9) 37.7 - 202 [167]	214 ± 109 (51.1) 90.8 - 386 [198]	255 ± 163 (64.1) 115 - 580 [198]	154 ± 55.5 (36.0) 72.0 - 232 [162]	127	189	219	145			
wn−CLapp (L/h) / kg	2.00 ± 1 (49.9) 0.479 - 2.97 [2.51]	3.04 ± 1.46 (47.9) 1.10 - 5.29 [3.05]	3.32 ± 2.04 (61.4) 1.65 - 6.65 [2.49]	2.45 ± 1.24 (50.7) 1.01 - 4.65 [2.16]	1.71	2.7	2.88	2.19			
CrCLurine (mL/min/1.73 m^2)	96.6 ± 9.16 (9.48) 85.8 - 109 [95.8]	69.1 ± 7.69 (11.1) 57.3 - 77.3 [68.7]	36.9 ± 3.75 (10.2) 32.1 - 42.4 [36.8]	17.2 ± 8.01 (46.5) 4.4 - 27 [15]	96.3	70.7	37.9	18.2			
dn−Cmax (ng/mL)/mg	0.75 ± 0.23 (30.8) 0.54 - 1.21 [0.642]	0.63 ± 0.14 (22.9) 0.37 - 0.78 [0.612]	0.86 ± 0.4 (46.2) 0.43 - 1.66 [0.789]	1.03 ± 0.558 (54.2) 0.41 - 2.25 [0.919]	0.721	0.653	0.817	0.973			
dn−AUC0−12h (ng*h/mL)/mg	5.04 ± 1.49 (29.6) 3.82 - 8.27 [4.66]	4.01 ± 1.18 (29.3) 2.39 - 5.58 [3.85]	4.35 ± 1.69 (38.7) 2.13 - 6.83 [4.05]	5.13 ± 1.09 (21.2) 3.2 - 6.59 [5.02]	4.89	4.13	4.33	5.05			

a n = 8 for Cmax and Tmax

Figure 86 Asenapine AUCt and Cmax vs. Creatinine Clearance – Study 25521

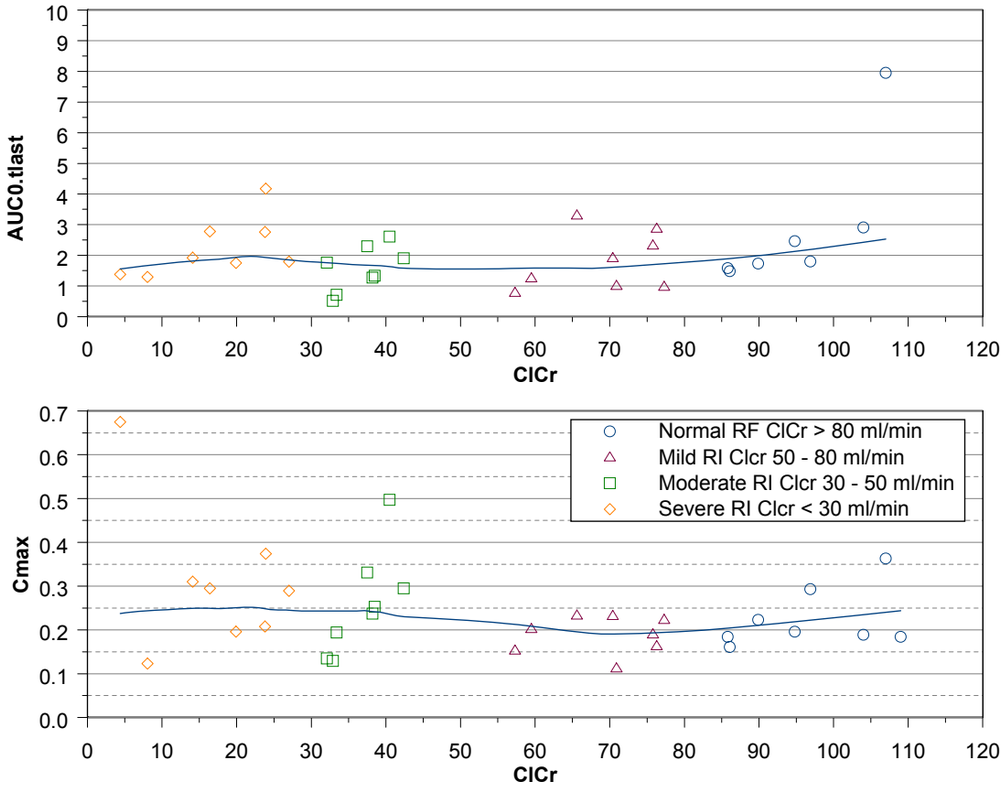


Table 106 Individual Asenapine Pharmacokinetic Metrics – Study 25521

Group	Subject	Cmax (ng/mL)	Tmax (h)	AUC_{0-12h} (ng*h/mL)	$AUC_{0-tlast}$ (ng*h/mL)	Clapp (L/h)	wn−Clapp (L/h)/kg	Tlast (hr)	Urine Creatinine CL (mL/min / 1.73 m^2)
Healthy volunteers	1	0.184	1.5					6.0	109
	2	0.161	4.0	1.14	1.48	202	2.97	23.0	86.1
	3	0.184	3.0	1.21	1.58	189	2.87	23.0	85.8
	4	0.293	1.5	1.44	1.80	167	2.72	24.0	96.9
	5	0.223	1.0	1.54	1.73	173	2.51	18.0	89.9
	6	0.189	1.0	1.38	2.91	103	1.07	48.0	104
	7	0.363	3.0	2.48	7.95	37.7	0.479	48.0	107
	8	0.196	3.0	1.40	2.46	122	1.40	48.0	94.8
Mild renal impairment	11	0.163	1.5	1.30	2.87	104	1.49	48.0	76.3
	12	0.233	1.5	1.68	3.30	90.8	1.10	48.0	65.6
	13	0.112	2.0	0.819	1.00	299	3.98	18.0	70.9
	14	0.232	2.0	1.23	1.91	157	2.15	48.0	70.4
	15	0.190	2.0	1.65	2.32	129	2.52	24.0	75.8
	16	0.223	0.5	0.974	0.974	308	4.22	12.0	77.3
	17	0.202	1.5	1.25	1.25	239	3.57	12.0	59.5
	18	0.153	1.5	0.716	0.777	386	5.29	30.0	57.3
Moderate renal impairment	21	0.253	1.5	1.33	1.33	225	2.25	12.0	38.5
	22	0.295	0.75	1.55	1.90	158	1.83	24.0	42.4
	23	0.497	1.0	2.05	2.61	115	1.65	30.0	40.5
	24	0.135	2.0	0.929	1.76	171	2.73	36.0	32.1
	25	0.237	3.0	1.27	1.27	237	2.91	12.0	38.2
	26	0.129	1.5	0.639	0.517	580	6.44	8.00	32.9
	27	0.331	2.0	1.88	2.29	131	2.08	24.0	37.5
	28	0.194	0.5	0.798	0.707	424	6.65	8.00	33.4
Severe renal impairment	31	0.123	4.0	0.959	1.29	232	4.65	24.0	8.05
	32	0.374	2.0	1.98	4.17	72.0	1.01	48.0	23.9
	33	0.208	1.5	1.47	2.76	109	1.85	48.0	23.8
	34	0.675	0.75	1.47	1.38	218	3.89	6.00	4.40
	35	0.295	0.75	1.95	2.78	108	1.37	36.0	16.4
	36	0.310	1.0	1.56	1.92	156	1.90	24.0	14.1
	37	0.289	1.0	1.56	1.79	167	2.51	18.0	27.0
	38	0.196	1.47	1.36	1.75	171	2.43	24.0	19.9

Table 107 Summary Statistics for Protein Binding of Asenapine by Degree of Renal Function – Study 25521

Group	Metrics	AsenapineFraction Bound (%)	
		Time Post Dose	
		1 hour	8 hours
Normal Renal Function CLcr ≥ 82.0 mL/min/1.73 m^2	N	8	8
	Summary Statistics	98.2 ± 0.196 (0.200) 97.9 - 98.5 [98.2]	98.1 ± 0.196 (0.200) 97.7 - 98.3 [98.2]
Mild Renal Impairment CLcr ≥ 52.0 and <78.0 mL/min/1.73 m^2	N	7	8
	Summary Statistics	98.1 ± 0.162 (0.165) 97.9 - 98.3 [98.1]	98.2 ± 0.191 (0.194) 98.0 - 98.5 [98.2]
Moderate Renal Impairment CLcr ≥ 32.0 and <48.0 mL/min/1.73 m^2	N	8	8
	Summary Statistics	98.2 ± 0.223 (0.227) 97.8 - 98.4 [98.3]	98.2 ± 0.177 (0.180) 97.9 - 98.4 [98.2]
Severe Renal Impairment CLcr < 28.0 mL/min/1.73 m^2	N	8	8
	Summary Statistics	98.2 ± 0.205 (0.209) 97.9 - 98.5 [98.1]	98.2 ± 0.245 (0.249) 97.7 - 98.5 [98.3]
Normal	Geometric mean	98.2	98.1
Mild	Geometric mean	98.1	98.2
Moderate	Geometric mean	98.2	98.2
Severe	Geometric mean	98.2	98.2

5.5.6.6.2 Renal Impairment - Study A7501017

Study A7501017 was a single dose, open label study to assess the effect of varying degrees of renal impairment on the pharmacokinetics of asenapine and desmethyl- asenapine following a 5 mg sublingual dose in 15 male and 18 female subjects aged 36 - 78 years old with varying levels of renal function*.

* Renal function was assessed at screening based on the mean value of 2 estimated CLcr values determined at least 72 hours apart with the Cockcroft-Gault equation:

Subjects were originally grouped per degree of impaiment as follows:

- Normal renal function — Clcr* > 80.0 mL/min — n = 8
- Mild renal insufficiency — Clcr* ≥ 51.0 ≤ 80.0 mL/min — n = 8
- Moderate renal insufficiency — Clcr* ≥ 30.0 and ≤ 50.0 mL/min — n = 8
- Severe renal insufficiency † — Clcr* < 30.0 mL/min — n = 8

† (Not on dialysis - The study center attempted to enroll at least 3 subjects with estimated CLcr < 20 mL/min, but not requiring dialysis.)

However 3 subjects had differing Clcr on the Day of testing and were assigned to a different analysis group as follows.

Subject	Enrollment Group	(CLcr range)	Day 1 CLcr Value	Analysis Group	(CLcr range)
10011034	2	(51 - 80 mL/min)	94.8 mL/min	1	(>80 mL/min)
10011036	2	(51 - 80 mL/min)	48.9 mL/min	3	(30 - 50 mL/min)
10011038	3	(30 - 50 mL/min)	69.9 mL/min	2	(51 - 80 mL/min)

Thus, data were analyzed for 9 subjects in Group 1 and 8 subjects each in Groups 2 through 4.

Blood samples for analysis of asenapine and des-methyl-asenapine were collected for 72 hours after the asenapine dose, with an additional sample collected at 96 hours for Groups 3 and 4. Samples for plasma protein binding were collected at 4 hours postdose and protein binding was determined by equilibrium dialysis.

Results are shown in Figure 87 to Figure 90 and Table 108 to Table 113. Mean plasma concentration vs. time profiles for both asenapine and desmethyl-asenapine in Figure 87 and Figure 88 appear higher in normals and subjects with mild renal impairment, however this is not borne out by plots of exposure and clearance vs. creatinine clearance, (see Figure 89 and Figure 90), or pharmacokinetic metrics or their geometric mean ratios for asenapine, (see Table 109 and Table 110). The reason for this apparent discrepancy is that although Cmaxs are higher in healthy subjects and subjects with mild renal insufficiency with time terminal exposures are higher in the subjects with moderate and severe insufficiency, (see Figure 87 and Figure 88).However, mean exposures to desmethyl-asenapine goes down in severe renal impairment possibly suggesting a decreased formation, (see Table 112).

Figure 91 to Figure 94 show that AUCfree is more variable than total AUC and that there is a complex relationship but upon close examination it is as expected, e.g. for desmethyl-asenapine mean unbound AUC is independent of renal function, even though total AUC and fraction are inversely related.

Figure 87 Mean Asenapine Concentration vs. Time Profiles by Degree of Renal Function – Study A7501017

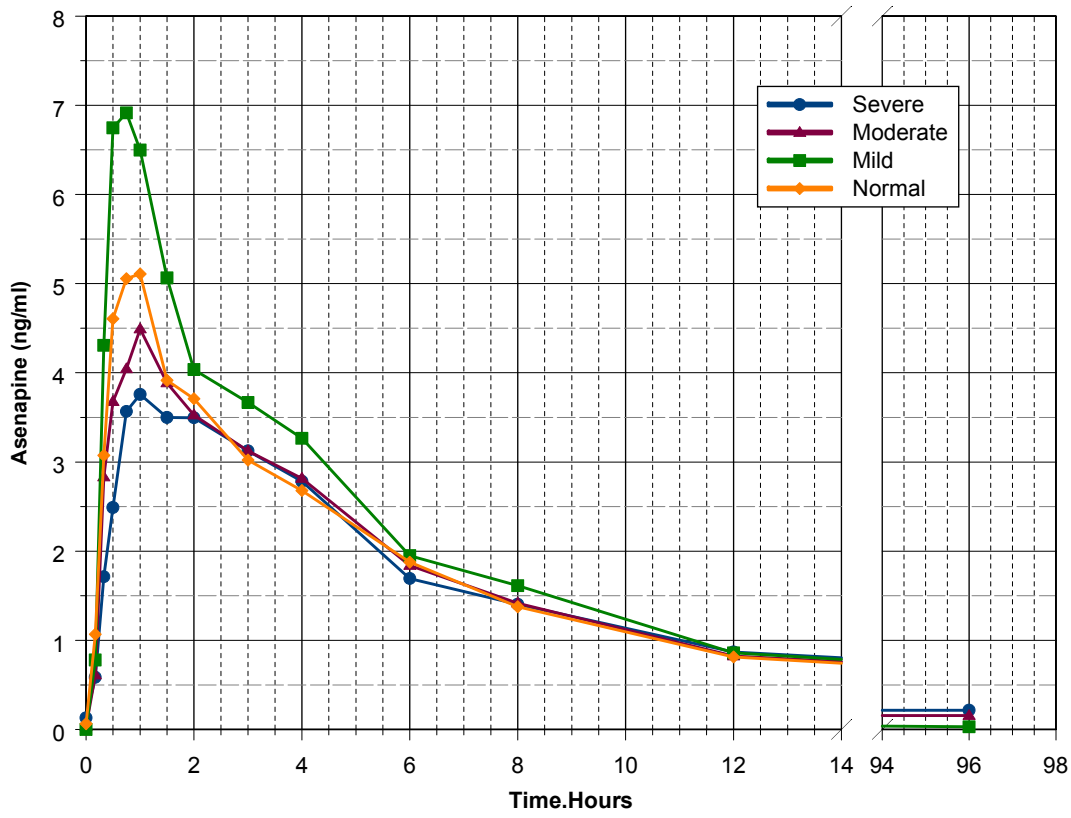


Figure 88 Mean Desmethyl-Asenapine Concentration vs. Time Profiles by Degree of Renal Function – Study A7501017

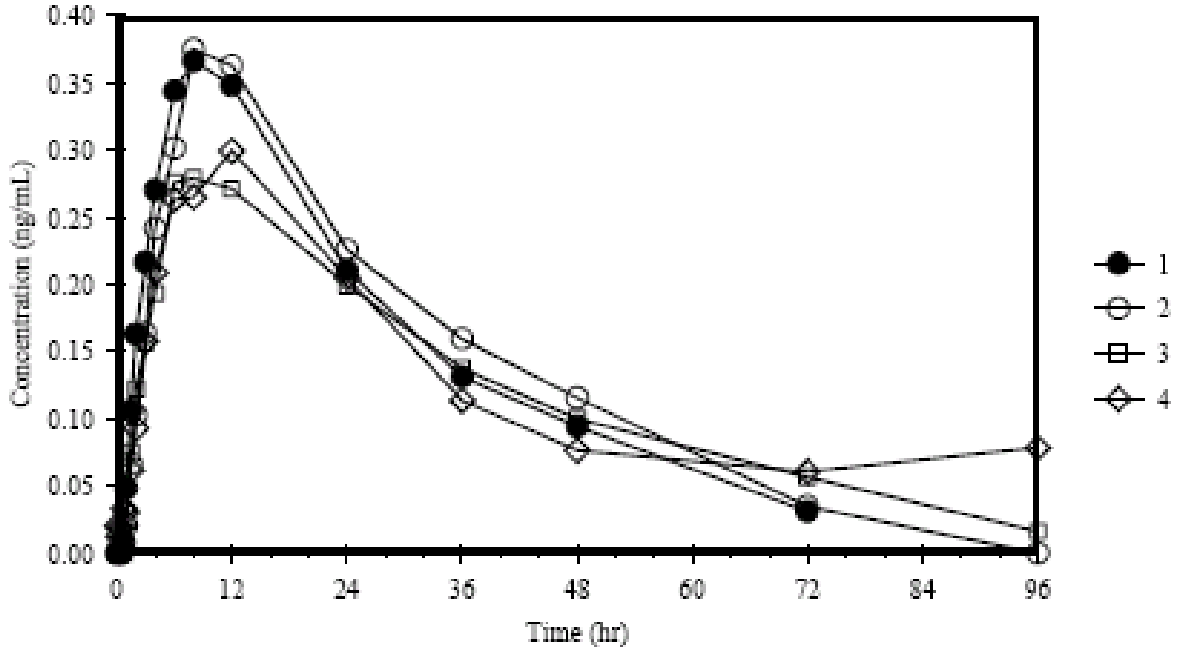
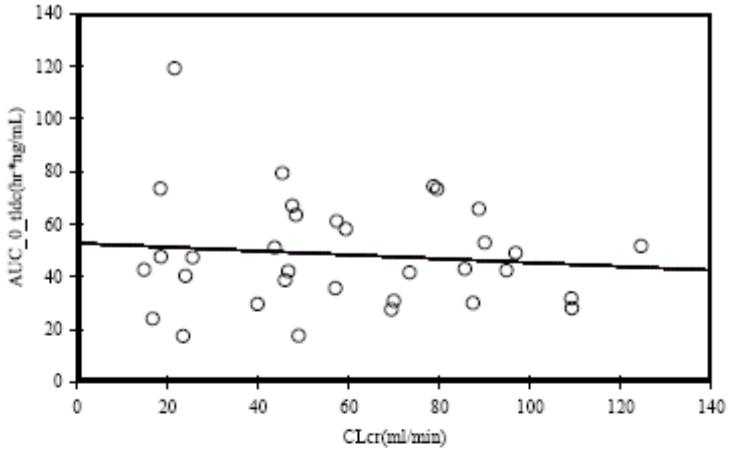
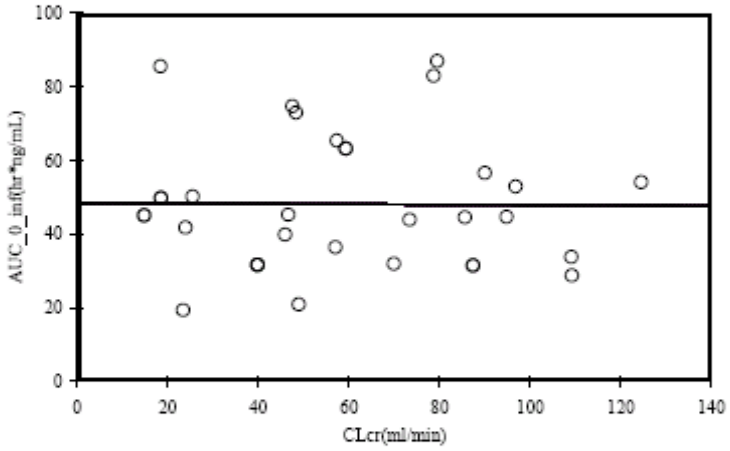


Figure 89 Plots of Asenapine AUCt, AUCinf, and Cl/F vs. Clcr – Study A7501017A





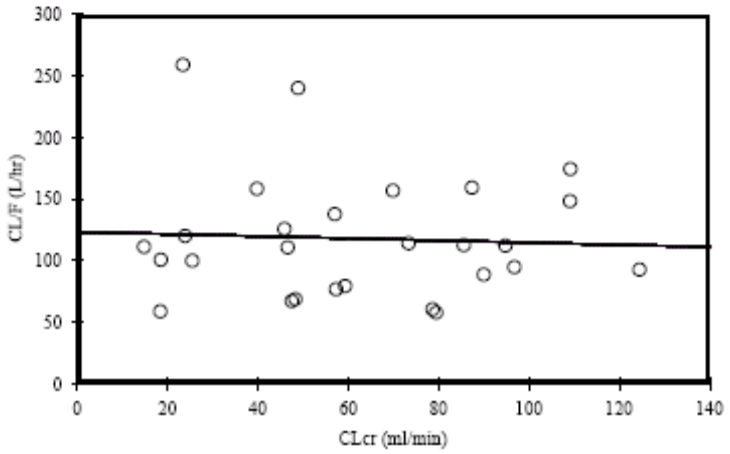
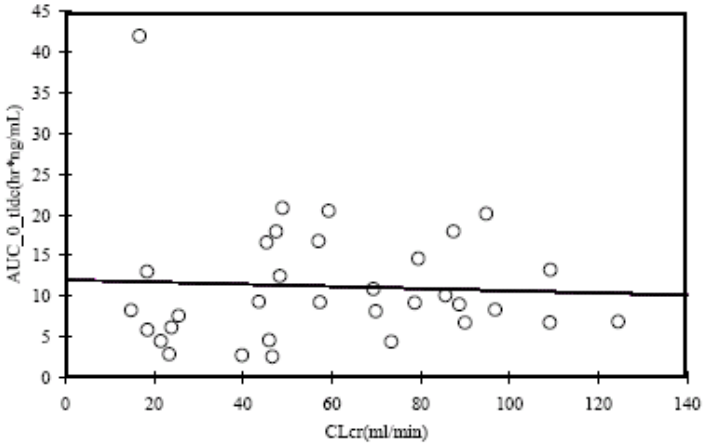


Figure 90 Plots of Desmethyl-Asenapine AUCt and AUCinf vs. Clcr – Study A7501017A



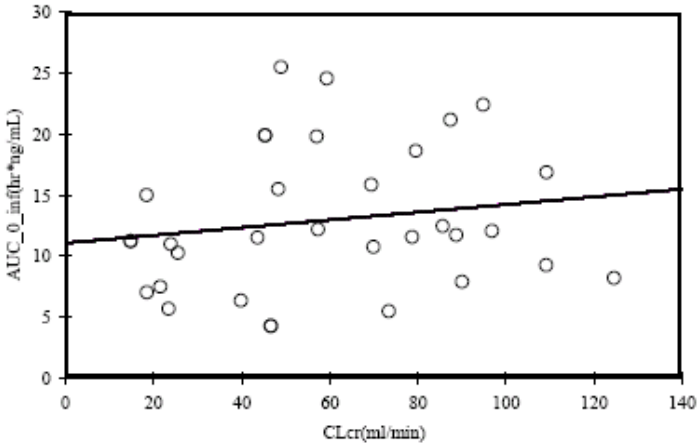


Table 108 Individual Subject Demographics for Renal Impairment Study A7501017

Renal Function	Renal Function Analysis Group	Subject	Age	Sex	(Hormonal Status)	Race	Height (cm)	Weight (kg)	BMI (kg/m2)	Smoking Status	Alcohol (Units / Wk)
Normal Renal Function Clcr* > 80.0 mL/min	Group 1	10011026	65	Female	(Postmenopausal)	Caucasian	167.6	77.3	27.5	Never Smoked	0
	Group 1	10011040	60	Female	(Postmenopausal)	Caucasian	162.5	84.5	32	Never Smoked	0
	Group 1	10011041	58	Female	(Postmenopausal)	Caucasian	165.1	63.2	23.2	Never Smoked	0
	Group 1	10011045	59	Female	(Postmenopausal)	Caucasian	156.5	75.3	30.7	Current Smoker	0
	Group 1	10011031	72	Female	(Postmenopausal)	Caucasian	160.0	68.6	26.8	Never Smoked	7
	Group 1	10011032	61	Male		Caucasian	176.5	88.4	28.4	Never Smoked	4
	Group 1	10011033	60	Male		Caucasian	187.3	104.5	29.8	Never Smoked	0
	Group 1	10011037	69	Male		Caucasian	171.4	88.4	30.1	Never Smoked	0
	Group 1	10011042	58	Male		Caucasian	182.8	86.3	25.8	Never Smoked	0
Mild Renal Insufficiency Clcr* ≥ 51.0 ≤ 80.0 mL/min	Group 2	10011002	71	Female	(Postmenopausal)	Caucasian	158.7	63.0	25	Never Smoked	0
	Group 2	10011034	64	Female	(Postmenopausal)	Caucasian	160.0	63.4	24.8	Never Smoked	0
	Group 2	10011035	64	Female	(Postmenopausal)	Caucasian	149.8	70.9	31.6	Never Smoked	0
	Group 2	10011043	65	Female	(Postmenopausal)	Caucasian	151.7	53.6	23.3	Never Smoked	0
	Group 2	10011038	56	Female	(Postmenopausal)	Caucasian	160.0	63.4	24.8	Never Smoked	0
	Group 2	10011011	63	Male		Black, Non Hispanic	177.8	75.5	23.9	Current Smoker	0
	Group 2	10011009	48	Male		Caucasian	170.2	92.3	31.9	Never Smoked	0
	Group 2	10011028	66	Male		Caucasian	176.5	83.6	26.8	Never Smoked	0
Moderate Renal Insufficiency Clcr ≥ 30.0 & ≤ 50.0 mL/min	Group 3	10011036	36	Female	(Premenopausal)	Black, Non Hispanic	161.3	83.6	32.1	Never Smoked	0
	Group 3	10011012	45	Female	(Premenopausal)	Caucasian	160.0	62.3	24.3	Current Smoker	0
	Group 3	10011014	60	Female	(Postmenopausal)	Caucasian	160.0	75.5	29.5	Never Smoked	0
	Group 3	10011024	50	Male		Black, Non Hispanic	184.1	108.6	32	Never Smoked	0
	Group 3	10011005	73	Male		Caucasian	179.0	89.0	27.8	Never Smoked	1
	Group 3	10011006	73	Male		Caucasian	167.6	69.0	24.6	Current Smoker	0
	Group 3	10011027	67	Male		Caucasian	184.8	110.0	32.2	Never Smoked	0
	Group 3	10011030	75	Male		Caucasian	172.7	96.4	32.3	Never Smoked	0
Severe Renal Insufficiency † Clcr* < 30.0 mL/min	Group 4	10011017	72	Female	(Postmenopausal)	Black, Non Hispanic	158.7	70.9	28.2	Never Smoked	0
	Group 4	10011023	74	Female	(Postmenopausal)	Black, Non Hispanic	162.5	54.0	20.4	Never Smoked	0
	Group 4	10011008	77	Female	(Postmenopausal)	Caucasian	160.0	61.8	24.1	Never Smoked	0
	Group 4	10011013	65	Female	(Postmenopausal)	Caucasian	166.4	90.5	32.7	Never Smoked	0
	Group 4	10011018	78	Female	(Postmenopausal)	Caucasian	163.8	65.4	24.4	Never Smoked	0
	Group 4	10011003	57	Male		Black, Non Hispanic	170.0	72.3	25	Current Smoker	0
	Group 4	10011020	52	Male		Black, Non Hispanic	166.4	68.6	24.8	Never Smoked	0
	Group 4	10011001	77	Male		Caucasian	176.5	87.3	28	Past Smoker	1

Table 109 Individual Asenapine Pharmacokinetic Metrics by Degree of Renal Impairment – Study A7501017

Groupa	CLcr (mL/min)	Subject	Cmax (ng/mL)	Tmax (hr)	AUCtlast (hr*ng/mL)	AUC(0 - ∞) (hr*ng/mL)	%AUC(0 - ∞) extrapolated	t½ (hr)	Vd/F (L)	CL/F (L/hr)	Fu
Renal Function Normal Renal Function Clcr* > 80.0 mL/min	85.6	10011026	6.57	0.700	42.9	44.5	3.74	15.0	2430	112	0.032
	109	10011032	5.64	0.530	31.6	33.8	6.32	28.6	6110	148	0.033
	96.8	10011033	4.52	0.750	48.9	52.9	7.62	31.5	4290	94.5	0.027
	94.8	10011034	4.93	1.00	42.3	44.7	5.39	21.9	3540	112	0.055
	125	10011037	7.92	1.05	51.5	54.1	4.69	19.0	2530	92.5	0.039
	88.7	10011040	3.76	1.00	65.7						0.039
	87.4	10011041	5.14	1.00	29.9	31.4	4.93	24.6	5660	159	0.038
	109	10011042	2.83	0.330	27.9	28.7	2.90	17.8	4470	174	0.036
	90.0	10011045	6.74	0.700	52.8	56.5	6.63	26.4	3370	88.4	0.037
Mild Renal Insufficiency Clcr* ≥ 51.0 ≤ 80.0 mL/min	57.0	10011002	6.27	1.05	35.5	36.4	2.35	12.3	2440	137	0.032
	69.4	10011009	2.54	1.97	27.4						0.095
	73.4	10011011	5.56	0.730	41.5	43.9	5.52	24.6	4040	114	0.044
	57.3	10011028	8.93	0.500	61.0	65.4	6.70	20.0	2200	76.5	0.04
	78.7	10011031	11.6	0.750	74.3	83.0	10.5	26.1	2270	60.3	0.029
	79.5	10011035	12.0	0.720	73.2	87.0	15.8	33.7	2800	57.5	0.028
	69.9	10011038	4.04	0.700	30.7	31.9	3.90	29.2	6610	157	0.031
	59.3	10011043	10.8	0.750	58.0	63.2	8.15	24.3	2770	79.1	0.028
Moderate Renal Insufficiency Clcr ≥ 30.0 & ≤ 50.0 mL/min	43.6	10011005	4.70	1.00	50.9						0.039
	45.9	10011006	3.21	2.00	38.6	39.8	3.12	13.3	2410	125	0.066
	46.6	10011012	4.54	1.47	41.9	45.3	7.41	40.8	6510	110	0.041
	47.5	10011014	5.73	0.750	66.9	74.7	10.5	35.7	3450	66.9	0.036
	45.3	10011024	7.09	1.00	79.2						0.032
	39.8	10011027	2.74	0.750	29.5	31.6	6.71	37.0	8450	158	0.047
	48.3	10011030	8.31	0.500	63.4	73.0	13.2	42.2	4170	68.5	0.036
	48.9	10011036	1.55	2.00	17.5	20.9	16.3	31.0	10700	240	0.039
Severe Renal Insufficiency † Clcr* < 30.0 mL/min	23.9	10011001	3.21	0.750	40.2	41.7	3.70	18.5	3190	120	0.036
	18.5	10011003	3.59	2.02	47.4	49.8	4.67	17.1	2470	100	0.046
	25.5	10011008	3.46	1.00	47.2	50.2	5.97	26.3	3780	99.6	0.039
	14.8	10011013	6.80	1.00	42.6	45.1	5.58	25.8	4130	111	0.038
	16.7	10011017	2.26	2.03	23.9						0.052
	18.4	10011018	6.79	2.97	73.4	85.5	14.2	42.0	3540	58.5	0.049
	21.5	10011020	6.06	0.750	119						0.047
	23.4	10011023	1.25	4.00	17.3	19.3	10.4	48.9	18300	259	0.037

Table 110 Asenapine Pharmacokinetic Metric Summary Statistics in Subjects with Varying Degrees of Renal Insufficiency after a Single 5 mg Sublingual Dose – Study A7501017

	Summary Statistics				Geometric Means				Geometric Mean Ratios (90% CI)		
	Group 1 (>80 mL/min)	Group 2 (51 - 80 mL/min)	Group 3 (30 - 50 mL/min)	Group 4 (<30 mL/min)	Group 1 (>80 mL/min)	Group 2 (51 - 80 mL/min)	Group 3 (30 - 50 mL/min)	Group 4 (<30 mL/min)	Mild : Normal	Moderate : Normal	Severe : Normal
N	9/8	8/7	8/6	8/6							
Tmax (hr)	0.8 ± 0.2 (31.8) 0.33 - 1.05 [0.75]	0.9 ± 0.5 (51.2) 0.5 - 1.97 [0.74]	1.2 ± 0.6 (48.7) 0.5 - 2 [1.00]	1.8 ± 1.2 (65.2) 0.75 - 4 [1.51]	0.74	0.82	1.06	1.51			
Cmax (ng/mL)	5.3 ± 1.6 (29.5) 2.83 - 7.92 [5.14]	7.7 ± 3.6 (46.8) 2.54 - 12 [7.6]	4.7 ± 2.3 (47.8) 1.55 - 8.31 [4.62]	4.2 ± 2.1 (50.6) 1.25 - 6.8 [3.525]]	5.12	6.84	4.21	3.65	1.34 0.878 - 2.04	0.822 0.54 – 1.25	0.713 0.468 – 1.09
AUC(0 - tlqc)[a] (hr*ng/mL)	43.7 ± 12.5 (28.5) 27.9 - 65.7 [42.9]	50.2 ± 18.8 (37.5) 27.4 - 74.3 [49.75]	48.5 ± 20.6 (42.5) 17.5 - 79.2 [46.4]	51.4 ± 32.1 (62.5) 17.3 - 119 [44.9]	42.1	47.0	44.1	43.9	1.12 0.767 – 1.62	1.05 0.719 – 1.52	1.04 0.716 – 1.52
AUC(0 - ∞) (hr*ng/mL)	43.3 ± 10.9 (25.2) 28.7 - 56.5 [44.6]	58.7 ± 22.0 (37.4) 31.9 - 87 [63.2]	47.6 ± 22.0 (46.2) 20.9 - 74.7 [42.55]	48.6 ± 21.4 (44.0) 19.3 - 85.5 [47.45]	42.1	55.0	43.2	44.5	1.31 0.911 – 1.87	1.03 0.705 – 1.50	1.06 0.726 - 1.54
% extrap	5.3 ± 1.6 (29.4) 2.9 - 7.62 [5.16]	7.6 ± 4.5 (59.7) 2.35 - 15.8 [6.7]	9.5 ± 4.8 (50.0) 3.12 - 16.3 [8.955]	7.4 ± 4.0 54.5 3.7 - 14.2 [5.775]	5.1	6.4	8.4	6.6			
Vd/F (L)	4050 ± 1348 (33.3) 2430 - 6110 [3915]	3304 ± 1584 (47.9) 2200 - 6610 [2770]	5948 ± 3196 (53.7) 2410 - 10700 [5340]	5902 ± 6100 103.4 2470 - 18300 [3660]	3854	3062	5227	4469			
L/kg	51.5 ± 20.2 (39.2) 28.6 - 89.6 [48.3]	49.6 ± 26.0 (52.3) 26.3 - 104.3 [39.5]	72.2 ± 37.7 (52.2) 34.9 - 128.0 [61.3]	95.1 ± 119.9 126.1 34.2 - 338.9 [49.9]	48.3	45.2	64.3	63.2			
CL/F (L/hr)	122.6 ± 33.2 (27.1) 88.4 - 174 [112]	97.3 ± 39.0 (40.1) 57.5 - 157 [79.1]	128.1 ± 64.9 (50.7) 66.9 - 240 [117.5]	124.7 ± 69.1 55.4 58.5 - 259 [105.5]	118.8	90.9	115.6	112.3	0.765 0.533 – 1.10	0.974 0.669 – 1.42	0.945 0.649 – 1.38
t½ (hr)	23.1 ± 5.7 (24.6) 15 - 31.5 [23.25]	24.3 ± 6.8 (28.0) 12.3 - 33.7 [24.6]	33.3 ± 10.6 (31.8) 13.3 - 42.2 [36.35]	29.8 ± 12.9 43.3 17.1 - 48.9 [26.05]	22.5	23.3	31.3	27.6			

a tlqc not defined by sponsor, abbreviation may indicate 'Time of Last Quantifiable Concentration'.

Table 111 Individual Desmethyl-Asenapine Pharmacokinetic Metrics by Degree of Renal Impairment– Study A7501017

Groupa	Groupa	CLcr (mL/min)	Subject	Cmax (ng/mL)	Tmax (hr)	AUC(0-tlqc) (hr*ng/mL)	AUC(0-∞) (hr*ng/mL)	%AUC(0-∞) Extrapolated	Λz (1/hr)	t½ (hr)	Fu
Renal Function Normal Renal Function Clcr* > 80.0 mL/min	1	85.6	10011026	0.454	5.93	10.1	12.5	19.0	0.0333	20.8	0.032
	1	109	10011032	0.308	2.95	6.77	9.26	26.9	0.0327	21.2	0.033
	1	96.8	10011033	0.220	8.0	8.34	12.0	30.8	0.0172	40.3	0.027
	1	94.8	10011034	0.720	7.93	20.1	22.4	10.1	0.0365	19.0	0.055
	1	125	10011037	0.248	8.07	6.89	8.21	16.0	0.0463	15.0	0.039
	1	88.7	10011040	0.274	12.0	8.99	11.7	23.3	0.0205	33.7	0.039
	1	87.4	10011041	0.712	12.0	18.0	21.2	15.1	0.0454	15.3	0.038
	1	109	10011042	0.343	12.0	13.2	16.9	21.5	0.0217	32.0	0.036
	1	90.0	10011045	0.310	6.00	6.76	7.90	14.4	0.0608	11.4	0.037
Mild Renal Insufficiency Clcr* ≥ 51.0 ≤ 80.0 mL/min	2	57.0	10011002	0.543	5.95	16.8	19.8	15.4	0.0286	24.2	0.032
	2	69.4	10011009	0.400	12.0	10.9	15.8	31.3	0.0300	23.1	0.095
	2	73.4	10011011	0.327	4.12	4.41	5.48	19.5	0.0520	13.3	0.044
	3	39.8	10011027	0.150	7.97	2.75	6.36	56.7	0.0266	26.0	0.04
	2	57.3	10011028	0.287	7.93	9.25	12.2	24.1	0.0372	18.6	0.029
	2	78.7	10011031	0.386	8.0	9.21	11.6	20.4	0.0370	18.7	0.028
	2	79.5	10011035	0.392	7.97	14.6	18.6	21.5	0.0223	31.1	0.031
	2	69.9	10011038	0.312	12.0	8.16	10.7	24.1	0.0332	20.9	0.028
	2	59.3	10011043	0.625	12.0	20.5	24.6	16.6	0.0256	27.1	0.032
Moderate Renal Insufficiency Clcr ≥ 30.0 & ≤ 50.0 mL/min	3	43.6	10011005	0.389	6.0	9.32	11.5	19.1	0.0349	19.9	0.039
	3	45.9	10011006	0.268	11.9	4.58					0.066
	3	46.6	10011012	0.159	5.97	2.58	4.28	39.6	0.0434	16.0	0.041
	3	47.5	10011014	0.265	24.0	17.9					0.036
	3	45.3	10011024	0.456	6.0	16.6	19.9	16.5	0.0242	28.6	0.032
	3	48.3	10011030	0.274	12.0	12.5	15.5	19.5	0.0196	35.3	0.047
	3	48.9	10011036	0.473	6.00	20.8	25.5	18.3	0.0266	26.0	0.036
Severe Renal Insufficiency † Clcr* < 30.0 mL/min	4	23.9	10011001	0.251	12.0	6.17	11.0	43.9	0.0272	25.5	0.036
	4	18.5	10011003	0.272	12.0	5.86	7.03	16.6	0.0581	11.9	0.046
	4	25.5	10011008	0.390	8.0	7.60	10.3	26.0	0.0284	24.4	0.039
	4	14.8	10011013	0.311	5.97	8.28	11.2	26.3	0.0279	24.9	0.038
	4	16.7	10011017	0.742	12.0	42.0					0.052
	4	18.4	10011018	0.396	12.0	13.0	15.0	13.2	0.0339	20.4	0.049
	4	21.5	10011020	0.162	12.0	4.49	7.49	40.1	0.0237	29.3	0.047
	4	23.4	10011023	0.114	12.0	2.87	5.68	49.5	0.0232	29.8	0.037

Table 112 Desmethyl-Asenapine Pharmacokinetic Metric Summary Statistics in Subjects with Varying Degrees of Renal Insufficiency after a Single 5 mg Sublingual Dose – Study A7501017

	Summary Statistics				Geometric Means				Geometric Mean Ratios (90% CI)		
Group	**Group 1**	**Group 2**	**Group 3**	**Group 4**	**Group 1**	**Group 2**	**Group 3**	**Group 4**	**Mild : Normal**	**Moderate : Normal**	**Severe : Normal**
CLcr Range	**>80 mL/min**	**51 - 80 mL/min**	**30 - 50 mL/min**	**<30 mL/min**	**>80 mL/min**	**51 - 80 mL/min**	**30 - 50 mL/min**	**<30 mL/min**			
N	9	8	8/6	8/7							
Tmax (hr)	8.32 ± 3.18 (38.2) 2.95 - 12 [8]	8.73 ± 2.98 (34.1) 4.12 - 12 [7.99]	9.99 ± 6.24 (62.5) 5.97 - 24 [6.99]	10.7 ± 2.38 (22.1) 5.97 - 12 [12]	7.68	8.24	8.78	10.4	0	-1	4
Cmax (ng/mL)	0.399 ± 0.192 (48.1) 0.22 - 0.72 [0.31]	0.409 ± 0.117 (28.7) 0.287 - 0.625 [0.389]	0.304 ± 0.124 (40.7) 0.15 - 0.473 [0.271]	0.33 ± 0.194 (58.7) 0.114 - 0.742 [0.292]	0.365	0.396	0.281	0.286	1.09 0.754 - 1.56	0.771 0.535 - 1.11	0.785 0.545 – 1.13
AUC_{0-t} (ng/mL)	11.0 ± 5.02 (45.6) 6.76 - 20.1 [8.99]	11.7 ± 5.21 (44.4) 4.41 - 20.5 [10.1]	10.9 ± 7.18 (66) 2.58 - 20.8 [10.9]	11.3 ± 12.8 (113) 2.87 – 42.0 [6.88]	10.2	10.7	8.34	7.95	1.05 0.61 - 1.81	0.822 0.477 – 1.42	0.783 0.455 – 1.35
AUC_{∞} (ng/mL x hr^{-1})	13.6 ± 5.4 (39.8) 7.9 - 22.4 [12]	14.9 ± 6.05 (40.8) 5.48 - 24.6 [14]	13.8 ± 8.1 (58.5) 4.28 - 25.5 [13.5]	9.67 ± 3.18 (32.9) 5.68 – 15.0 [10.3]	12.7	13.6	11.6	9.23	1.08 0.729 - 1.59	0.917 0.601 – 1.40	0.728 0.486 – 1.09
AUCextrap (%)	19.7 ± 6.57 (33.4) 10.1 - 30.8 [19]	21.6 ± 5.02 (23.3) 15.4 - 31.3 [21]	28.3 ± 16.4 (57.8) 16.5 - 56.7 [19.3]	30.8 ± 13.9 (45.2) 13.2 - 49.5 [26.3]	18.7	21.1	25.1	27.9			
$t_{½}$ (hr)	23.2 ± 9.85 (42.5) 11.4 - 40.3 [20.8]	22.1 ± 5.52 (24.9) 13.3 - 31.1 [22]	25.3 ± 6.77 (26.8) 16 - 35.3 [26]	23.8 ± 6.1 (25.7) 11.9 - 29.8 [24.9]	21.4	21.5	24.5	22.9			

Table 113 Asenapine Fraction Unbound by Degree of Renal Impairment – Study A7501017

Degree of Renal Function	Group 1 Normal >80 mL/min	Group 2 Mild 51 - 80 mL/min	Group 3 Moderate 30 - 50 mL/min	Group 4 Severe <30 mL/min
N	9	8	8	8
Summary Statistics	3.7 ± 0.8 (20.6) 2.7 - 5.5 [3.7]	4.1 ± 2.3 (55.4) 2.8 - 9.5 [3.2]	4.2 ± 1.1 (25.3) 3.2 - 6.6 [3.9]	4.3 ± 0.6 (14.4) 3.6 - 5.2 [4.3]
Geometric Mean	3.7	3.7	4.1	4.3

Figure 91 Fraction Unbound of Asenapine and Desmethyl-Asenapine vs. AUCinf by Renal Function – Study A7501017

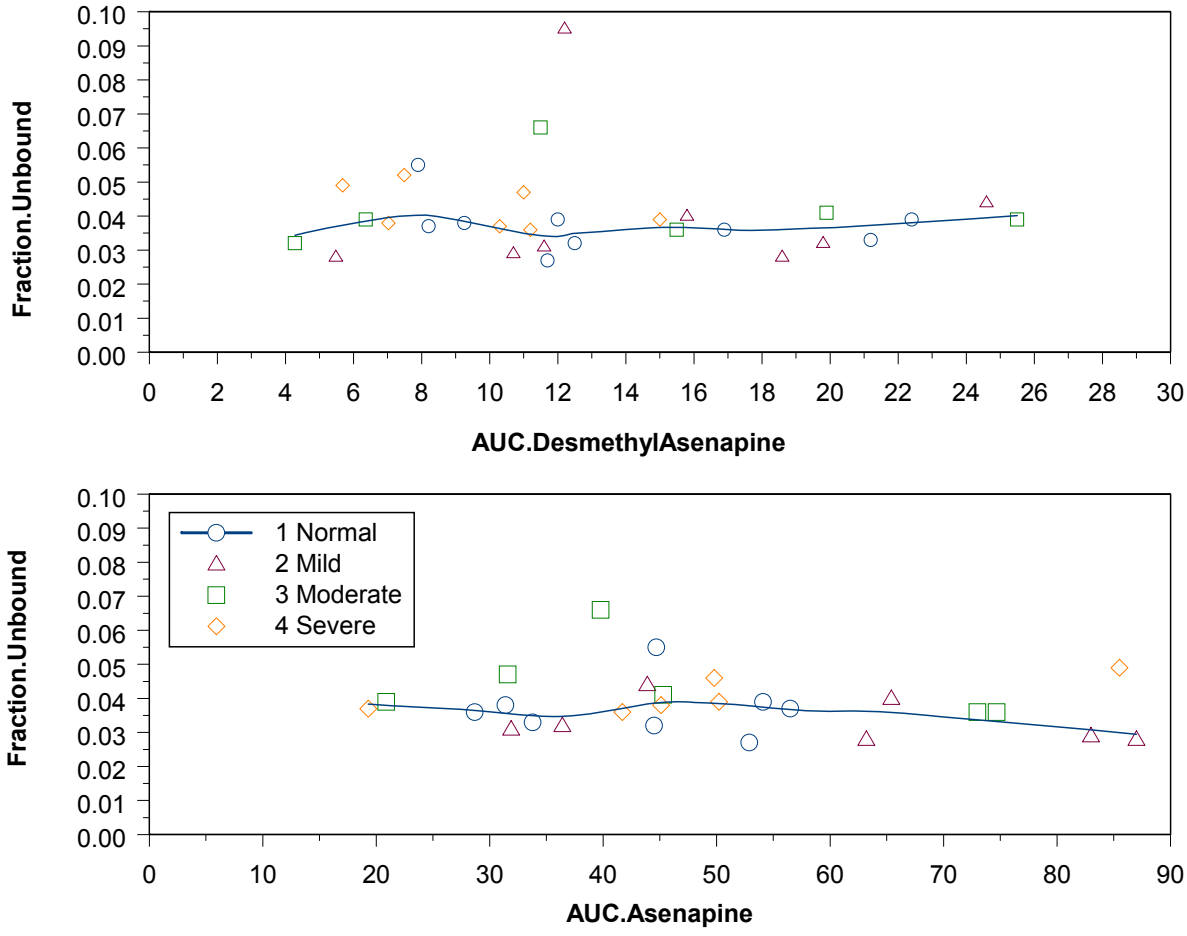


Figure 92 Desmethyl-Asenapine Unbound AUC vs. Creatinine Clearance – Study A7501017

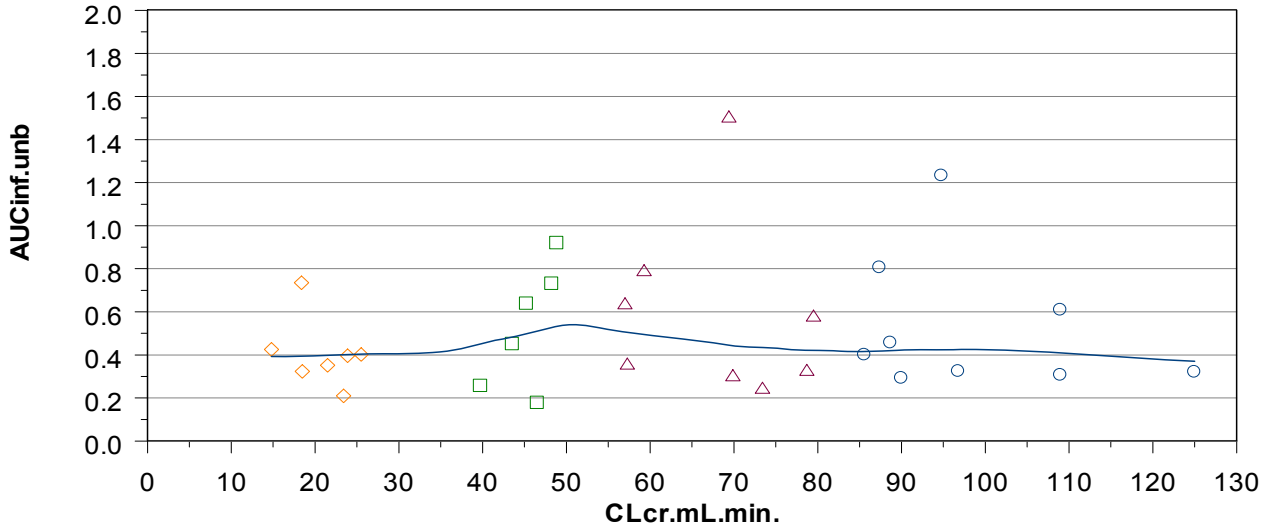


Figure 93 Desmethyl-Asenapine Total AUC vs. Creatinine Clearance – Study A7501017

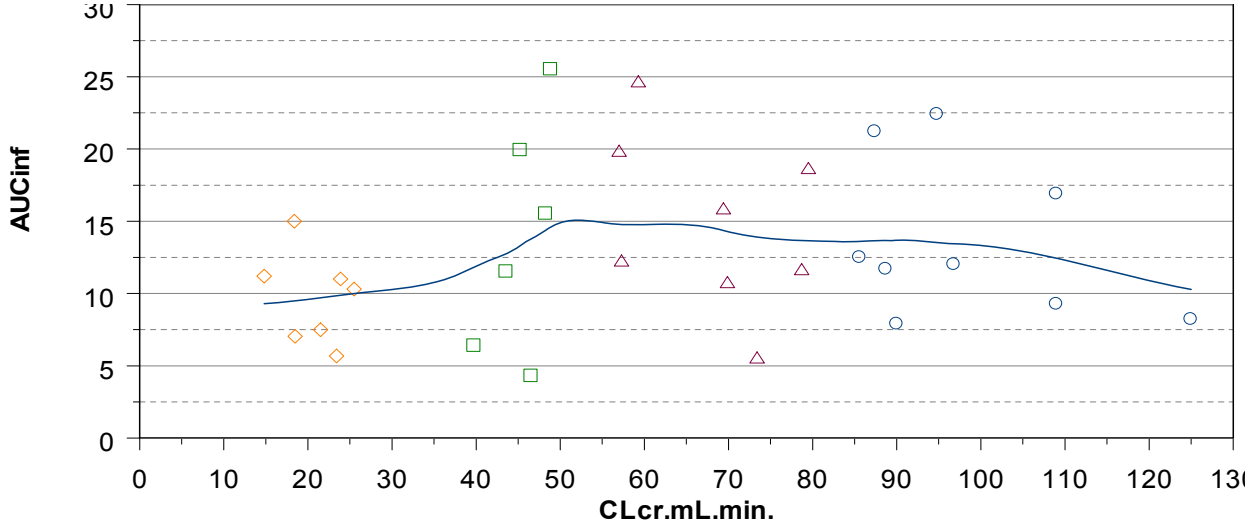
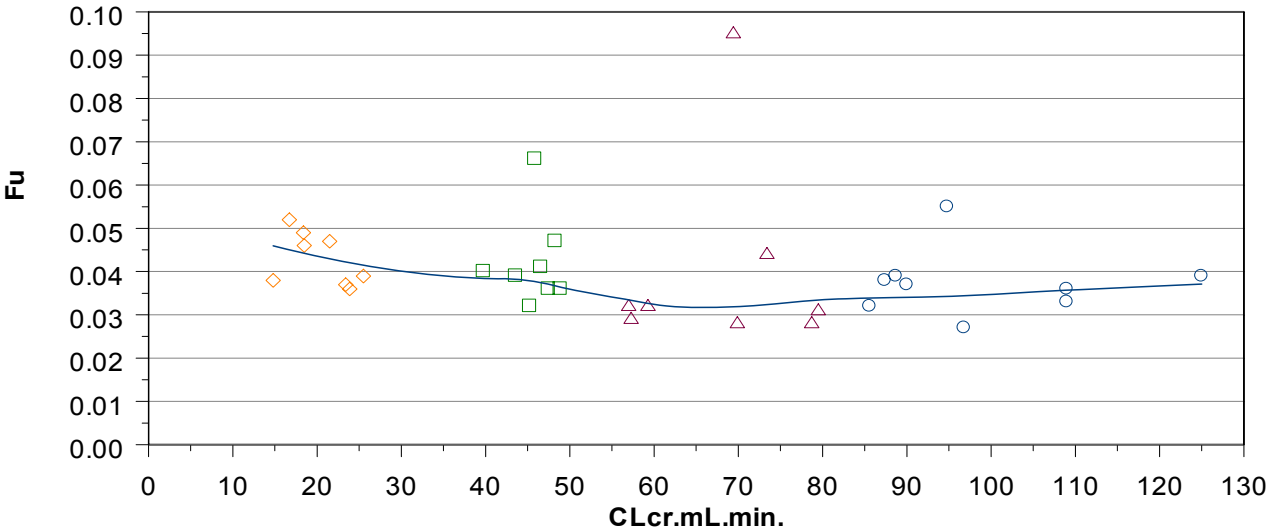


Figure 94 Asenapine Free Fraction vs. Creatinine Clearance



5.5.7 Extrinsic Factors

5.5.7.1 Effect of Water on Sublingual Bioavailability - Study 25537

Study 25537 examined the effect of drinking water at varying time intervals after a 10 mg QD dose of asenapine administered sublingually in 16 healthy male volunteers in a 4 x 4 latin square design.

As shown in Figure 95, Figure 96 and Table 114 there is little to no difference in mean exposures to asenapine and desmethyl-asenapine when water administration is administered 10 or 30 minutes after dose administration. However when water is taken less than 10 minutes after asenapine administration the exposure to asenapine decreases, presumably due to transfer of unabsorbed asenapine from the oral cavity to the stomach and increased first pass effect by way of GI absorption as compared to sublingual administration.

As an arm without water was not included and as dosing was QD rather than BID it is difficult to compare exposures in this study to exposures in other studies however, comparison of pharmacokinetic metrics of asenapine and desmethyl-asenapine from this study for the doses taken with water 10 or more minutes after the administration of asenapine as shown in shown in Table 114 appear to be comparable to their pharmacokinetic metrics when taken without water under a BID regimen, (see Table 53, Table 54, and Table 55).

Since, taking asenapine orally appears to be related to acute hepatotoxicity and since there appears to be a very narrow therapeutic index, water should not be taken for at least 10 minutes after the administration of asenapine.

Figure 95 Asenapine Mean Steady-State 0 – 6 hour Concentration vs. Time Profiles when Water is taken at Various Times after Drug Administration – Study 25537

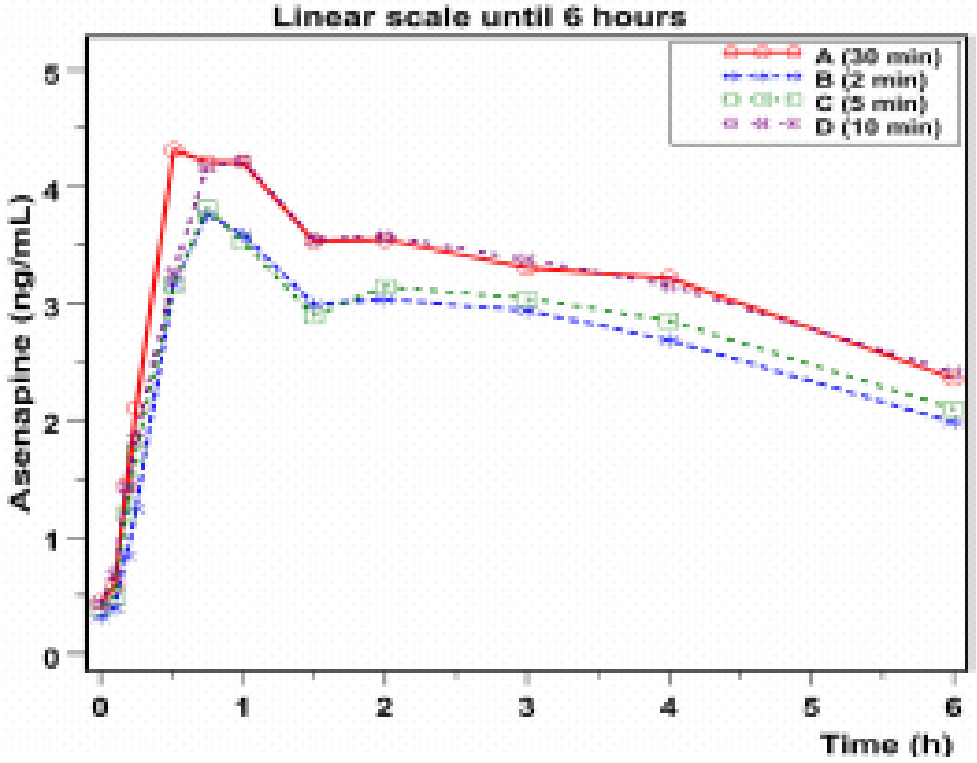


Figure 96 Asenapine Mean Steady-State 0 - 24 hour Concentration vs. Time Profiles when Water is taken at Various Times after Drug Administration – Study 25537

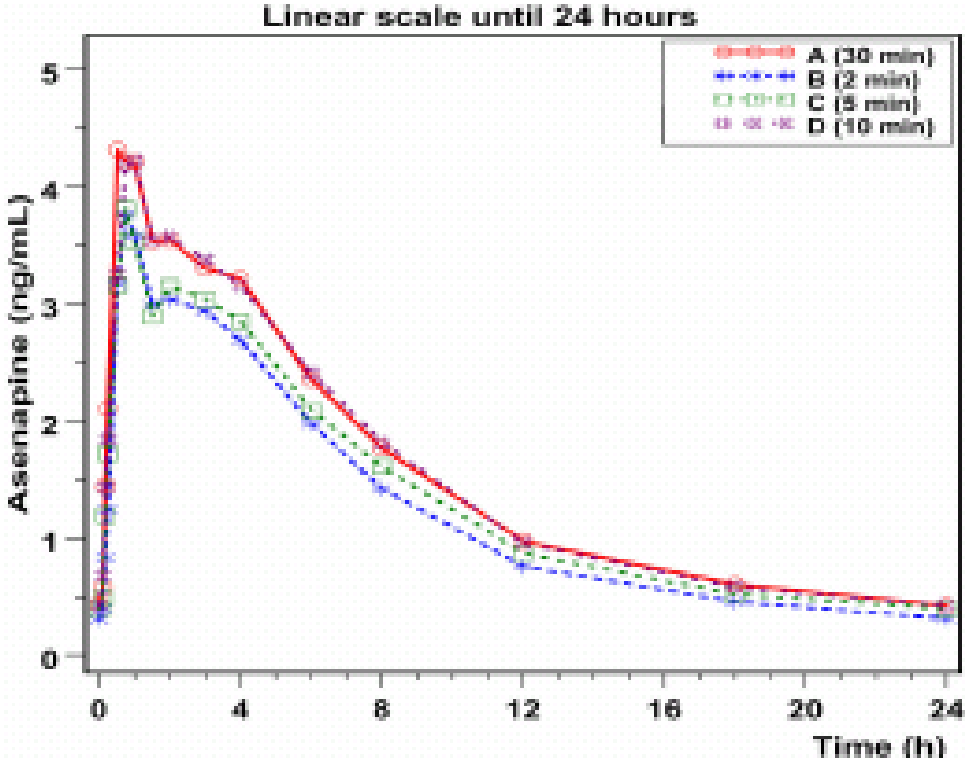


Table 114 Effect of Water at Varying Times on Asenapine and Desmethyl-aseanpine Pharmacokinetics after Asenapine 10 mg Sublingually – Study 25537

	Treatments				Geometric Mean Ratio (90% CI)		
	A (30 min)	B (2 min)	C (5 min)	D (10 min)	B : A	C : A	D : A
N	20	17	22	18			
Asenapine							
Tmax (h)	0.750 0.517 - 4.00	1.00 0.75 - 4.00	0.875 0.50 - 4.0	0.75 0.517 - 3.00			
Cmax (ng/mL)	4.99 ± 2.05	4.15 ± 2.09	4.38 ± 1.91	4.69 ± 2.22	0.79 0.62 - 1.01	0.88 0.69 - 1.12	0.98 0.77 - 1.24
AUC_{0-24} (ng*h/mL)	36.3 ± 11.3	29.8 ± 10.2	32.5 ± 11.1	35.9 ± 15.6	0.81 0.65 - 1.00	0.90 0.73 - 1.11	0.99 0.80 - 1.23
CL/f (L/h)	313 ± 149	414 ± 305	371 ± 241	354 ± 218			
wn - CL/f (L/h/kg)	4.01 ± 1.89	5.28 ± 3.84	4.80 ± 3.48	4.59 ± 3.05			
Cmin,av (ng/mL)	0.427 ± 0.135	0.309 ± 0.0927	0.390 ± 0.133	0.408 ± 0.196			
t½ (h)*	30.5 ± 8.20	27.6 ± 16.5	30.8 ± 12.4	37.4 ± 14.4			
Desmethyl-Asenapine							
Tmax (h)	6.00 2.03 - 8.02	6.00 2.00 - 8.02	4.00 2.00 - 12.0	6.00 2.00 - 12.0			
Cmax (ng/mL)	1.49 ± 0.867	1.49 ± 0.520	1.42 ± 0.642	1.38 ± 0.586	1.04 0.85 - 1.26	0.93 0.77 - 1.14	0.92 0.76 - 1.12
AUC_{0-24} (ng*h/mL)	23.4 ± 13.8	21.6 ± 7.49	20.6 ± 8.54	21.8 ± 9.90	0.95 0.80 - 1.14	0.86 0.72 - 1.03	0.92 0.77 - 1.10
Cmin,av (ng/mL)	0.492 ± 0.255	0.431 ± 0.181	0.415 ± 0.152	0.437 ± 0.227			
t½ (h)*	18.5 ± 4.21	13.9 ± 2.46	23.6 ± 7.38	15.4 ± 5.82			

* n=3 for B, n=4 for A and C and n=6 for D.
ANOVA based on n=15 subjects ('completers' group). ⌈: population mean.
Source: Appendix BI, Listing 8 - 1 and 9 - 1.

5.5.7.2 Effect of Charcoal on Relative Bioavailability – SL vs. Oral – Study 25540

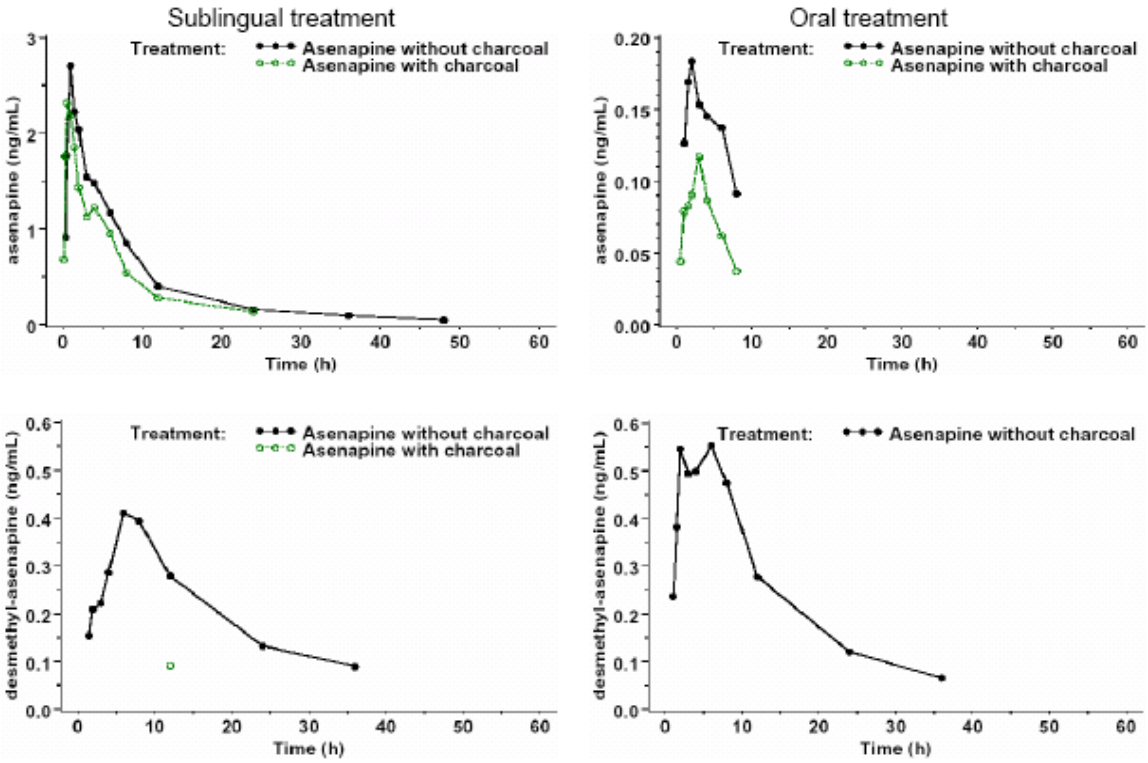
Study 25540 was an open label, randomized, parallel design single dose study in 16 healthy male volunteers to investigate the effect of concurrently administered activated charcoal to prevent gastro-intestinal absorption and to effect asenapine and desmethyl-asenapine pharmacokinetics after sublingual and oral administration of asenapine 5 mg.

Figure 97 and
Table 115 show the following:

- In the absence of activated charcoal, exposure to asenapine is lower after oral administration and peak exposure to desmethyl-asenapine is higher.
- After sublingual administration exposure to asenapine is only slighty affected by activated charcoal.
- In contrast after oral administration exposure to asenapine is significantly decreased by activated charcoal.
- Activated charcoal decreases exposure to desmethyl-asenapine after both sublingual and oral adminstration.

Although the results are specific to concurrently administered activated charcoal a similar effect albeit to a smaller degree is expected to delayed administration of activated. Thus activated charcoal should always be considered in an overdose situation with asenapine.

Figure 97 Asenapine and Desmethyl-Asenapine Mean Concentration vs. Time Profiles for Sublingual and Oral Administration of a Single 5 mg Dose when Administered with and without Activated Charcoal – Study 25540



Curves based on n = 7 subjects for the sublingual treatment and based on n=8 subjects for the oral treatment.

Data were taken from Figures 4.2-1 to 4.2-4 in Appendix BI.

Table 115 Asenapine and Desmethyl-Asenapine Pharmacokinetic Metrics for Sublingual and Oral Administration of a Single 5 mg Dose when Administered with and without Activated Charcoal – Study 25540

Route of Administration	Parameter (unit)	Asenapine		Desmethyl-Asenapine	
		with charcoal	without charcoal	with charcoal	without charcoal
Sublingual (n=7)	Tmax (h)	0.53 (0.33 - 2.0)	1.0 (0.5 - 2.0)	12.0 (8.00 - 12.0)	6.0 (4.0 - 8.0)
	Cmax (ng/mL)	2.58 (1.88)	3.02 (1.38)	0.0963 (0.0476)	0.428 (0.210)
	$AUC_{0\text{-tlast}}$ (ng·h/mL)	15.4 (12.0)	20.3 (5.75)	0.882 (0.981)	7.59 (4.13)
	$AUC_{0\text{-}\infty}$ (ng·h/mL)	16.2 (12.4)	21.3 (6.11)	—	10.3 ** (3.34)
	$t_{½}$ (h)	11.1 (5.46)	15.9 (5.04)	—	15.1 ** (4.32)
Oral (n=8)	Tmax (h)	3.0 (1.0 - 4.0)	2.0 (1.5 - 4.0)	—	3.00 (1.98 - 8.07)
	Cmax (ng/mL)	0.138 (0.0627)	0.204 (0.0791)	—	0.598 (0.117)
	$AUC_{0\text{-tlast}}$ (ng·h/mL)	0.612 (0.275)	1.38 (0.621)	—	8.38 (1.47)
	$AUC_{0\text{-}\infty}$ (ng·h/mL)	0.868 * (0.287)*	1.87 (0.768)	—	9.56 (1.63)
	$t_{½}$ (h)	4.19 * (0.671)*	6.75 (3.72)	—	10.5 (2.72)

* n = 7
** n = 6

5.5.7.3 Effect of Food Administered Concurrently and 4 hours after Administration – Study 41029

Study 41029 was an open-label, randomized, 3 way cross-over study to investigate the effect of a high-fat high-caloric meal eaten either concurrently or 4 hours after a single 5 mg sublingual dose of asenapine on the pharmacokinetics of asenapine and desmethyl-asenapine in 26 healthy males 18 - 55 years of age.

Although the control treatment was stated as being under fasted conditions, all subjects ingested 200 ml of a 'liquid breakfast' and 200 ml of an 'isotonic-sports' drink 1 hour prior to dosing.

All subjects received the following three treatments in randomized order:

Treatment A: Asenapine 5 mg SL "fasted"
Treatment B: Asenapine 5 mg SL after consumption of a high-fat meal. *
Treatment C: Asenapine 5 mg SL followed by a high-fat meal 4 h after dosing. *

* No further meals were allowed until 8 h post-dose

There was a seven day interperiod washout.

Figure 98, Figure 99, and Table 116 show not only that food decreases exposure to asenapine when administered concurrently (~ 20%), but also decreases exposures (but not peak concentrations) when administered 4 hours after the dose (~ 10%). However as this study was not conducted under true fasted conditions the magnitude of the decrease may actually be larger. As asenapine has a narrow therapeutic window with regards to hepatotoxicity even small changes and metabolic shunting could be clinically significant.

In fact the pattern of the concentration vs. time profiles indicated that this is likely due to an increase in clearance. Since asenapine is a high intrinsic clearance drug this may be due to slower blood flow through the liver and more stripping of drug off of plasma proteins as it passes through the liver or splanchic blood vessels.

Figure 98 Effect of Food Administration on Asenapine Mean Concentration vs. Time Profiles – Study 41029

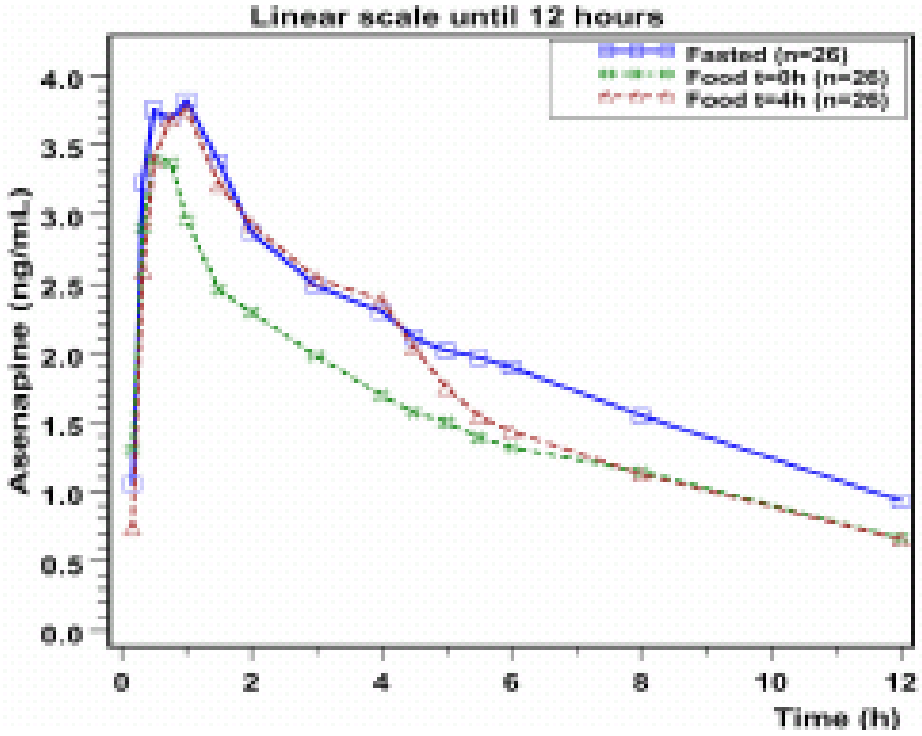


Figure 99 Effect of Food Administration on Desmethyl-Asenapine Mean Concentration vs. Time Profiles – Study 41029

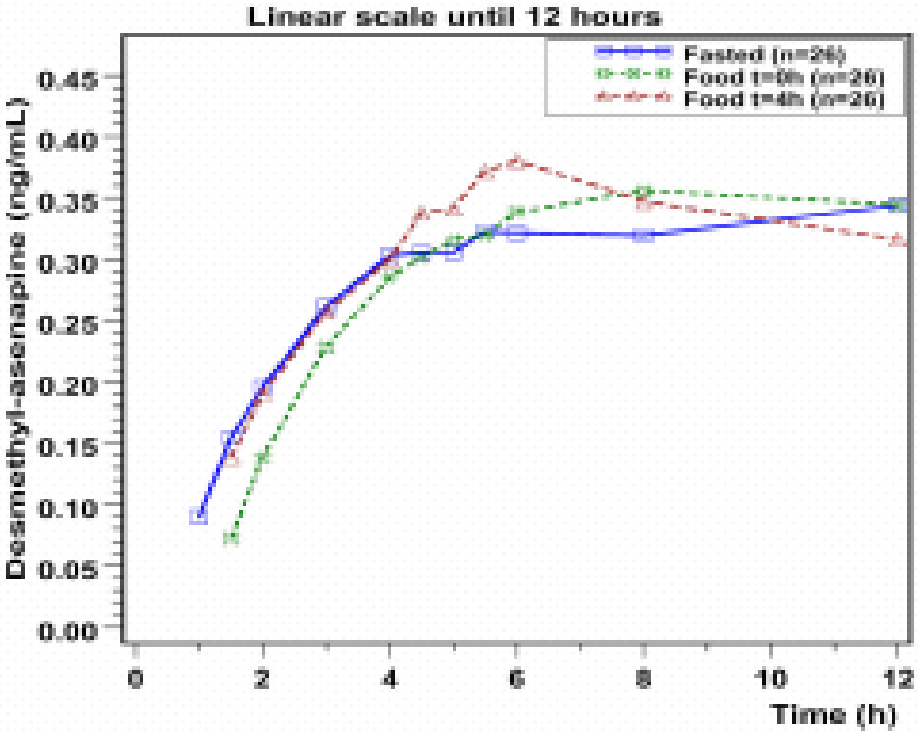


Figure 100 Effect of Food Administration on Asenapine Semi-log Mean Concentration vs. Time Profiles – Study 41029

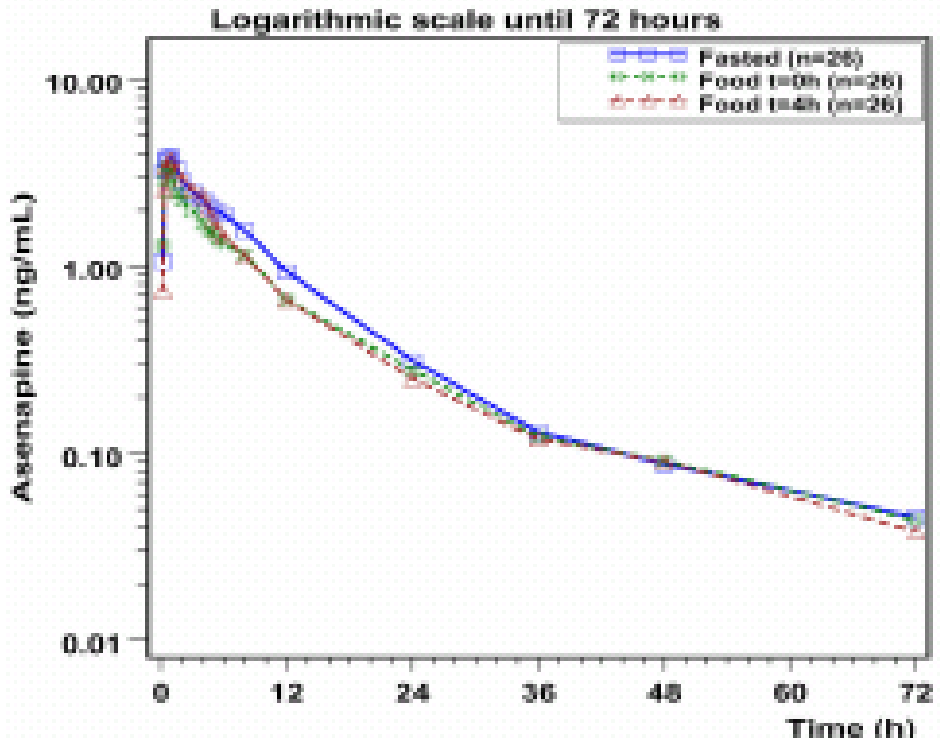


Figure 101 Effect of Food Administration on Desmethyl-Asenapine Semi-log Mean Concentration vs. Time Profiles – Study 41029

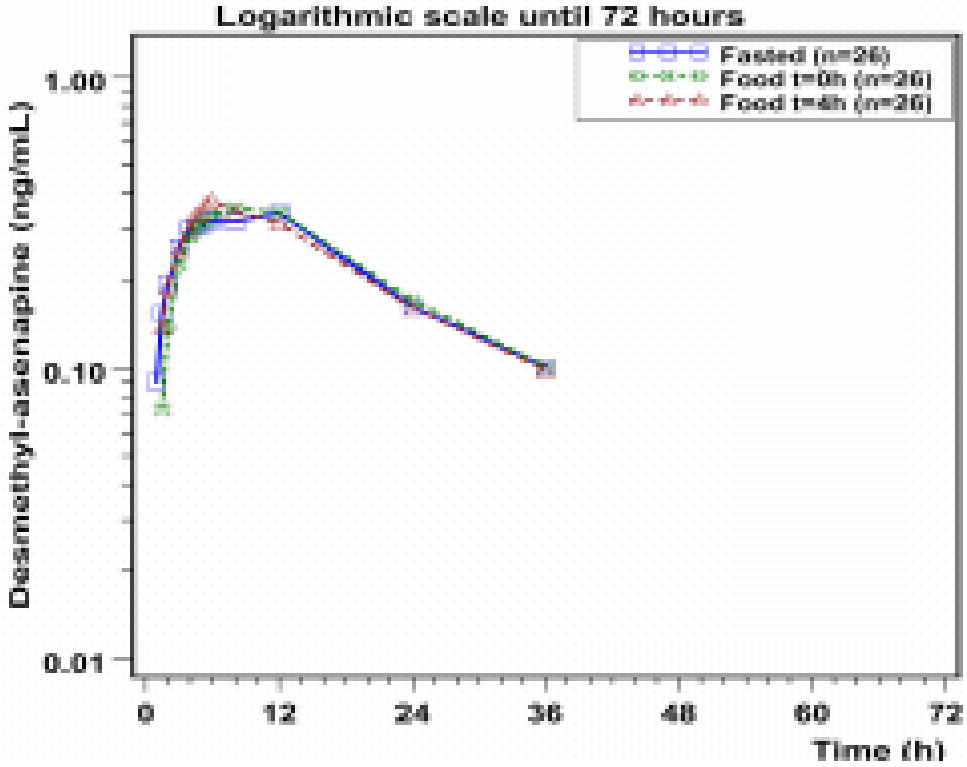


Table 116 Effect of Food on the Pharmacokineticsof Asenapine and N-Desmethyl-Asenapine after a Single Dose of Asenapine 5 mg Sublingually – Study 41029

Analyte (n)	Metric	Summary Statistics			Geometric Mean Ratios (90% CI)	
		(A) Fasted	(B) Fed t=0h	(C) Fed t=4h	B : A	C : A
Asenapine (n=26)	Tmax (h)	0.98 0.38 - 3.00	0.75 0.32 - 4.00	0.76 0.33 - 4.00		
	Cmax (ng/mL)	4.46 ± 2.57	3.89 ± 2.24	4.27 ± 2.10	0.90 0.73 - 1.11	1.02 0.83 - 1.26
	AUC∞ (ng/mL x hr^{-1})*	38.5 ± 15.6	30.8 ± 14.1	32.6 ± 11.7	0.79 0.66 - 0.94	0.87 0.73 - 1.03
	CL/f (L/h)*	163 ± 107	203 ± 105	182 ± 95.0		
	wn - CL/f (L/h/kg)*	2.16 ± 1.44	2.71 ± 1.57	2.44 ± 1.44		
	t½ (h)*	22.4 ± 12.3	22.6 ± 10.2	20.6 ± 6.75		
N - Desmethyl - Asenapine (n=26)	Tmax (h)	7.00 4.00 - 12.0	7.9 8.00 - 12.0	6.00 3.00 - 12.0		
	Cmax (ng/mL)	0.395 0.167	0.402 ± 0.139	0.407 ± 0.192		
	AUC∞ (ng/mL x hr^{-1})*	10.9 ± 3.68	11.0 ± 3.30	10.9 ± 4.23		
	CL/f (L/h)*	489 ± 182	478 ± 163	634 ± 829		
	wn - CL/f (L/h/kg)*	6.60 ± 3.13	6.37 ± 2.54	8.16 ± 10.3		
	t½ (h)*	16.4 ± 7.03	16.3 ± 5.81	15.6 ± 5.28		

Presented mean refers to arithmetic mean.

* for N - desmethyl - asenapine n=24 for Treatments A and B and n=23 for Treatment C.

5.5.7.4 Effect of Smoking a Cigarette in Chronic Smokers on Asenapine – Study 25545

Study 25545 was an open label, randomized, two-way cross-over, bioequivalence trial to assess the effect of smoking during sublingual asenapine dosing on the pharmacokinetics of asenapine and desmethyl–asenapine after a single 5 mg sublingual dose of asenapine in 24 healthy, smoking male volunteers aged 18 - 45 years.

During the smoking phase of the study the subjects smoked from 5 minutes before to 10 minutes after asenapine administration.

Although asenapine is a CYP1A2 substrate the effect of smoking on the presumed product of this enzyme, 11-hydroxy-asenapine was not measured.

In addition to induction, smoking causes vasoconstriction and might be expected to decrease absorption acutely even in this population, however this was not seen, (see Figure 102, Figure 103, and Table 117).

In conclusion no effect of smoking was seen on the pharmacokinetics of asenapine or desmethyl-asenapine, although as the study was conducted in smokers no decrease in exposure is expected as subjects are already induced. In spite of this the presence of induction the low peak concentrations and AUCs seen in this study may be indirect evidence of induction (see Figure 102, Figure 103, and Table 117).

However, the effect of smoking in a non-induced population of non-smokers is still unknown. As schizophrenics tend to be heavy smokers the effect of smoking is more likely to be evident in patients with bipolar illness or if the drug is used off label for schizoaffective disorder where intermittent smoking may be more relevant.

Figure 102 Mean Concentration vs. Time Profiles of Asenapine in Chronic Smokers While Smoking and Not Smoking - Study 25545

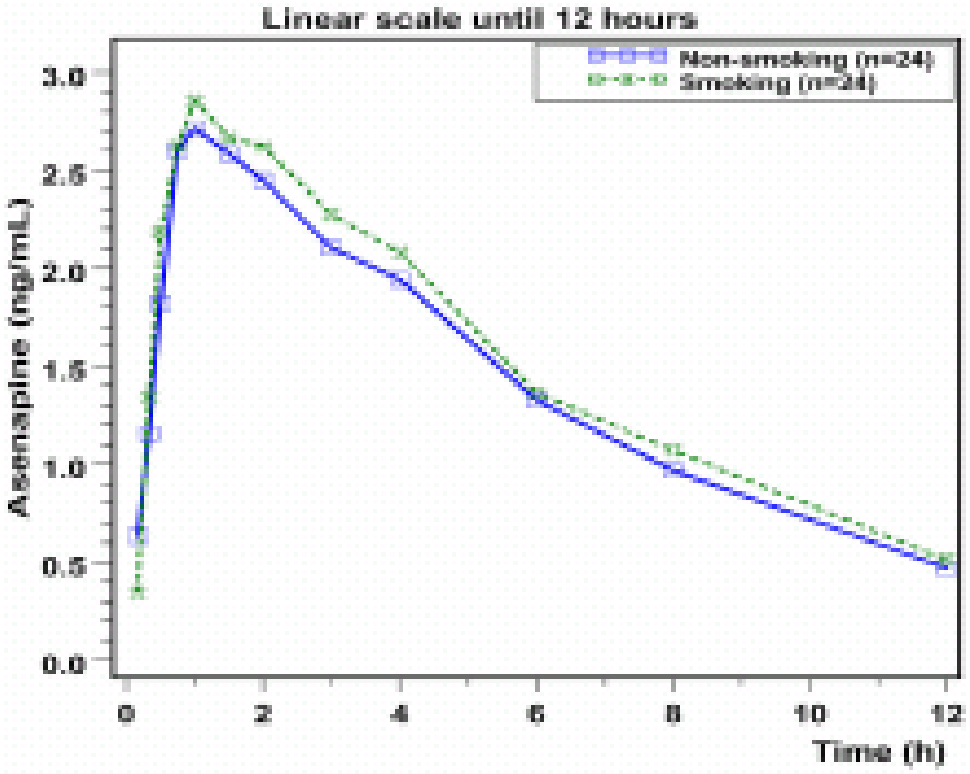


Figure 103 Mean Concentration vs. Time Profiles of Desmethyl-Asenapine in Chronic Smokers While Smoking and Not Smoking - Study 25545

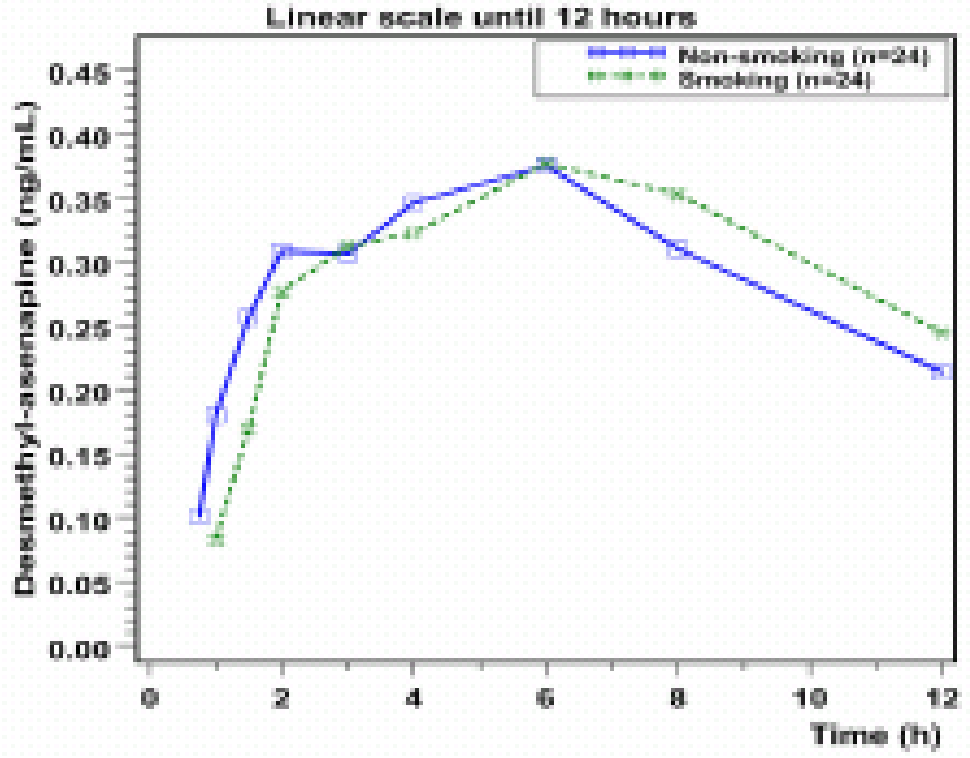


Table 117 Effect of Smoking a Cigarette on Asenapine and Desmethyl-Asenapine Pharmacokinetic Metrics in Chronic Smokers – Study 25545

	Asenapine			Desmethyl-Asenapine		
	Summary Statistics		GMR (90% CI)	Summary Statistics		GMR (90% CI)
	A: (+)-Cigarette	B: (-)-Cigarette	A:B With: Without Cigarette	A: (+)-Cigarette	B: (-)-Cigarette	A:B With: Without Cigarette
N	24	24	—	24	24	—
Tmax (h)	1.0 0.5 - 4.0	1.0 0.5 - 4.0	—	6.0 2.08 - 8.0	6.0 1.02 - 8.0	—
Cmax (ng/mL)	3.16 ± 1.73	3.00 ± 1.51	1.02 0.87 - 1.20	0.423 ± 0.153	0.427 ± 0.175	—
$AUC_{0-\infty}$ ($ng/mL \times hr^{-1}$)	25.6 ± 11.2	24.3 ± 10.1	1.06 0.91 - 1.24	7.33 ± 2.18 [a]	6.81 ± 2.01	—
CL/f (L/h)	237 ± 115	254 ± 139	—	n.c.	n.c.	—
wn - CL/f (L/h/kg)	3.16 ± 1.50	3.42 ± 1.95	—	n.c.	n.c.	—
t½ (h)	15.8 ± 12.1	17.1 ± 10.7	—	10.91 ± 2.971	11.1 ± 3.76	—

Presented mean refers to arithmetic mean. n.c.= not calculated
a n=23
Source: Appendix BI, Table 5 - 2.1.

5.5.7.5 Drug - Drug Interactions

5.5.7.5.1 Effect of Imipramine and Asenapine on Each Other - CYP2D6 Competitive Inhibition – Study 25526

This was a single centre, open label, randomized, six-sequence, three-period cross-over study in 24 healthy male subjects aged 18 - 55 years of age, in which a single dose of asenapine 5mg SL or imipramine 75 mg po was each administered alone or simultaneously. Treatments were as follows:

Treatment A Asenapine 5 mg SL x 1 alone
Treatment B Imipramine 75 mg PO x 1 alone
Treatment C Combined treatment of Asenapine 5 mg SL x 1 and Imipramine 75 mg PO x 1

As per the protocol imipramine was dosed after asenapine:

During treatments B and C, 50 mL of water was given with the imipramine dose.
In the combination treatment arm [C] imipramine was administered immediately before the asenapine dose.
During treatment A, 50 mL of water was given prior to asenapine dosing."

There was a washout period of at least 1 week between successive drug administrations.

The pharmacokinetics of asenapine and N-desmethyl asenapine was assessed in absence and presence of imipramine and the pharmacokinetics of imipramine and desipramine assessed in absence and presence of asenapine. Plasma samples were obtained through 72 hours.

Demographic characteristics are shown in Table 118.

Table 118 Demographic Characteristics at Screening All Subjects - Treated Group – Study 25526

N	Age [years]	Body Weight [kg]	Height [cm]	Body Mass Index [kg/m^2]
25	35 ± 12 18 - 54 [37]	78.6 ± 9.5 59.7 - 96.9 [77.3]	181 ± 6.8 165 - 194 [181]	24.1 ± 2.7 19.1 - 29.8 [24.3]

No differences in pharmacokinetics were shown between groups, (see Table 119 and Table 120), although there was trend for higher asenapine concentrations (~10%) in the presence of imipramine. However this was a single dose study and asenapine is a mechanism based inhibitor. Consequently when the drugs are administered simultaneously there may not be time for inactivation of CYP2D6 by asenapine to occur. Although the rationale for dosing imipramine prior to asenapine is so that ingestion of water will not send asenapine to the stomach this is also likely to minimize inhibition because

a) Imipramine is administered first
b) Inhibition is more likely to occur with oral administration both due to the higher asenapine concentrations in the liver during first pass as well as the presentation of asenapine first if it were to be administered first.

Consequently, the multiple dose study with paroxetine, study 25525, is more applicable to the actual clinical dosing in practice.

In addition, the low dose of asenapine used, 5 mg will also minimize presentation to the GI tract and subsequent mechanism based inhibition.

One possibility that was considered was the possibility that any effect of asenapine that might be evident in a delay in Tlag for desipramine in the asenapine treated group. Such as effect is seen, however a delay in Tlag for imipramine is also evident, (see Table 120, Table 121, and Figure 104). Consequently there is no clear evidence for competitive inhibition from the present study, however this does not preclude mechanism based noncompetitive inhibition, (see §5.5.7.5.2).

It should be noted that subject 008 was discontinued from the study for smoking however approximately 48 hours after taking imipramine he was found unconscious. Although according to the records it appears the cause might have been drinking and cannabis use, as according to the records he remembered the following:

'passing out at the train station and waking up in the hospital. He could not recall how and when he left neither the hospital, nor a conversation with the physician about a diagnosis. He recalled walking around town in Nijmegen all day long, feeling "out off the world". He apparently spent the night in a nearby hotel." '

"Physical examination was performed; an agitated, drunk man with a few cuts and bruises. He smoked constantly; there were no signs of psychosis or neurologic abnormalities. ECG, standing and supine vital signs were normal, heart rate elevated (98 bpm).

Laboratory results were not clinically relevant abnormal, except for an alcohol promillage of 2.2%. Due to agitation, a urine drug screen was not performed."

Upon examination this subject had the 4th highest exposures to imipramine and desipramine both by Cmax and 24 hour concentrations. This raises the possibility that this was at least partially due to the imipramine.

Examination of AEs with structurally similar compounds, indicate that some cause extreme sedation and when used in combination with alcohol or other CNS depressants can cause varying degrees of coma. Asenapine in some studies was described as causing severe somnolence. Consequently, this might be a pharmacokinetic and / or pharmacodynamic interaction.

Table 119 Asenapine and Desmethyl-Asenapine Pharmacokinetic Metrics in the Presence and Absence of Imipramine - Study 25526

Analyte	Asenapine					Desmethyl-Asenapine				
Metrics	Summary Statistics		Geometric Means		Geometric Mean Ratio (90% CI)	Summary Statistics		Geometric Means		Geometric Mean Ratio (90% CI)
Parameter (unit)	Asenapine	Asenapine + Imipramine	Asenapine	Asenapine + Imipramine		Asenapine	Asenapine + Imipramine	Asenapine	Asenapine + Imipramine	
n	24	24	—	—	23	24	24	23	—	—
Tmax (h)	0.75 0.50 - 3.0	0.875 0.50 - 2.0	—	—	—	6.00 2.00 - 8.05	3.0 1.5 - 12.0	—	—	—
Cmax (ng/mL)	4.87 (34.1) 2.67 - 9.01	5.39 (36.6) 0.874 - 10.5	4.56	5.33	1.17 1.05 - 1.30	0.490 (33.5) 0.313 - 1.08	0.541 (28.3) 0.299 - 0.881	0.476	0.521	1.09 1.03 - 1.17
AUCtlast (ng/mL x hr^{-1})	35.4 (27.3) 19.5 - 52.1	36.4 (24.6) 8.93 - 50.1	33.8	36.9	1.09 1.01 - 1.18	10.1 (37.7) 5.74 - 23.3	10.2 29.3 5.73 - 17.4	9.59	9.77	1.02 0.95 - 1.09
AUC∞ (ng/mL x hr^{-1})	38.1 (29.4) 21.9 - 63.8	39.2 (25.2) 10.3 - 54.6	36.1	39.7	1.10 1.01 - 1.20	11.7 (34.8) 7.04 - 25.2	12.1 (29.1) 7.13 - 20.0	11.1	11.6	1.04 0.98 - 1.11
CL/F (L/h)	143 (28.9) 78.3 - 228	144 (54.6) 91.5 - 488	—	—	—	445 (28.0) 188 - 675	427 (28.4) 238 - 667	—	—	—
Vz/F (L)	4934 (54.6) 1138 - 12392	5391 (48.1) 2186 - 10964	—	—	—	9085 (29.6) 3331 - 15967	9181 (45.6) 4338 - 26230	—	—	—
t½ (h)	25.5 (59.9) 8.13 - 66.8	28.7 (56.4) 9.94 - 83.0	—	—	—	14.6 (28.6) 9.29 - 24.3	15.4 (40.0) 9.07 - 34.2	—	—	—

Values are mean (%CV) range expect for Tmax where values are median and range.

Table 120 Imipramine and Desmethyl- Imipramine Pharmacokinetic Metrics in the Presence and Absence of Asenapine - Study 25526

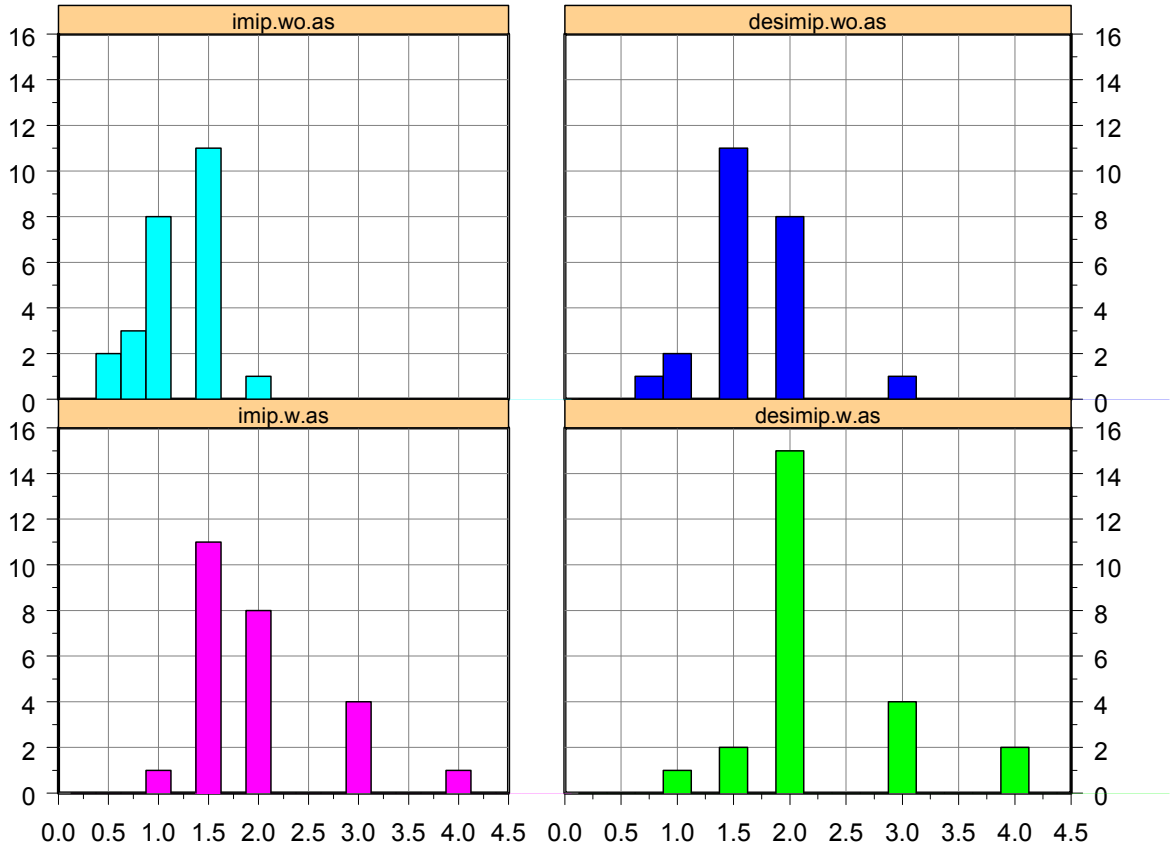
Analyte	Imipramine					Desipramine				
Metrics	Summary Statistics		Geometric Means		Geometric Mean Ratio (90% CI)	Summary Statistics		Geometric Means		Geometric Mean Ratio (90% CI)
Parameter (unit)	Imipramine	Asenapine + Imipramine	Imipramine	Asenapine + Imipramine		Imipramine	Asenapine + Imipramine	Imipramine	Asenapine + Imipramine	
n	24	24				24	24			
Tlag (h)	1.0 0.5 – 2.0	2.0 1.0 – 4.0				1.5 0.75 – 3.0	2.0 1.0 – 4.0			
Tmax (h)	2.50 1.50 - 4.00	2.00 1.50 - 4.00				3.00 1.50 - 24.0	4.00 1.50 - 24.2			
Cmax (ng/mL)	44.6 (47.1) 10.4 - 98.7	45.0 (44.4) 17.7 - 83.8	41.9	42.0	1.00 0.91 - 1.11	12.8 (45.4) 3.45 - 25.3	13.4 (37.1) 6.22 - 23.4	12.2	12.7	1.04 0.98 - 1.11
AUCtlast (ng/mL x hr^{-1})	483 (60.5) 64.3 - 1060	505 (56.4) 164 - 1153	423	440	1.04 0.97 - 1.12	463 (87.0) 11.4 - 1390	466 (78.3) 78.8 - 1235	340	343	1.01 0.96 - 1.06
AUC∞ (ng/mL x hr^{-1})	542 (58.2) 91.4 - 1175	571 (56.7) 183 - 1364	483	501	1.04 0.97 - 1.10	801* (102) 154 - 3223	889 (105) 133 - 3461	521	560	1.08 0.99 - 1.17
CL/F (L/h)	210 83.1) 63.9 - 820	173 (52.5) 55.0 - 410				191* (71.3) 22.1 - 463	185 (74.9) 20.6 - 537			
Vz/F (L)	2956 (40.7) 1358 - 6788	2902 (30.4) 1175 - 4507				6334* (51.3) 2641 - 16095	6442 (45.3) 2687 - 14757			
t½ (h)	12.3 (37.7) 4.68 - 23.1	13.7 (44.5) 6.87 - 31.7				32.9* (58.1) 12.6 - 82.8	41.4 (96.1) 13.7 - 190			

Values are mean (%CV) range expect for Tmax where values are median and range.

Table 121 Runs Analysis for Lag Times for Imipramine and Desipramine in the Absence and Presence of Asenapine – Study 25526

	Asenapine	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Imipramine	-	2	1	1.5	0.75	1.5	1.5	1.5	1.5	1	1	1.5	0.5	1	1	0.75	1	1.5	0.75	1.5	1.5	1.5	1	0.5	1	1.5
	+	2	1	2	1.5	1.5	2	1.5	1.5	2	2	3	2	1.5	2	2	1.5	4	1.5	1.5	3	3	3	1.5	1.5	1.5
	Runs	*	*	+	+	*	+	*	*	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*
Desipramine	-	3		2	1	1.5	2	2	1.5	1.5	2	2	2	1.5	1.5	1.5	1.5	2	1		1.5	1.5	1.5	0.75	1.5	2
	+	3		4	2	2	4	2	2	2	2	3	2	2	2	2	2	3	1.5	1	2	2	3	1.5	2	2
	Runs	*		+	+	+	+	*	+	+	*	+	*	+	+	+	+	+	+		+	+	+	+	+	+

Figure 104 Comparison of Tlags for Imipramine and Desipramine in the Absence and Presence of Asenapine – Study 25526[a]



a imip = imipramine; desimip = desipramine; as = asenapine; w = with; wo = without

5.5.7.5.2 CYP2D6 Interactions - Study 25525

Study 25525 was an open label, randomized, parallel group, pharmacokinetic interaction trial between asenapine, paroxetine and dextromethorphan in healthy male subjects aged 18 – 55 years of age.

Treatments were as follows:

Treatment Sequence A:	Day 1:	Paroxetine 20 mg PO x 1
	Days 4 - 16:	Asenapine 5 mg SL BID
	Day 12:	Dextromethorphan 30 mg x 1
	Day 14:	Paroxetine 20 mg PO x 1
Treatment Sequence B:	Day 2:	Asenapine 5 mg SL x 1
	Days 7 - 15:	Paroxetine 20 mg PO QD
	Day 11:	Dextromethorphan 30 mg x 1
	Day 13:	Asenapine 5 mg SL x 1

Seventeen subjects were included in sequence A and there were thirteen completers.

Thirty subjects were included in sequence B and there were twenty-six completers.

In both arms the 8 hour Urinary Metabolic Ratio of DX to DM was determined at screening and during treatment.

The single dose pharmacokinetics of paroxetine, asenapine, and desmethyl-asenapine were assessed.

The sponsor used inconsistent nomenclature throughout the report for the two sequences. Table 122 shows the study design and the nomenclatures used for this report.

Table 122 Study Design for Paroxetine / Asenapine Drug-Drug Interaction Study - Study 25525

Objective		Effect of Asenapine on Paroxetine & Dextromethorphan		Effect of Paroxetine on Asenapine & Dextromethorphan	
Nominal Designations Used	*Treatment Sequence*	A		B	
	CSR Statistical Analysis Arm[8]	B		A	
	PK Report SAS Analysis Arm	A		B	
	Treatment Arm	A		B	
	Pharmacokinetic Arm	A		B	
Treatments	*Screening*	DM 30 mg PO to determine 8 hour DX:DM UMR		DM 30 mg PO to determine 8 hour DX:DM UMR	
	Day 1		Paroxetine 20 mg SD		Placebo
	Day 2				Asenapine 5 mg SL
	Day 3		Placebo		
	Day 4	Asenapine 1 mg SL BID			
	Day 5	Asenapine 3 mg SL BID			
	Day 6	Asenapine 5 mg SL BID		Paroxetine 20 mg PO QD	
	Day 7				
	Day 8				
	Day 9				
	Day 10				
	Day 11				DM 30 mg PO to determine 8 hour DX:DM UMR
	Day 12		DM 30 mg PO to determine 8 hour DX:DM UMR		
	Day 13		Placebo Paroxetine		Placebo Asenapine
	Day 14		Paroxetine 20 mg SD		Asenapine 5 mg SL
	Day 15				
	Day 16				

[8] The reversal of the nominal designation was per the clinical study report. The statistical report and these nomenclature were used to assign the the precipitant to Table 127 and Figure 109 for the effect on dextromethorphan as the labeling that the sponsor used on tables was confusing. After the briefing on May 12, 2008 it was discovered that this reversal of the coding did not occur after all and the attribution of the effects of asenapine and paroxetine had been reversed. It has therefore been corrected in this final version.

5.5.7.5.2.1 Evaluation of Asenapine as a CYP2D6 Inhibitor (Effect of Asenapine on Paroxetine)

In sequence A (aka Arm B; aka Concentration Profile Arm A), the effect of multiple doses of asenapine on the (single dose) pharmacokinetics of paroxetine was studied. In addition, the effect of asenapine on the metabolic ratio of dextromethorphan as a probe substrate for CYP2D6 was investigated. The baseline Dextromethorphan : Dextorphan (DM/DX) ratio was determined at screening. Paroxetine 20 mg was administered as a single dose on day 1 and placebo on day 3. On Day 4 titration with asenapine SL BID was begun and 5 mg SL BID was administered from days 6 – 16. On Day 12, dextromethorphan (30 mg single dose) was co-administered, and on Day 13 and 14, single doses of placebo and paroxetine 20 mg PO were administered respectively.

As shown in Figure 105 and Table 123 asenapine 5 mg SL BID approximately doubles both the exposure and peak concentrations of paroxetine.

Figure 105 Single Dose Concentration vs. Time Profiles of Paroxetine 20 mg in the Absence of and Presence of Asenapine 5 mg BID in CYP2D6 Extensive Metabolizers – Study 25525

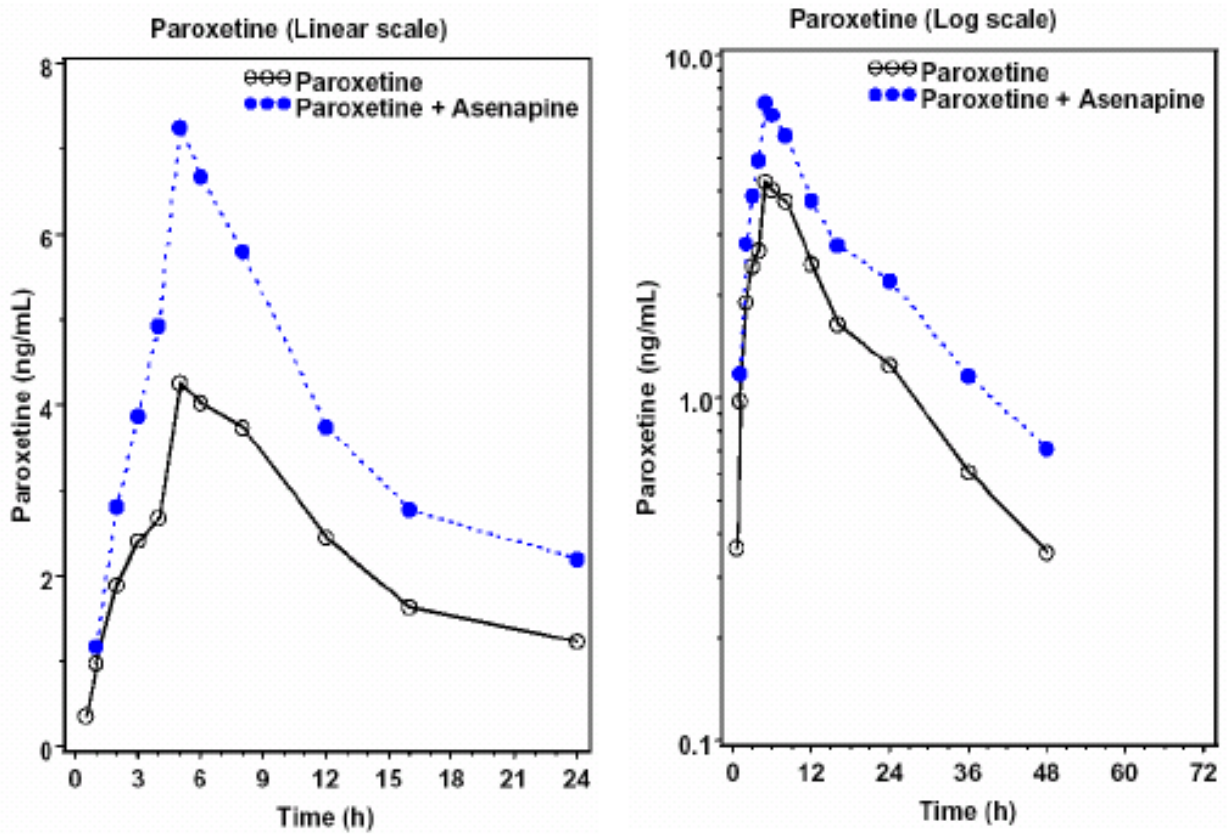


Table 123 Effect of Asenapine 5 mg SL BID on the Pharmacokinetics of Paroxetine 20 mg – Study 25525

	Summary Statistics		Geometric Means		Paroxetine +/- Asenapine Geometric Mean Ratio (90% CI)
	Paroxetine	Paroxetine & Asenapine	Paroxetine	Paroxetine & Asenapine	
N	15	15	15	15	—
Tmax (h)	5.6 ± 2.06 (36.8) 1.02 - 8 [6]	5.2 ± 1.08 (20.8) 3 - 8 [5]	5.03	5.1	—
Cmax (ng/mL)	4.46 ± 3.93 (88) 0.673 - 13.5 [2.72]	7.49 ± 5.83 (77.8) 1.93 - 21.9 [5.49]	3.15	5.73	1.82 1.59 - 2.09
AUCtlast (ng/mL x hr^{-1})	74.1 ± 79.2 (107) 7.65 - 241 [40.6]	128 ± 127 (99.5) 21.2 - 426 [86.4]	43.2	83.7	1.94 1.71 - 2.20
AUC∞ (ng/mL x hr^{-1})	77.7 ± 80.9 (104) 8.62 - 245 [42.9]	136 ± 137 (101) 23.7 - 470 [92.3]	46.9	90	1.92 1.70 - 2.17
AUCextrap (%)	7.71 ± 4.94 (64) 1.56 - 18.6 [5.38]	6.82 ± 5.07 (74.4) 1.77 - 22.7 [6.39]	6.41	5.54	—
Tlast (h)	47.2 ± 16 (33.9) 24 - 72 [48]	52.8 ± 15.6 (29.5) 24 - 72 [48]	44.5	50.5	—
CL/F (L/h)	708 ± 742 (105) 81.7 - 2319 [466]	321 ± 272 (84.8) 42.5 - 845 [217]	427	222	—
wn−CL/F (L/h/kg)	9.16 ± 10.7 (117) 1.05 - 37.5 [4.74]	4.08 ± 3.74 (91.6) 0.552 - 11.8 [2.56]	5.25	2.74	—
Vz/F (L)	10318 ± 8671 (84) 1385 - 28679 [7447]	5531 ± 4593 (83) 1230 - 15302 [3654]	7064	4025	—
wn−Vz/F (L/kg)	130 ± 115 (88.6) 18.3 - 357 [91.4]	71.4 ± 68 (95.3) 15.5 - 247 [42]	87	49.6	—
t½ (h)	12.9 ± 3.09 (24) 8.89 - 20 [12.8]	11.8 ± 2.69 (22.8) 6.12 - 16 [11.6]	12.6	11.5	—

5.5.7.5.2.2 Evaluation of CYP2D6 Inhibition on Asenapine (Effect of Paroxetine on Asenapine)

In sequence B (aka Arm A; aka Concentration Profile Arm B), the effect of multiple doses of paroxetine on the (single dose) pharmacokinetics of asenapine was studied. In addition, the effect of paroxetine on the metabolic ratio of dextromethorphan as a probe substrate for CYP2D6 was investigated. The baseline DM/DX ratio was determined at Screening. After a placebo dosing on Day 1, asenapine (5 mg) was given at Day 2. Paroxetine 20 mg once daily was given for 9 days (Day 7-15). On Day 11, dextromethorphan (30 mg single dose) was co-administered. On Days 12 and 13, placebo and asenapine (5 mg single dose) were co-administered, respectively.

The maximum usual starting dose for paroxetine is 20 mg QD and the maximum labeled dose is 60 mg QD for the IR formulation or 75 mg QD for the MR formulation.

There was a slightly lower exposure to asenapine in the presence of steady-state dosing of paroxetine but this was not significant, (see Figure 107 and Table 125).

In contrast, there was a 26% increase in exposure to desmethyl-asenapine (see Figure 108 and Table 125), presumably due to inhibition of CYP2D6 N-oxidation.

For desmethyl-asenapine, pre-dose concentrations above LLOQ, (0.05 ng/mL), were found for 8 of the 26 subjects during the second dosing period in arm B, (see Table 124).

Table 124 Predose Desmethyl-Asenapine Concentrations in Selected Subjects

Subject	Desmethyl-Asenapine C0 (ng/mL)	AUC_{0-72} correction
20	0.0537	3.87
24	0.133	9.58
28	0.0611	4.40
35	0.116	8.35
38	0.138	9.94
40	0.0789	5.68
122	0.121	8.71
129	0.0616	4.44

When these 8 subjects are excluded from the analysis as was done by the sponsor, or when the maximum possible AUCs attributable to these high baseline concentrations are subtracted as was done by this reviewer, the increase in exposures to desmethyl-asenapine are only around 10%, (see Table 126).

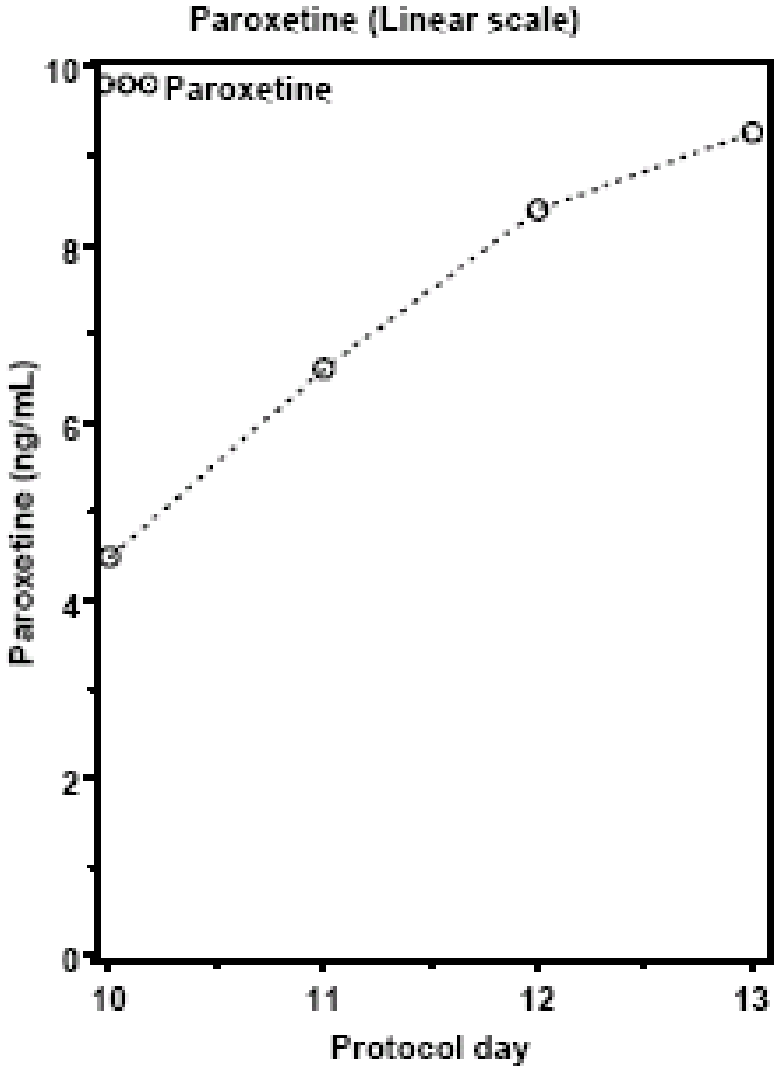
According to the sponsor,*"bioanalysis indicated that dextromethorphan interferes with the desmethyl-asenapine assay and as dextromethorphan was given 48 h before asenapine dosing in the second period this might be the explanation as washout from asenapine in first dosing period was long enough."*

The sponsor's claims were checked and there appears to be a 40% interference from DM and DX at 200 and 50 ng/mL respectively. Since concentrations of dextrorphan (DX) and dextromethorphan (DM) are typically less than 10 ng/ml at 48 hours post-dose, and since the amount of interference is on the order of 0.54 - 0.138 ng/ml it's uncertain if this is the true reason for the interference.

In contrast, Figure 106 shows that even after 7 days of dosing paroxetine trough concentrations are still increasing at a dose of 20 mg qd. Although paroxetine does exhibit nonlinear kinetics, even at a higher

dose of 30 mg mean half-life is 15 -22 hours with maximal half-lives of 65 hours. Conseqeuntly, steady-state should have already been reached (7 days = 156 hours). Instead it's likely that irreversible inhibition from the initial dose of asenapine 7 days before, was still inhibiting the elimination of paroxetine and this increased paroxetine resulting in the inhibition of CYP2D6 metabolism of N-desmethyl-asenapine, as well as the remaining inactivated CYP2D6 from the previouse dose of asenapine are acting together to increase the exposure to N-desmethyl-asenapine.

Figure 106 Mean Paroxetine Trough Concentrations vs. Time - Study 25525



Consequently, the degree of accumulation of desmethyl-asenapine and paroxetine when both are given in combination could be quite high under clinical dosing conditions and could result in an increased incidence of hepatotoxicity or other toxicities. Thus the present study clearly does not provide sufficient assurances of safety under clinical use.

Figure 107 Single Dose Concentration vs. Time Profiles of Asenapine 5 mg SL in the Absence and Presence of Paroxetine 20 mg qd in CYP2D6 EMs and PMs after a single 30 mg dose of Detromethorphan – Study 25525

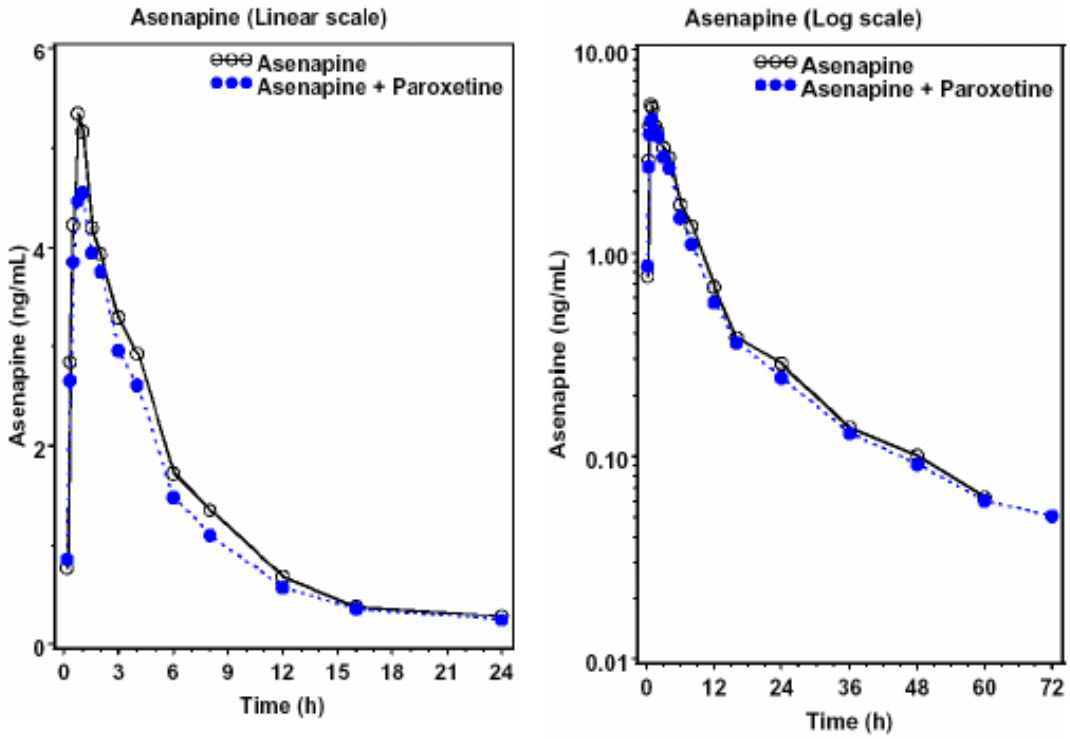


Figure 108 Single Dose Concentration vs. Time Profiles of Desmethyl-Asenapine after Asenapine 5 mg SL in the Absence and Presence of Paroxetine 20 mg qd in CYP2D6 EMs and PMs after a single 30 mg dose of Dextromethorphan – Study 25525

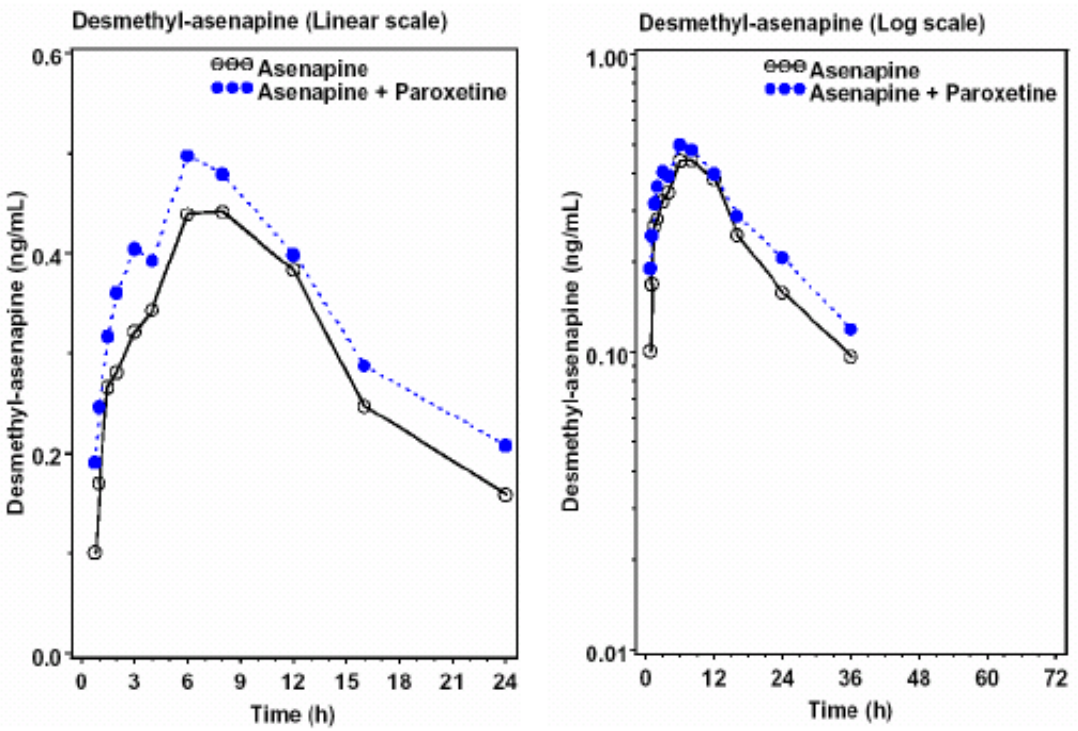


Table 125 Effect of Paroxetine 20 mg qd on the Pharmacokinetics of Asenapine 5 mg SL BID in Study 25525 Arm: [B] Asenapine vs. Asenapine + Paroxetine

	Summary Statistics		Geometric Means		Asenapine +/- Paroxetine Geometric Mean Ratio (90% CI)
	Asenapine	Asenapine & Paroxetine	Asenapine	Asenapine & Paroxetine	
N	26	26	26	26	
Tmax (h)	1.04 ± 0.63 (60.4) 0.5 - 3 0.875	1.07 ± 0.53 (49.2) 0.33-3 3 1	0.928	0.979	
Cmax (ng/mL)	5.7 ± 2.09 (36.6) 1.67 - 11.7 5.29	4.95 ± 1.8 (36.3) 2.49 - 9.02 4.52	5.33	4.66	0.87 0.80 - 0.96
AUCtlast (ng/mL x hr^{-1})	36.4 ± 10.9 (29.9) 19.5 - 65.9 34.5	32.6 ± 8.99 (27.6) 18.6 - 50.5 30.1	35	31.4	0.90 0.84 - 0.96
AUC∞ (ng/mL x hr^{-1})	38.4 ± 11.7 (30.5) 20.1 - 68.2 36.1	34.7 ± 9.62 (27.8) 19.3 - 55.4 32.4	36.8	33.4	0.91 0.85 - 0.97
AUCextrap (%)	4.91 ± 3.14 (63.9) 1.42 - 12.3 3.78	5.78 ± 4.13 (71.4) 1.09 - 23.1 4.81	4.14	4.89	
CL/f (L/h)	142 ± 42.3 (29.9) 73.3 - 249 139	156 ± 44.8 (28.8) 90.2 - 260 154	136	150	
wn−CL/f (L/h/kg)	1.77 ± 0.612 (34.5) 0.77 - 3.39 1.69	1.94 ± 0.616 (31.8) 1.01 - 3.47 1.83	1.67	1.85	
Vz/f (L)	4506 ± 1878 (41.7) 1979 - 8042 3884	5759 ± 3110 (54) 2040 - 17976 5228	4136	5182	
wn−Vz/f (L/kg)	55.9 ± 23.9 (42.9) 20.8 - 98.6 45.5	71.5 ± 40.2 (56.2) 26.5 - 225 65.2	51	63.9	
t½ (h)	22.6 ± 9.52 (42.2) 12.3 - 54.2 19	26.9 ± 16.3 (60.6) 8.74 - 96.4 23.3	21.1	24	

Table 126 Effect of Paroxetine 20 mg qd on the Pharmacokinetics of Desmethyl-Asenapine in Study 25525 Arm: [B] asenapine vs. asenapine + paroxetine

	Summary Statistics		All Subjects			Excluding Subjects with Baseline Values above LLOQ 0.05 ng/mL		
			Geometric Means		GMR (90% CI)	Geometric Means		GMR (90%)
	Asenapine	Asenapine + Paroxetine	Asenapine	Asenapine + Paroxetine	Asenapine + Paroxetine : Asenapine	Asenapine	Asenapine + Paroxetine	Asenapine + Paroxetine : Asenapine
n	26	26	26	26	26	18	18	18
Tmax (h)	7.1 ± 2.45 (34.5) 1.5 - 12 [7.02]	6.47 ± 2.49 (38.5) 2 - 12 [6]	6.6	5.91				
Cmax (ng/mL)	0.52 ± 0.31 (59.5) 0.18 - 1.43 [0.42]	0.55 ± 0.20 (37.2) 0.28 – 1.0 [0.52]	0.45	0.517	1.14 1.03 - 1.26	0.41	0.46	1.11 1.01 - 1.23
AUCtlast (72 hours) (ng/mL x hr^{-1})	9.1 ± 4.95 (54.5) 1.8 - 23.8 [8.29]	11.8 ± 6.12 (51.8) 5.64 - 26.2 [9.14]	7.96	10.6	1.33 1.18 - 1.49	7.36	8.73	1.18 1.05 - 1.34
						8.01	8.82[a]	1.10
AUC∞ (ng/mL x hr^{-1})	11.7 ± 5.58 (47.8) 2.59 - 26.6 [10.8]	14.2 ± 5.9 (41.7) 8 - 28.2 [11.3]	10.5	13.2	1.26 1.11 - 1.42	10.1	11.3	1.12 0.99 - 1.27
%extrap (%)	23.2 ± 12 (51.8) 5.42 - 48.4 [22.7]	18.7 ± 12.4 (66) 3.2 - 50.2 [13.7]	19.9	15.5				
CL/F (L/h)	514 ± 322 (62.6) 178 - 1835 [439]	383 ± 126 (32.8) 169 - 594 [420]	453	361				
wn−CL/F (L/h) / kg	6.25 ± 3.32 (53.1) 2.14 - 18.8 [5.72]	4.72 ± 1.55 (32.8) 2.11 - 8.21 [4.81]	5.58	4.44				
Vz/F (L)	13809 ± 7702 (55.8) 2694 - 30718 [11927]	11507 ± 6588 (57.2) 2546 - 27382 [9946]	11692	9915				
wn−Vz/F (L/kg)	166 ± 85.2 (51.2) 32.3 - 343 [151]	139 ± 72.6 (52.2) 30.5 - 317 [121]	144	122				
t½ (h)	20.5 ± 11.4 (55.4) 7.23 - 51.6 [19.2]	21.1 ± 9.97 (47.2) 6.91 - 48.7 [18.6]	17.9	19.1				

a GMR – Geometric Mean Ratio
b calculated by subtracting baseline

5.5.7.5.2.3 Comparative Evaluation of Asenapine and Paroxetine as CYP2D6 Inhibitors (Effects on Dextromethorphan)

Table 127 shows the comparative effects of asenapine and paroxetine on dextromethorphan.

The DX/DM ratio after paroxetine is about 7.5% of the DX/DM ratio after asenapine demonstrating that paroxetine is a more potent inhibitor. However the degree of effect on the DX/DM ratio is due to a combination of changes in both dextrorphan and dextromethorphan. Examination of the relative exposures to dextromethorphan is a better measure of the relative potency, and Table 127 shows dextromethorphan post dosing to pre-dosing GMRs of 13.1 for paroxetine compared with 1.55 for asenapine, however these are just means. When individual values are compared some subjects in the paroxetine group have exposures of nearly 45 times higher in the presence of paroxetine, whereas no one receiving asenapine had an increase of even 10 fold, (see Figure 109). However this was the low dose of asenapine and the effect would likely be greater with the 10 mg dose.

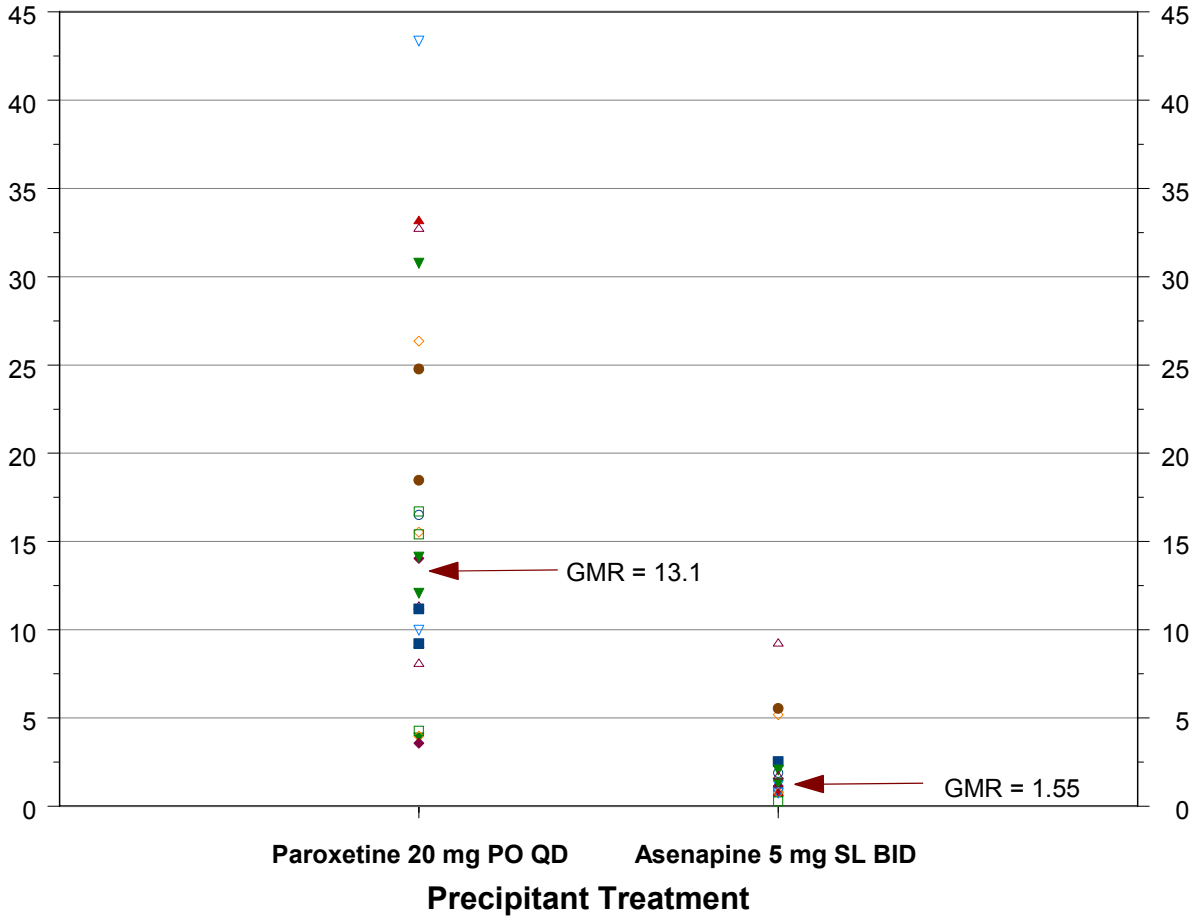
To demonstrate why comparing DX/DM ratios is flawed we need to remember that with inhibition the numerator DX will decrease and denominator DM will increase so the estimate of the degree of inhibition will be compounded consequently this is an invalid way of comparing the relative degree of inhibition with different compounds. Since the increased exposure to dextromethorphan is what is clinically important we need to compare the relative increases. Consequently the ratio of asenapine DX/DM / paroxetine DX/DM ratios is 13.44 (i.e. 0.43 / 0.032 or the inverse of 7.5%) whereas if we simply compare the GMRs of DM pre and post dosing for the two treatments we find that paroxetine has a 8.45 greater effect on dextromethorphan (i.e. 13.1 / 1.55).

Table 127 Summary of Dextromethorphan and Dextrorphan, and Dextrorphan/Dextromethorphan Ratio in Urine

Treatment Arm	Objective Substrate	Objective Substrate + Test Precipitant	N	Parameter (unit)	Summary Statistics of Individual Ratios of Dextromethorphan Recovery in Urine During – Treatment : Pre - Treatment[a]	Geometric Means		Geometric Mean Ratio During - Treatment : Pre – Treatment (95% CI)
						Pre - Treatment	During - Treatment	
Arm A (Effect of Asenapine on CYP2D6)	Paroxetine 20 mg	Paroxetine 20 mg + Asenapine 5 mg SL BID	15	Dextromethorphan (µg)	2.3 ± 2.5 (104.8) 0.3 - 9.2 [1.3]	43.6	67.7	1.55 0.93 - 2.59
				Dextrorphan (µg)		311	205	0.66 0.49 - 0.89
				Dextrorphan / Dextromethorphan ratio		7.14	3.03	0.43 0.32 - 0.56
				Approximate Amount Recovered (µg)		354.6	272.7	
				Recovery		1.18 %	0.91 %	Expected Direction
Arm B (Effect of Paroxetine on CYP2D6)	Asenapine 5 mg SL	Asenapine 5 mg SL + Paroxetine 20 mg QD	23	Dextromethorphan (µg)	16.2 ± 10.6 (65.4) 3.6 - 43.4 [14.1]	21.1	277	13.1 9.57 - 17.9
				Dextrorphan (µg)		250	104	0.41 0.29 - 0.60
				Dextrorphan / Dextromethorphan ratio		11.8	0.375	0.032 0.023 - 0.043
				Approximate Amount Recovered (µg)		271.1	381	
				Recovery		0.90 %	1.27 %	?

a Values are mean ± SD, (%CV), Range, [Median]

Figure 109 Ratio of Amount of Dextromethorphan Recovered in an 8 hour Urine Collection under Steady-State Dosing of Asenapine or Paroxetine as Compared to the Amount Recovered at Baseline – Study 25525



5.5.7.5.3 Effect of Valproate on Asenapine - Effect on 2C9, 3A4(?) and Glucuronidation - Study 25527

Study 25527 was an open-label, randomized, two-way cross-over study to investigate the effect of steady state valproate on the single dose pharmacokinetics of 5 mg asenapine in 24 healthy male subjects aged 18 – 55 years of age.

Treatment A: Asenapine 5 mg SL x 1
Treatment B: Days 1-9: Valproate (Depakine® enteric tablet): 500 mg, PO BID
Day 6: Asenapine (Org 5222) placebo: SL
Day 7: Asenapine (Org 5222) 5 mg SL

There was a washout of at least 2 weeks between successive treatment periods.

The pharmacokinetics of asenapine, N-desmethyl asenapine, and asenapine N-glucuronide were measured in absence and presence of valproate. The pharmacokinetics of valproate and its metabolites were not assessed.

Subject demographics are shown in Table 128, and pharmacokinetic metrics are shown in Table 129.

Table 128 Demographic Characteristics by Treated Group – Study 25527

Sequence	N	Age [years]	Weight [kg]	Height [cm]	Body Mass Index [kg/m^2]
AB	24	30 ± 7.7 19 - 41 [29]	79.3 ± 10.4 69.1 - 106.5 [77.0]	183 ± 7.5 172 - 196 [184]	23.5 ± 2.2 20.7 - 27.7 [23.1]
BA	24	33 ± 11.3 19 - 53 [32]	77.8 ± 9.6 62.6 - 91.8 [76.3]	179 ± 7.0 171 - 193 [178]	24.2 ± 2.2 20.8 - 27.4 [24.7]

There was no clear effect of valproate on total asenapine Cmax or AUC, (seeTable 129 and Figure 110).

The extent of exposure for desmethyl - asenapine as expressed by AUC∞ was on average 30% lower in the presence of valproate whereas no effect was seen on Cmax, (see Table 129 and Figure 111). This may indicate decreased formation of desmethyl–asenapine by inhibition of CYP2C9, which is polymorphic.

The effect of valproate on the pharmacokinetics of asenapine–glucuronide was to decrease both AUC∞ and Cmax on average by 85%, meaning exposure in the presence of valproate was 1/7 the exposure in the absence of valproate, (see Table 129 and Figure 112). This appears to indicate that Valproate competes with glucuronidation by UDPGT1A4 with not much effect on active secretion.

Regarding side effects there were more side effects for asenapine when given in combination with valproate as compared to when given alone. The greater values are as follows:

Fatigue 6 (25%) vs. 2 (8%)
Headache 6 (25%) vs. 1 (4%)

Unfortunately the effect of asenapine on valproate was not examined. In addition, there still exists the possibility of a pharmacodynamic intereaction via mitochondrial metabolism that this study was not designed to detect.

Table 129 Asenapine, Desmethyl-Asenapine, and Asenapine Glucuronide 5 mg SL Single Dose PK Parameters in the Absence and Presence of Valproate 500 mg PO BID – Study 25527

Parameter (unit)	Asenapine			Desmethyl-Asenapine			Asenapine-Glucuronide		
	Asenapine	Asenapine + Valproate	GMR (90% CI)	Asenapine	Asenapine + Valproate	GMR (90% CI)	Asenapine	Asenapine + Valproate	GMR (90% CI)
N	24	24	—	24	24	—	24	24	—
Tmax (h)	0.875 0.333 - 1.50	0.750 0.333 - 1.50	—	6.00 1.50 - 12.0	3.50 1.50 - 12.0	—	4.00 3.00 - 6.02	3.03 2.00 - 6.05	—
Cmax (ng/mL)	5.74 (50.5) 2.38 - 15.9	5.79 (46.2) 1.64 - 15.5	1.02 0.91 - 1.15	0.409 (32.5) 0.252 - 0.791	0.399 (42.7) 0.149 - 0.943	0.94 0.85 - 1.04	6.01 (48.9) 2.21 - 12.7	0.987 (64.9) 0.250 - 2.58	0.15 0.13 - 0.18
	5.18 [a]	5.30 [a]		0.39 [a]	0.37 [a]		5.34 [a]	0.81 [a]	
AUCtlast (ng/mL x hr^{-1})	34.3 (29.5) 16.6 - 56.7	33.2 (26.8) 16.2 - 53.0	0.98 0.90 - 1.06	8.19 (41.0) 4.48 - 19.1	5.74 (57.7) 0.829 - 18.1	0.65 0.55 - 0.76	70.9 (49.6) 18.0 - 152	6.50 (74.2) 0.125 - 18.4	0.06 0.04 - 0.10
	32.7 [a]	32.0 [a]		7.69 [a]	4.96 [a]		62.1 [a]	3.92 [a]	
AUCtlast (ng/mL x hr^{-1})	35.9 (29.8) 17.1 - 58.3	35.3 (27.4) 17.5 - 55.4	0.99 0.91 - 1.08	9.70 (36.9) 5.54 - 21.2	7.14 (44.4) 3.65 - 19.1	0.70 0.64 - 0.77	76.2 (46.8) 25.3 - 159	10.4 (40.5) 4.93 - 21.8	0.14 0.12 - 0.16
	34.2 [a]	33.9 [a]		9.52 [a]	6.67 [a]		72.3 [a]	9.82 [a]	
CL/f (L/h)	154 (36.2) 85.8 - 293	154 (31.7) 90.3 - 286	—	541 (29.0) 224 - 859	752 (31.5) 249 - 1304	—	133 (51.2) 51.0 - 321	905 (39.7) 372 - 1644	—
t½ (h)	22.9 (37.9) 8.27 - 38.8	27.6 (37.8) 9.24 - 57.4	—	14.2 (28.0) 7.72 - 24.2	10.3 (21.0) 6.74 - 14.7	—	9.36 (74.0) 4.53 - 33.8	5.08 (33.7) 2.86 - 9.25	—

a Geometric Mean

Figure 110 Mean Asenapine Concentration vs. Time Profiles in the Absence and Presence of Valproate – Study 25527

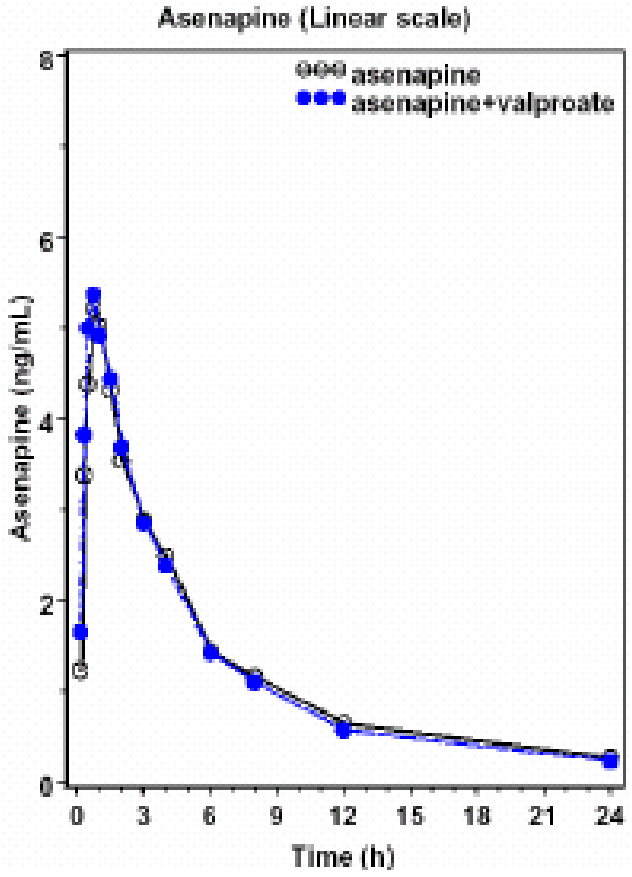


Figure 111 Mean Desmethyl-Asenapine Concentration vs. Time Profiles in the Absence and Presence of Valproate – Study 25527

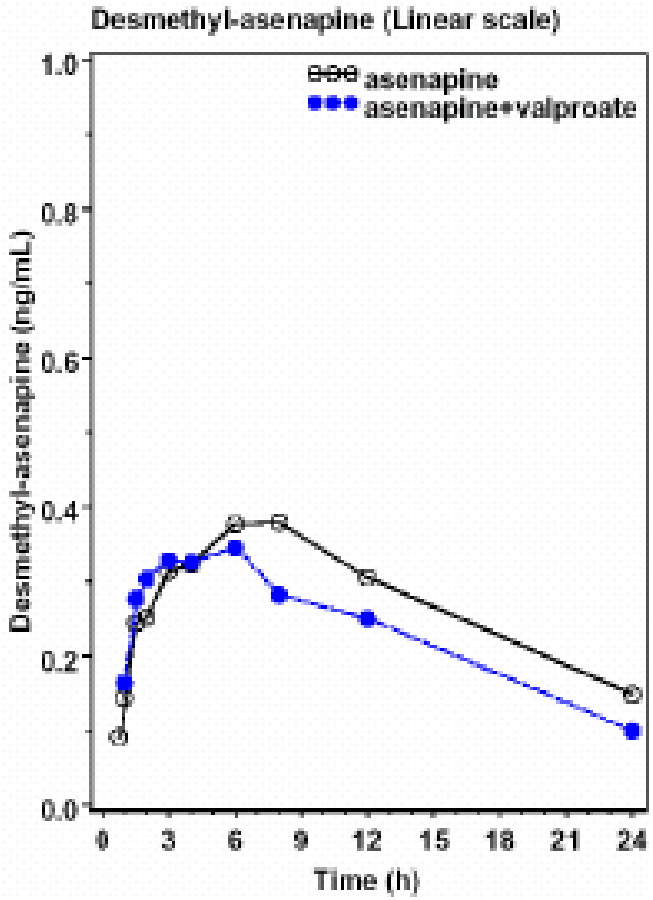
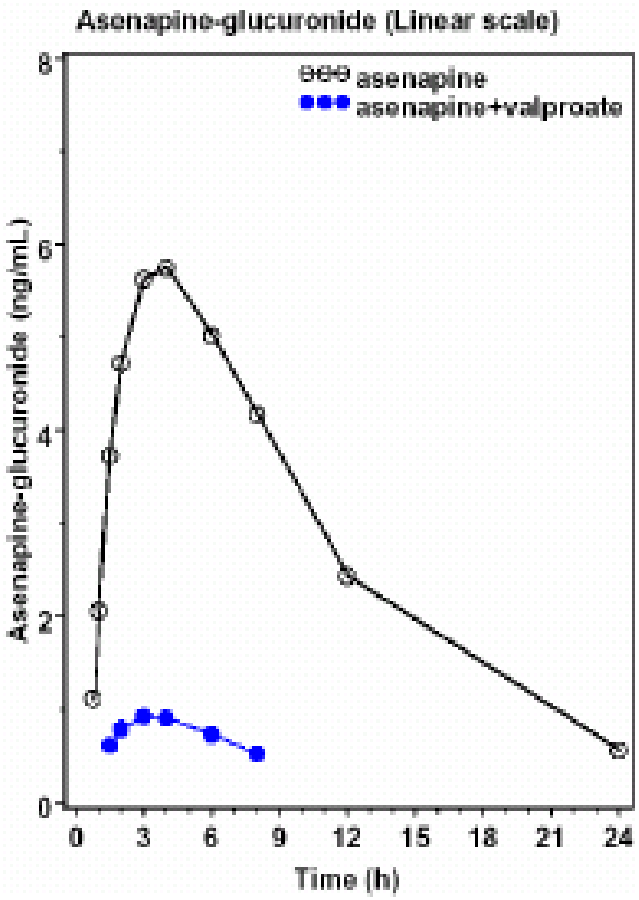


Figure 112 Mean Asenapine Glucuronide Concentration vs. Time Profiles in the Absence and Presence of Valproate – Study 25527



5.5.7.5.4 Effect of Carbamazepine on Asenapine - Study 25528

Study 25528 was a single center, open label, single arm study in 24 healthy male subjects 18 - 45 years of age. A single dose of asenapine was administered sublingually before and during treatment with carbamazepine.

Treatments consisted of the following:

Day 1 and Day 20: Asenapine 5 mg SL once on each day

Days 4-7: Carbamazepine 200 mg PO BID
Days 8-22: Carbamazepine 200 mg PO BID

The pharmacokinetics of asenapine, N-desmethyl asenapine, asenapine N-oxide, and asenapine N-glucuronide were assessed after dosing on Day 1 (without carbamazepine) and on Day 20 (with carbamazepine).

The CYP3A4 inducing effect of carbamazepine was measured by determining the ratio of 6β-OH cortisol/cortisol in urine collected prior to and during carbamazepine treatment.

Subject demographics are shown in Table 130, and pharmacokinetic metrics are shown in Table 134.

Table 130 Subject Demographics - Study 25528

N	Age (years)	Weight (kg)	Height (cm)	BMI (kg/m^2)
29	31.3 + 8.0 18 - 45 [31.0]	78.0 + 10.7 58.5 - 97.0 [79.0]	179.7 + 6.3 168 - 198 [180.0]	24.07 + 2.42 18.9 - 28.4 [24.1]

Carbamazepine induces both CYP3As and CYP2C19, and Table 131 demonstrates that at least cortisol 6- β–hydroxylation by CYP3A4 was induced.

Table 131 Effect of Carbamazepine on 6β–Hydroxy-Cortisol Urine Excretion Evidencing CYP3A4 Induction - Study 25528

Parameter (unit)	Summary Statistics		Geometric Means		Geometric Mean Ratio Day 19 / Day -1 [95% CI]
	Day -1	Day 19	Day -1	Day 19	
Free cortisol (µg)	48.4 (59.2) 15.0 - 131	32.8 (50.5) 8.54 - 70.0	41.6	28.7	0.69 [0.55 - 0.87]
6β–hydroxy-cortisol (µg)	254 (36.2) 117 - 521	702 (36.8) 184 - 1252	239	651	2.73 [2.32 - 3.20]
6β–hydroxy-cortisol / free cortisol	6.25 (39.5) 2.03 - 12.2	24.4 (38.6) 11.0 - 46.0	5.75	22.7	3.95 [3.26 - 4.78]

Results are shown in Figure 110 to Figure 112 and Table 134. Results indicate that carbamazepine induces the elimination of asenapine resulting in a secondary decrease in glucuronidation. In addition, the lower concentrations early on in both of their concentration vs. time profiles with more similar concentration vs. time curves later on indicates that elimination is driving the earlier phase of the declining

profile while redistribution may be driving the later phase. In addition, there is a much greater percentage decrease in N-desmethyl-asenapine exposure (30%) compared with the decreases in asenapine and asenapine glucuronide exposures (i.e. 15% for each). This may indicate that elimination of both asenapine and N-desmethyl-asenapine is mediated by CYP3A4, and for both of them the most likely reaction induced is 11-hydroxylation.

Table 132 shows the sponsor's summary of the categorical incidence AEs. The text in red highlights a possible increase in severe AEs when the drugs are taken in combination. When examined these severe AEs were somnolence.

Table 132 Sponsor's Summary of the Categorical Incidence AEs – Study 25528

Incidence of AEs	Placebo	Asenapine	Carbamazepine		Asenapine + Carbamazepine 400 mg
			200 mg	400 mg	
	N=29	N=27	N=26	N=26	N=24
	n (%)	n (%)	n (%)	n (%)	n (%)
Any AE	2 (6.9%)	25 (92.6%)	16 (61.5%)	24 (92.3%)	23 (95.8%)
Without any AE	27 (93.1%)	2 (7.4%)	10 (38.5%)	2 (7.7%)	1 (4.2%)
Any drug related AE	0 (0.0%)	25 (92.6%)	16 (61.5%)	24 (92.3%)	23 (95.8%)
Severe AEs	0 (0.0%)	1 (3.7%)	0 (0.0%)	1 (3.8%)	3 (12.5%)
Subjects with any SAE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Discontinations due to AEs	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (7.7%)	0 (0.0%)
Deaths	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

When AEs are examined by Treatment what jumps out is that fatigue is also much greater when the drugs are combined, (see Table 133).

Table 133 Selected Adverse Events by Treatment – Study 25528[a]

	Placebo	Asenanpine	Carbamazepine		Asenapine + Carbamazepine 400mg	Overall
			200 mg	400 mg		
Administration site conditions						
Asthenia	–	–	1 (1, 3.8%)	–	1 (1, 4.2%)	2 (2, 6.9%)
Miscellaneous						
Drug Withdrawal Syndrome	–	–	–	–	1 (1, 4.2%)	1 (1, 3.4%)
Fatigue	–	3 (2, 7.4%)	6 (6, 23.1%)	5 (5, 19.2%)	11 (11, 45.8%)	25 (17, 58.6%)
Thoracic and mediastinal disorders						
Respiratory, Total	–	–	–	4 (3, 11.5%)	5 (2, 8.3%)	9 (5, 17.2%)
Cough	–	–	–	–	1 (1, 4.2%)	1 (1, 3.4%)
Nasal Congestion	–	–	–	1 (1, 3.8%)	1 (1, 4.2%)	2 (2, 6.9%)
Pharyngolaryngeal Pain	–	–	–	2 (2, 7.7%)	2 (2, 8.3%)	4 (4, 13.8%)
Rhinorrea	–	–	–	1 (1, 3.8%)	1 (1, 4.2%)	2 (2,6.9%)

a n (y, z %): n = number of incidences of particular adverse event
y = number of subjects with particular adverse event
z = percentage of subjects with particular adverse event (refer to the number of subjects treated)
Note: Percentages refer to the number of subjects received the respective treatment at least once.

Figure 113 Mean Asenapine Concentration vs. Time Profiles in the Absence and Presence of Carbamazepine – Study 25528

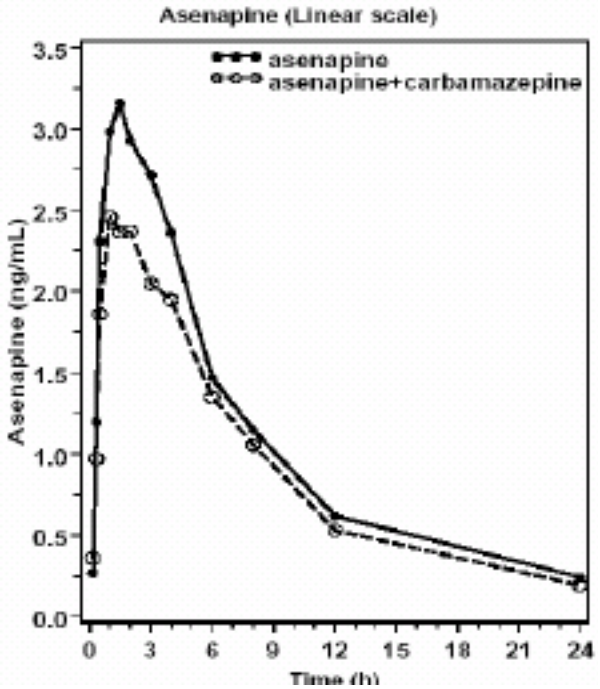


Figure 114 Mean Desmethyl-Asenapine Concentration vs. Time Profiles in the Absence and Presence of Carbamazepine – Study 25528

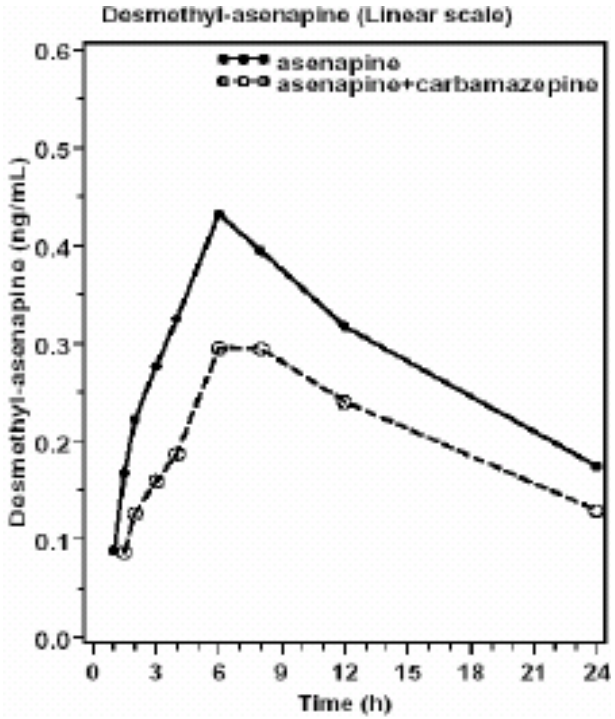


Figure 115 Mean Asenapine Glucuronide Concentration vs. Time Profiles in the Absence and Presence of Carbamazepine – Study 25528

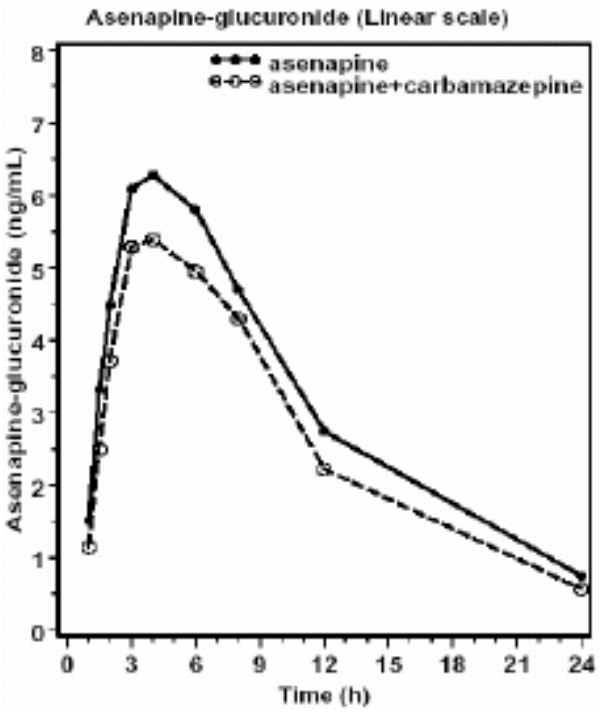


Table 134 Asenapine, Desmethyl-Asenapine, & Asenapine Glucuronide 5 mg SL SD PK Parameters in the Absence and Presence of Carbamazepine 400 mg PO BID – Study 25527

Parameter (unit)	Asenapine			Desmethyl-Asenapine			Asenapine-Glucuronide		
	Asenapine	Asenapine + Carbamazepine	GMR (90% CI)	Asenapine (n=24)	Asenapine + Carbamazepine	GMR (90% CI)	Asenapine (n=23)	Asenapine + Carbamazepine	GMR (90% CI)
N	24	24	—	24	24	—	23	23	—
Tmax (h)	1.25 0.50 - 2.0	1.00 0.50 - 4.0	—	6.00 3.00-12.0	6.00 6.00-12.0	—	4.00 3.00 - 8.00	4.00 3.00 - 8.02	—
Cmax (ng/mL)	3.46 (26.3) 1.67 - 5.76	2.94 (32.7) 1.44 - 5.27	0.84 0.74 - 0.95	0.447 (23.1) 0.245 - 0.617	0.314 (25.1) 0.140 - 0.474	0.70 0.66 - 0.74	6.54 (36.5) 2.12 - 10.7	5.80 (33.8) 2.69 - 9.90	0.90 0.82 - 0.99
AUCtlast (ng/mL x hr^{-1})	29.7 (28.4) 14.3 - 45.9	24.3 (24.1) 15.0 - 35.5	0.83 0.76 - 0.90	9.01 (30.0) 3.65 - 13.9	6.05 (35.3) 2.40 - 10.5	0.66 0.61 - 0.71	84.2 (45.8) 22.4 - 160	67.6 (36.0) 24.1 - 126	0.84 0.75 - 0.94
AUC∞ (ng/mL x hr^{-1})	31.0 (27.5) 14.8 - 47.1	25.6 (22.2) 15.6 - 36.1	0.84 0.77 - 0.91	11.0 (29.8) 4.28 - 16.8	7.72 (29.8) 4.00 - 13.2	0.70 0.65 - 0.76	93.2 (44.9) 34.0 - 175	75.4 (33.9) 33.0 - 132	0.84 0.74 - 0.96
CL/F (L/h)	175 (31.9) 106 - 338	206 (23.7) 139 - 321	—	478 (37.8) 283 - 1110	675 (32.7) 361 - 1190	—	107 (48.4) 46.2 - 238	123 (40.7) 61.2 - 245	—
Vz/F (L)	5167 (57.9) 1403 - 12437	5729 (63.1) 1853 - 15200	—	11296 (46.1) 4965 - 25844	14475 (34.4) 8417 - 27983	—	1597 (55.8) 579 - 4699	1887 (81.4) 758 - 6191	—
t½ (h)	20.6 (47.8) 6.45 - 46.1	19.4 (61.6) 7.29 - 49.8	—	18.3 (67.0) 8.35 - 63.3	15.7 (37.4) 9.86 - 33.6	—	12.7 (73.7) 4.12 - 40.2	12.4 (103) 3.71 - 51.6	—

a Values are Mean (CV %) range; Median range

5.5.7.5.5 Effect of Cimetidine on Asenapine - Study 25529

Study 25529 was an open-label, randomized, two-way cross-over study to investigate the effect of cimetidine at steady state on the single dose pharmacokinetics of 5 mg asenapine in 12 healthy male subjects aged 18 – 45 years of age.

Treatments were as follows:

Treatment A: Asenapine 5 mg SL x 1
Treatment B: Days 1-7 Cimetidine 800 mg b.i.d. with a single Asenapine 5 mg sublingual dose on Day 5.

During treatment with cimetidine the inhibitory effects of cimetidine on CYPs 1A2, 2D6, and 3A4 were assessed as follows:

- **CYP1A2:** Plasma 6 hour paraxanthine/caffeine ratio during treatment (Day 3) to pre-treatment (Day - 1) (Caffeine 100 mg)
- **CYP2D6:** Urine 8 hour dextrorphan/dextromethorphan ratio during treatment (Day 3) to pre-treatment (Day - 1) (Dextromethorphan 30 mg)
- **CYP3A4:** Urine 24 hour 6β–OH cortisol/cortisol ratio during treatment (Day 3) to pre-treatment (Day - 1)

There was a washout period of at least 2 weeks between successive treatment periods.

The pharmacokinetics of asenapine, N-demethyl-asenapine, asenapine N-oxide, and asenapine N-glucuronide were measured in the absence and presence of cimetidine.

Results:

Demographics

Subject demographics are shown in Table 135.

Table 135 Subject Demographics - Study 25529

N	Age (years)	Height (cm)	Weight (kg)	BMI (kg / m^2)
29	32.8 18 - 43 [33.0]	180.2 163 - 195 [180.0]	77.90 57.0 - 90.0 [80.0]	23.95 19.8 - 27.5 [24.03]

Controls for P450 CYP Inhibition

Cimetidine is an imidazole that binds directly to the heme of certain P450s accounting for its ability to inhibit multiple isozymes.

Figure 116 Structure Cimetidine

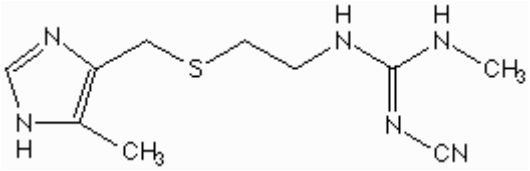


Table 136 to Table 138 show the effect of cimetidine on positive controls for P450 isozyme activity, there is a mean 34% decrease in CYP1A2 activity, a mean 75% decrease in CYP2D6 activity, and a mean 25% decrease in CYP3A4 activity.

Effect of Cimetidine on Plasma Paraxanthine/Caffeine Ratio (CYP1A2 Inhibition)

Table 136 6 Hour Plasma Caffeine and Paraxanthine Concentrations and Ratios in the Absence and Presence of Cimetidine – Study 25529

Metrics	Summary Statistics		Geometric Means		Geometric Mean Ratio Day 3/Day -1 [95% CI]
	Pre-Cimetidine	With Cimetidine	Pre-Cimetidine	With Cimetidine	
	Day -1	Day 3	Day - 1	Day 3	
Caffeine (ng/mL)	1144 (27.5) 604 - 1930	2103 (50.9) 1150 - 6030	–	–	–
Paraxanthine (ng /mL)	673[a] (33.9) 436 - 1370	963 (85.9) 365 - 3200	–	–	–
Paraxanthine / Caffeine Ratio	0.621 (30.8) 0.267 - 1.10	0.422 (48.2) 0.181 - 0.953	0.59	0.38	0.64 0.56 - 0.73

a Estimates based on n=23 subjects (Caffeine: n=24)
For Subject 12, Day - 1, an exceptionally low paraxanthine concentration was measured (129 ng/mL). The outlier resulted from a bioanalytical rerun as the original run did not meet the acceptance criteria. In the non - accepted run the paraxanthine concentration was much higher than 129 ng/mL. So it was decided to exclude this outlier from further calculations.

Effect of Cimetidine on Urine Dextrorphan/Dextromethorphan Ratio (CYP2D6 Inhibition)

Table 137 8 Hour Urine Dextromethorphan and Dextrorphan Concentrations and Ratios in the Absence and Presence of Cimetidine – Study 25529

Metrics	Summary Statistics		Geometric Means		Geometric Mean Ratio Day 3/Day -1 [95% CI]
	Pre-Cimetidine	With Cimetidine	Pre-Cimetidine	With Cimetidine	
	Day -1	Day 3	Day - 1	Day 3	
Dextromethorphan (µg)	81.6 (185) 2.29 - 586	136 (164) 3.98 - 934	–	–	–
Dextrorphan (µg)	127 (72.5) 13.7 - 343	73.1 (63.2) 9.29 - 165	–	–	–
Dextrorphan / Dextromethorphan Ratio	9.11 (98.5) 0.0234 - 32.8	2.05 (110) 0.0206 - 8.81	4.35	1.07	0.25 0.17 - 0.36

a For subject 108, the urine sample of Day 3 was lost and consequently no assessments on dextromethorphan and cortisol were available during treatment. Estimates based on n=23 (#: n=22) subjects

Effect of Cimetidine on Urine Cortisol and 6β–Hydroxycortisol Ratio (CYP3A4 Inhibition)

Table 138 24 Hour Urine Cortisol and 6β–Hydroxycortisol Excretion and Ratios in the Absence and Presence of Cimetidine – Study 25529

Metrics	Summary Statistics		Geometric Means		Geometric Mean Ratio Day 3/Day -1 [95% CI]
	Pre-Cimetidine	With Cimetidine	Pre-Cimetidine	With Cimetidine	
	Day -1	Day 3	Day - 1	Day 3	
Free cortisol (µg)	34.4 (47.2) 17.9 - 91.7	21.8 (36.5) 6.58 - 37.1	31.7	20.2	0.64 [0.52 - 0.78]
6β–hydroxy–cortisol (µg)	197 (39.0) 65.9 - 341	100 (53.8) 33.6 - 286	182	89.4	0.49 [0.43 - 0.57]
6β–hydroxy-cortisol / free cortisol	6.19 (39.5) 2.78 - 12.5	4.63 (30.2) 2.23 - 7.80	5.74	4.42	0.77 [0.68 - 0.87]

Estimates based on n=23 subjects

Effect of Cimetidine on Asenapine

Figure 117 to Figure 119 demonstrate the effect of cimetidine on asenapine, desmethyl-asenapine, and asenapine-glucuronide.

Table 139 on the following page also shows that the exposure to asenapine, desmethyl-asenapine, and asenapine glucuronide in the absence and presence of cimitidine. Exposure to asenapine doesn't change, although the exposure to asenapine glucuronide increases slightly, (~22% on average), whereas the exposure to desmethyl-asenapine approximately doubles.

Figure 117 Mean Asenapine Concentration vs. Time Profiles in the Absence and Presence of Cimetidine – Study 25529

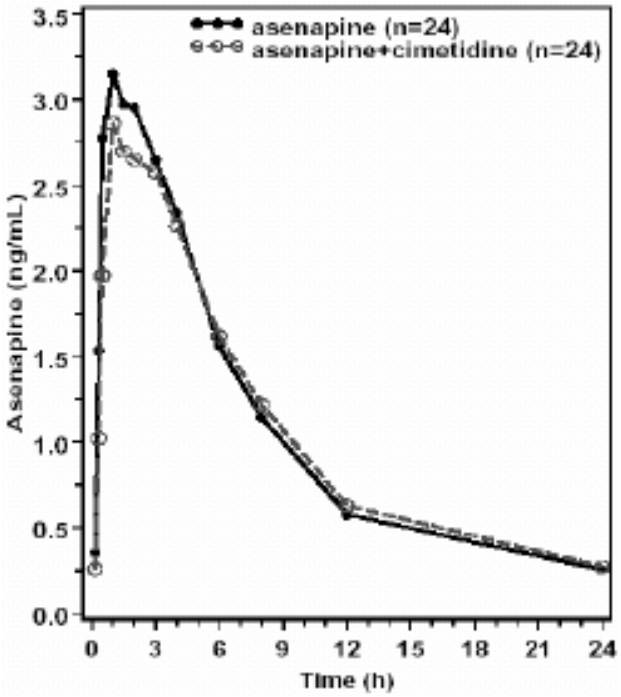


Figure 118 Mean Desmethyl-Asenapine Concentration vs. Time Profiles in the Absence and Presence of Cimetidine – Study 25529

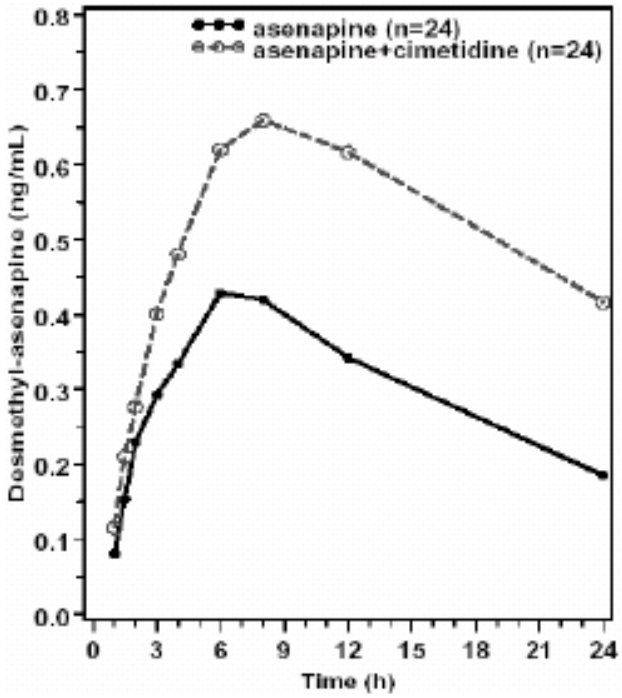


Figure 119 Mean Asenapine Glucuronide Concentration vs. Time Profiles in the Absence and Presence of Cimetidine – Study 25529

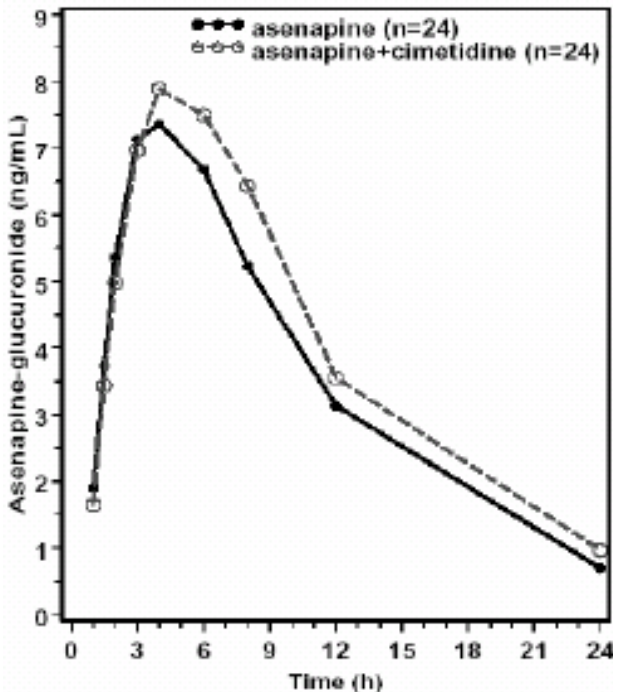


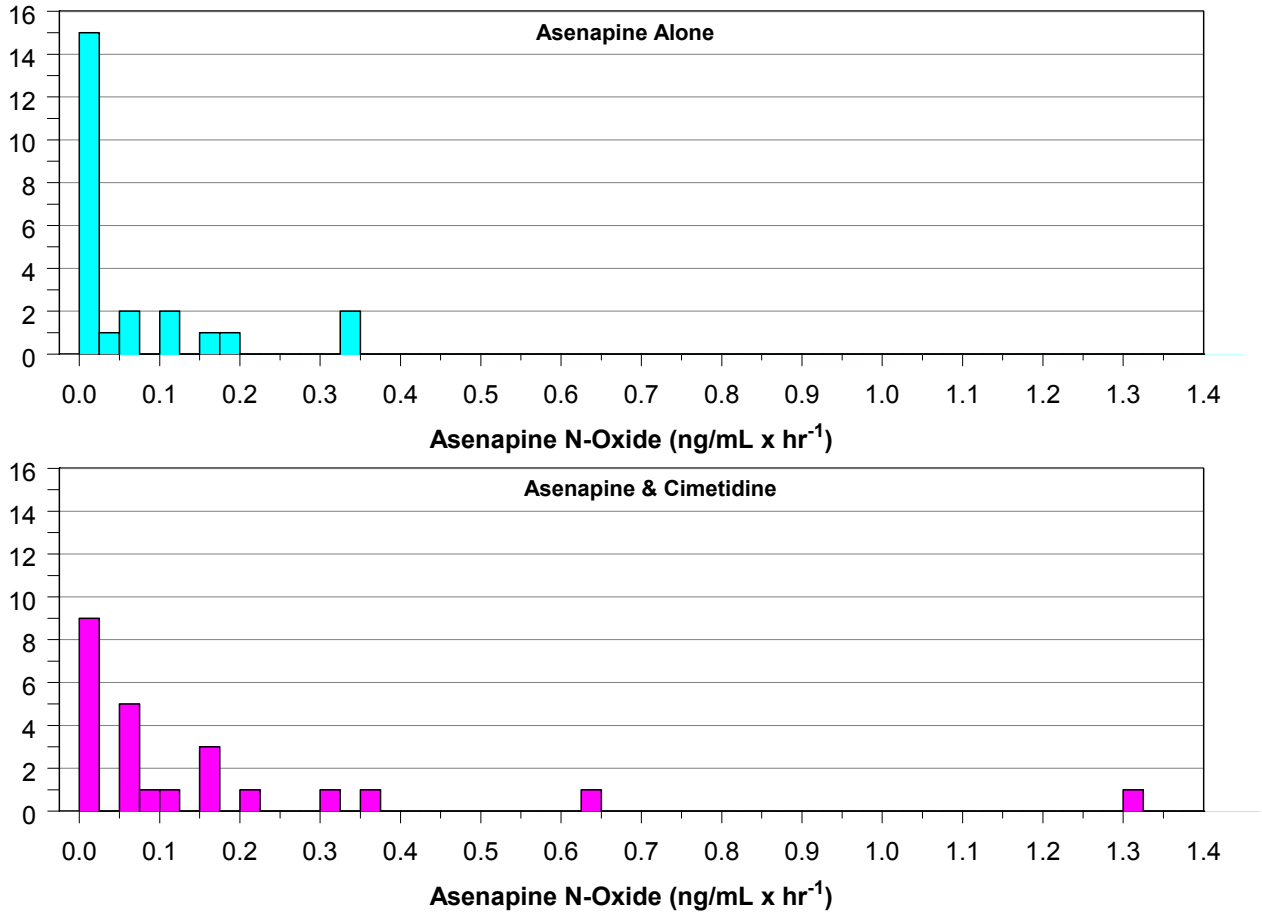
Table 139 Asenapine, Desmethyl-Asenapine, and Asenapine Glucuronide 5 mg SL Single Dose PK Parameters in the Absence and Presence of Cimeitdine 800 mg PO BID – Study 25527

Parameter (unit)	Asenapine			Desmethyl-Asenapine			Asenapine-Glucuronide		
	Asenapine	Asenapine + Cimetidine	Geometric Mean Ratio (90% CI)	Asenapine	Asenapine + Cimetidine	Geometric Mean Ratio (90% CI)	Asenapine	Asenapine + Cimetidine	Geometric Mean Ratio (90% CI)
N	24	24	—	24	24	—	24	24	—
Tmax (h)	1.0 0.5 - 3.0	1.0 0.5 - 3.0	—	6.00 3.00 - 12.0	8.00 4.00 - 24.0	—	4.0 3.0 - 8.0	4.0 3.0 - 8.0	—
Cmax (ng/mL)	3.80 (51.4) 1.75 - 11.1	3.20 (38.2) 1.66 - 6.76	0.87 0.77 - 0.98	0.458 (33.0) 0.238 - 0.826	0.697 (32.4) 0.163 - 1.14	1.50 1.32 - 1.70	7.79 (40.8) 3.96 - 17.4	8.29 (32.4) 2.42 - 13.4	1.07 0.95 - 1.21
$AUC_{0-tlast}$ (ng·h/mL)	30.4 (29.1) 17.7 - 53.9	30.6 (32.3 16.8 - 51.3	0.99 0.90 - 1.10	9.79 (34.4) 3.17 - 16.1	21.6 (29.8) 4.92 - 31.9	2.22 1.90 - 2.58	92.8 (37.8) 32.4 - 163	107 (32.6) 16.4 - 157	1.15 0.97 - 1.36
AUC_{0-inf} (ng·h/mL)	33.0 (31.4) 18.1 - 58.4	33.7 (32.1) 18.1 - 56.3	1.01 0.91 - 1.13	11.4 (32.2) 3.91 - 18.0	25.1 (28.1) 6.25 - 43.5	2.22 1.91 - 2.58	99.2 (35.6) 43.5 - 168	119 # (26.6) 46.7 - 169	1.22 1.11 - 1.34
CL/f (L/h)	166 (30.4) 85.6 - 277	165 (34.3) 88.8 - 276	—	472 (43.1) 264 - 1217	215 (56.7) 109 - 761	—	93.4 (39.6) 48.2 - 186	74.9 # (39.2) 47.9 - 173	—
Vz/f (L)	6250 (47.9) 1798 - 15702	7648 (57.2) 2835 - 18716	—	10302 (34.3) 5233 - 17401	6516 (57.4) 3000 - 20360	—	1376 (48.8) 482 - 3975	1362 # (53.3) 667 - 3650	—
$t_{1/2}$ (h)	29.1 (62.0) 7.19 – 93.1	33.9 (55.7) 14.1 - 86.5	—	16.3 (40.4) 8.96 - 37.7	21.5 (37.8) 10.7 - 43.9	—	11.7 (60.8) 4.81 - 34.5	13.7 # (56.9) 4.17 - 36.0	—

a Values are Mean (CV %) min – max; except for Tmax where values are median, min – max

Although the sponsor claimed that asenapine N-oxide metrics weren't reported as it was largely undetectable, this reviewer was still able to calculate AUCs and compare them between treatments. As descriptive statistics were not helpful comparative histograms are plotted and show in Figure 120. Figure 120 indicates that there may be a slight trend for slightly higher N-oxide AUCs in the presence of cimetidine.

Figure 120 Histograms of Asenapine N-Oxide AUC_{0-72} in the Absence and Presence of Cimetidine –Study 25529



However the pharmacokinetics dosn't quite make sense, (see metabolic scheme, and indicates decreased elimination of N-desmethyl-asenapine by CYP2D6. In addition other pathways that might be affected include 11- hydroxylation, due to CYP3A4 or possible inhibition of 1A2.

Correlation between Phenotyping Assessments and Asenapine Pharmacokinetics might be helpful but were not done even though samples were collected.

"Correlation analyses (including scatter plots) of AUC versus the paraxanthine/caffeine ratio are presented in Appendix BI, Figures 10 - 1 and Analyses 10 - 1. None of the plots nor the correlation analyses indicated a correlation between exposure to asenapine and metabolites and the paraxanthine/caffeine ratio. The strongest correlation observed was with AUC0 - inf of asenapine - glucuronide on Day 5 of treatment B (administration of asenapine during cimetidine treatment) with the paraxanthine/caffeine ratio on Day 3 (r= - 0.31, p>0.05).
The results are somewhat confusing.

Correlation analyses (including scatter plots) of AUC versus the dextrorphan / dextromethorphan ratio are presented in Appendix BI, Figures 10 - 2 and Analyses 10 - 2. Neither any of the plots nor the correlation analyses indicated a relevant correlation between exposure to asenapine or metabolites and the dextrorphan/ dextromethorphan ratio except an incidental significant correlation for AUC0 - inf of asenapine - glucuronide on Day 5 (administration of asenapine during cimetidine treatment) with the ratio Day 3/Day - 1 of the dextrorphan/dextromethorphan ratio (r=0.51, p=0.022).

Results of correlation analyses (including scatter plots) of the PK parameters AUC0 - tlast and AUC0 - ∞ of asenapine and metabolites with the urinary 6β–hydroxycortisol/free cortisol ratio are given in Appendix BI, Figures 10 - 3 and Analyses 10 - 3. Neither any of the plots nor the correlation analyses indicated a relevant correlation between exposure to asenapine or metabolites and the 6β–hydroxycortisol/free cortisol ratio except an incidental significant correlation for AUC0 - tlast of asenapine - glucuronide on Day 5 of treatment B (administration of asenapine during cimetidine treatment) with the Day 3/Day - 1 ratio of the 6β–hydroxycortisol/free cortisol ratio (r= - 0.47, p=0.022)."

Safety

Mainly mild dizziness was reported for one subject after asenapine alone and for five subjects after administration of asenapine plus cimetidine. Dizziness started between 0.5 and 4.5 hours after dosing, the duration varied between one and 30 minutes, only Subject 19 reported mild dizziness for about eight hours.

Incidence of AEs	Treatment A		Treatment B			
	Placebo (N=29) n (%)	Asenapine (N=25) n (%)	Caffeine/ Dextro-methorphan (N=24) n (%)	Cimetidine (N=24) n (%)	Cimetidine+Caffeine/ Dextromethorphan (N=24) n (%)	Cimetidine+ Asenapine (N=24) n (%)
Subjects with any AE	1 (3.4%)	20 (80.0%)	0 (0.0%)	4 (16.7%)	1 (4.2%)	22 (91.7%)
Subjects without any AE	28 (96.6%)	5 (20.0%)	24 (100.0%)	20 (83.3%)	23 (95.8%)	2 (8.3%)
Subjects with any drug related AE*	1 (3.4%)	20 (80.0%)	0 (0.0%)	4 (16.7%)	0 (0.0%)	22 (91.7%)
Subjects with any severe AE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (25.0%)
Subjects with any SAE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Subjects discontinued due to an AE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Deaths	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

* Relationship specified as 'definite', 'probable', 'possible'
N = number of subjects receiving the respective treatment at least once, n = number of subjects with at least one AE in the respective category
Source: Appendix F4, Table 4.1.1

"asenapine. Mainly mild dizziness was reported for one subject after asenapine alone and for five subjects after administration of asenapine plus cimetidine. Dizziness started between 0.5 and 4.5 hours after dosing, the duration varied between one and 30 minutes, only Subject 19 reported mild dizziness for about eight hours. Subject 14 had a syncope on his way back from the toilet (the subject had difficulties to urinate in the study room, therefore he was allowed to go to the toilet under supervision of the investigator), the syncope occurred at about three hours after dosing of asenapine during treatment with cimetidine and lasted for two minutes; the first available blood pressure value was recorded at the end of the syncope, the value was still low (84/53 mmHg, pulse rate 44 bpm), but increased in the next minutes (six minutes later: 110/64 mmHg, pulse rate 48 bpm). The systolic blood pressure remained below 110 mmHg for the next hour and increased thereafter. Twenty minutes after the syncope the subject reported moderate dizziness. Fifteen minutes after the start of this event the subject received an infusion with 5% glucose solution. (see Section 8.1.4). The event resolved immediately. For three other subjects blood pressure was measured at the time of the occurrence of dizziness (always at the end of the event), the measurements revealed a decreased blood pressure in Subject 17 (92/58 mmHg, pulse rate 44 bpm), a slightly decreased blood pressure in Subject 111 (147/88 mmHg, pulse rate 65 bpm, see Appendix G, Listing 12.1)."

Listing 12.2 **Listing of Clinically Relevant Abnormal Vital Signs Values.**

Vital sign parameter	Subject number	Treatment	Assessment Name	Assessment Day (*)	Actual date	Relative time	Actual time	Baseline (*)	Value	Absolute change (*)
Supine systolic blood pressure (mmHg)	14	B	Unplanned	5 #	05JUL2005	AFTER 10 MIN	12:40	117	84 L	-33 L
	21	A	P2 Day 1	1	22JUL2005	+01:00	10:55	113	78 L	-35 L
Supine diastolic blood pressure (mmHg)	15	B	Unplanned	4 #	04JUL2005	AFTER 10 MIN	08:28	64	46 L	-19 L
Supine pulse rate (bpm)	14	B	Unplanned	5 #	05JUL2005	AFTER 10 MIN	12:40	60	44 L	-16 L
							14:02	60	44 L	-16 L
	17	B	Unplanned	5 #	05JUL2005	AFTER 10 MIN	14:10	74	44 L	-30 L
							14:12	74	49 L	-25 L

5.5.7.5.6 Effect of Fluvoxamine on Asenapine - Study 41033

Study 41033 was an open-label, randomized, two-way crossover study to assess the effect of fluvoxamine on asenapine in 26 healthy non-smoking male subjects between 18 and 55 years of age

Treatments were as follows:

Treatment A (asenapine alone):	Day 1: Asenapine 5 mg SL x 1.
T**reatment B (asenapine + fluvoxamine)**:	Days 1-7: Fluvoxamine 25 mg po BID Day 5: Asenapine 5 mg SL x 1

There was a minimum 1 week interperiod washout.

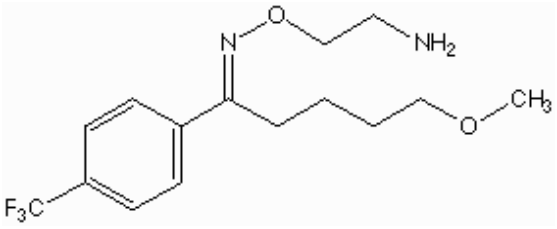
The inhibitory effect of fluvoxamine on CYP1A2 during treatment was assessed as follows:

> Caffeine 100 mg po x 1 on Days -1 and 3 of the asenapine and fluvoxamine treatment with the paraxanthine/caffeine ratio determined at 6 hours post-dose and compared with the pre-dose ratio.

The pharmacokinetics of asenapine, N-demethyl-asenapine, and asenapine 11-O-sulfate were measured in the absence and presence of fluvoxamine.

The structure of fluvoxamine is shown in Figure 121 for information.

Figure 121 Fluvoxamine Structure



Results:

Demographics

Subject demographics are shown in Table 140.

Table 140 Subject Demographics - Study 41033

N	Age (years)	Height (cm)	Weight (kg)	BMI (kg / m^2)
26	33.6 ± 10.8 21–53 [31.5]	183.4 ± 8.5 161.5-201.0 [184.0]	85.8 ± 10.3 68.4-106.7 [86.6]	25.45 ± 1.91 22.7-29.3 [25.25]

Effect of Fluvoxamine on Plasma Paraxanthine/Caffeine Ratio (CYP1A2 Inhibition)

Table 141 shows that fluvoxamine affects the probe compound.

Decrease in 6 hour caffeine concentrations by half and a 3 fold increase in paraxanthine concentrations.

Table 141 6 Hour Plasma Caffeine and Paraxanthine Concentrations and Ratios in the Absence and Presence of Fluvoxamine 25 mg PO BID – Study 41033

Metrics	Summary Statistics		Geometric Means		Geometric Mean Ratio Day 3/Day -1 [95% CI]
	Pre-Fluvoxamine	With Fluvoxamine	Pre-Fluvoxamine	With Fluvoxamine	
	Day -1	Day 3	Day - 1	Day 3	
Caffeine (ng/mL)	691 (29.5) 368 - 1160	438 (71.4) 97.0 - 1320	666	349	0.52 [0.39 - 0.70]
Paraxanthine (ng/mL)	999 (46.9) 286 - 2590	2735 (36.1) 1570 - 5900	903	2593	2.87 [2.41 - 3.43]
Paraxanthine / Caffeine Ratio	0.781 (33.6) 0.437 - 1.29	0.163 (72.1) 0.0437 - 0.61	0.740	0.136	0.18 [0.15 - 0.22]

Effect of Fluvoxamine on Asenapine and Metabolites (CYP1A2 Inhibition)

Figure 122 to Figure 124 and Table 142 show that fluvoxamine increases the exposure to asenapine by 30%, decreases exposure to asenapine 11-O-sulfate by 30%, and increases exposure to desmethyl-asenapine by 2 fold. The metabolic scheme, (Figure 15), shows that the increase in exposure to desmethyl-asenapine is likely due to inhibition of 11-hydroxylation of desmethyl-asenapine. This will result in shunting to N-oxidation, although increased formylation is also a possibility. The shunting to N-oxidation will result in greater inhibition of CYP2D6 and as a suicide substrate result in even greater inhibition and thus result in nonlinear accumulation of desmethyl-asenapine upon multiple dosing. It's also possible that the increased inhibition of CYP2D6 with result in increased hepatotoxicity.

Figure 122 Mean Asenapine Concentration vs. Time Profiles in the Absence and Presence of Fluvoxamine – Study 41033

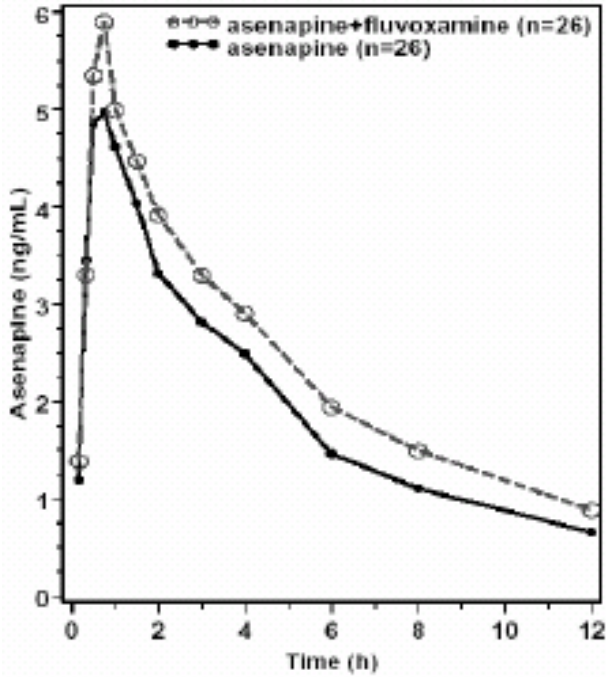


Figure 123 Mean Desmethyl-Asenapine Concentration vs. Time Profiles in the Absence and Presence of Fluvoxamine – Study 41033

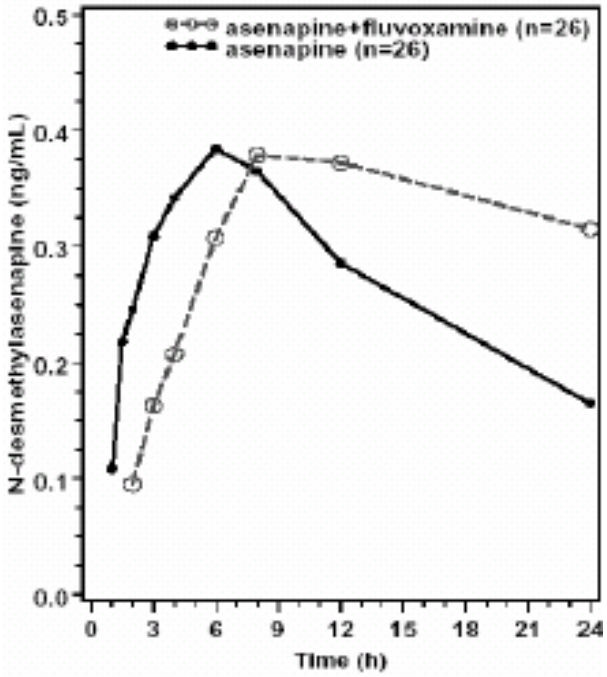


Figure 124 Mean Asenapine 11-O-Sulfate Concentration vs. Time Profiles in the Absence and Presence of Fluvoxamine – Study 41033

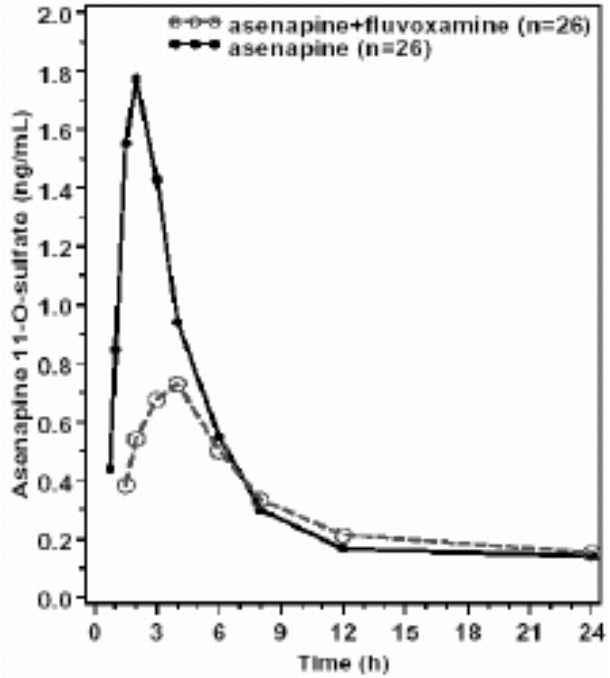


Table 142 Asenapine, Desmethyl-Asenapine, and Asenapine 11-O-sulfate 5 mg SL Single Dose PK Parameters in the Absence and Presence of Fluvoxamine 25 mg PO BID – Study 41033

Parameter (unit)	Asenapine			N – Desmethyl-Asenapine			Asenapine 11 - O - Sulfate		
	Asenapine	Asenapine + Fluvoxamine	GMR (90% CI)	Asenapine	Asenapine + Fluvoxamine	GMR (90% CI)	Asenapine	Asenapine + Fluvoxamine	GMR (90% CI)
N	26	26		26	26		26	26	
Tmax (h)	0.75 0.33 - 1.52	0.75 0.50 - 2.00		6.00 3.00 - 12.0	12.0 6.00 - 24.0		2.00 1.00 - 3.02	4.00 1.50 - 8.00	
Cmax (ng/mL)	5.40 (40.2) 2.67 - 10.9	6.11 (42.8) 1.64 - 13.9	1.13 0.99 - 1.30	0.413 (34.6) 0.109 - 0.650	0.415 (42.3) 0.107 - 0.770	0.99 0.83 - 1.18	1.95 (75.6) 0.115 - 7.17	0.784 (78.9) 0.052 - 2.69	0.40 0.30 - 0.52
AUC_{tlast} ($ng/mL \times hr^{-1}$)	34.5 (32.1) 18.8 - 69.9	44.9 (38.6) 20.0 - 106	1.29 1.15 - 1.45	8.34 (43.6) 1.67 - 15.9	16.1 (43.3) 3.54 - 30.7	1.97 1.66 - 2.35	10.6 (82.2) 0.621 - 34.8	8.80 (88.2) 0.203 - 30.3	0.71 0.52 - 0.98
AUCinf ($ng/mL \times hr^{-1}$)	37.6 (34.2) 21.1 - 78.0	49.0 (40.9) 22.3 - 121	1.29 1.14 - 1.46	10.4 (37.6) 3.33 - 18.7	22.0 (44.2) 6.25 - 54.2	2.10 1.82 - 2.43			
CL/F (L/h)	147 (32.2) 64.1 - 237	117 (37.3) 41.3 - 224		536 (47.0) 255 - 1429	259 (50.8) 87.8 - 761				
Vz/F (L)	5417 (58.2) 1620 - 15166	4429 (45.2) 2062 - 9336		11833 (64.8) 5529 - 44366	10644 (55.9) 3561 - 33529				
$t_{½}$ (h)	27.6 (61.9) 9.33 - 69.1	27.8 (42.8) 12.5 - 64.0		15.7 (38.7) 8.65 - 39.2	29.5 (38.9) 17.6 - 63.9		20.5# (38.2) 9.54 - 36.7	26.7## (93.8) 8.95 - 102	

Values are Mean, CV (%), min – max

5.5.8 Population Pharmacokinetics

The sponsor conducted two sets of population pharmacokinetic analyses that were reported in the following reports:

- INT00036661 Phase I and Phase II Safety Studies
- INT00036719 Phase II and Phase III Efficacy Studies in Acute Excerbations of Schizophrenia and Mania

The population PK model was developed using the phase I and II study data from single and multiple dose data with intensive PK sampling in healthy subjects and some patients with schizophrenia.

The data from the Phase II and III studies were then used to validate the population PK model previously developed, see Table 151 for these studies.

The purpose of this exercise appears to be two-fold: to make a decision on risks associated with design of Phase III studies and to develop drug-disease models for future modeling and stimulation.

5.5.8.1 Population Pharmacokinetic Modeling of Phase I and Phase II Safety Studies

The phase I and II studies used to develop the population pharmacokinetic mode are shown in Table 143 on the following page. Dosages with PK data range from 0.8 mg BID to 20 mg BID for up to 16 days.

All of the phase I and II studies utilized intense pharmacokinetic sampling, although the studies in healthy volunteers collected from 4 – 6 samples in the first hour post dosing with the first sample typically collected at 10 minutes (0.17 hours) and as early as 6 minutes post dosing. In contrast sampling in the studies in patients typically obtained the first sample at 1 hour post-dose although in one study the first sample was obtained at 0.5 hours, (see Table 143).

Table 143 Phase I/II Studies included in the Development of the Population Pharmacokinetic Model

Study # (Phase)	SD / MD	Study Design	Subjects	Dose	Use IOV[a]	Fed/ Fasted	Analytic Method	LLOQ (ng/mL)	Sampling Days	PK Sampling Times (hr postdose)	Data to be Used
25537 (1)	MD	Effect of water	Vols	1, 3, 5 mg once daily (3- day titration) followed by 10 mg once daily for 28 days.	Yes	Fasted	LC-MS	0.025	Days 10, 17, 24 and 31	Predose, 0.1, 0.18, 0.25, 0.52, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, and 24.	Water 10 and 30 min after dosing
25542 (1)	MD	S/T	Male Vols	Titrated up (over 3 or 4 days) to 3, 5, 10, or 15 mg BID and remaining at that dose for 6 or 7 days; 2 mg SD; 5 mg SD	Yes	No food 0.5 h after dosing	LC-MS	0.100, Or 0.025 (Group 5)	Groups 1-3: Day 9: Group 4: Day 11: same as Groups 1-3; Group 5: Days 1 and 8:	Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 12.5, 13, 13.5, 14, 15, 16, 18, 20, 24, 30, 36, 48 and 72; Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36, 48, and 72.	Asenapine
25545 (1)	SD	2-way crossover study in smokers	Male Vol Smokers	5 mg	Yes	Fasted	LC-MS	0.025	Days 1 and 8:	Predose, 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48 and 60.	All
25546 (1)	SD then MD	S/T PK	Japanese and Caucasian Vols	1, 3, 5 mg SD 1, 3, 5, 10 mg BID up to 9 days	Yes	No food 0.5 hours before or after dosing	LC-MS	0.025	SD period: Day 1: MD period: Last day of dosing:	Predose, 0.17, 0.33, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36, 48 and 72. same timepoints.	Asenapine
A7501001 (1)	MD	Parallel, study of effect of asenapine, quetiapine, and placebo on QTc	Pxts with Schizo-phrenia	5-10 and 15-20 mg BID up to 16 days	Yes	Fed	LC-MS	0.100	Days 1, 10, and 16 (pAM dose): Day 16:	Predose, Predose, 1, 2, 3, 4, 6, 8, and 12 16, 24, 36 and 48.	Asenapine
A7501015 (1)	SD	3-treatment, 3-way crossover, BE Study	Vols	5 mg	Yes	Fasted	LC-MS	0.025	Days 1, 8 and 15:	Predose, 0.17, 0.33, 0.50, 0.75, 1.0, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48.	All
A7501016 (1)	SD	2-way X-over, BE study	Vols	5 mg	Yes	Fasted	LC-MS	0.025	Days 1 and 8:	Predose, 0.17, 0.33, 0.50, 0.75, 1.0, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48.	All
041001 (2)	MD	Dose- titration MTD study	Pxts	0.2 - 0.8 mg BID up to 17 days	Yes	Fasted	GC-MS	0.020	At screening. Then at each day of up-titration 1-2 hours prior to the morning dose. Then at 2 days after attainment of the maximum dose at 1.5 hours after the morning dose. Then at final dose:	Predose, 1, 1.5, 2, 10, 24, 36, and 48.	Asenapine
041007 (2)	MD	Dose- titration MTD study	Pxts	0.2 – 4.8 mg BID up to 18 days	Yes	Fasted	GC-MS	0.020	Block 1: Predose on Days 2-5, 8, 11, 14 and 15. Blocks 2 and 3: Each day of up-titration following the morning dose. All Blocks: At final dose,	Predose, 1, 1.5, 2, 4, 8, 12, 24, 36, 48, and 72.	Asenapine
041012 (2)	MD	Dose- titration MTD study	Pxts	2 to 20 mg BID up to 10 days	Yes	Fasted	GC-MS	0.020	Each titration day: Predose. Endpoint day:	Predose, 1.0, 1.5, 2, 4, 8, and 12.	Asenapine
041014 (2)	MD	2-way X-over relative BE S/T	Pxts	3x5, and 15 mg BID for 7 days	Yes	Fed	GC-MS	0.020 ng/	At screening. Days 5 and 7	Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12. Day 7: 24.	All

a IOV – Inter-occasion variability

The sponsor's description of their Pop PK model development follows:

"Base Model Development

A 2-compartment model with first-order absorption (nonlinear mixed effects modeling [NONMEM] subroutine ADVAN4) was fit to the <natural log of the> asenapine concentrations. The dependent variable was log-transformed concentration. An apparent first order absorption rate constant (ka) and a lag-time parameter (Tlag) were used to characterize the absorption process. The disposition kinetics were modeled using a parameterization involving apparent oral clearance (CL/F), apparent central volume (V2), apparent intercompartmental clearance (Q), and apparent peripheral volume (V3). Although CL, V2, Q, and V3 are typical for NONMEM subroutine TRANS4 parameterizations, TRANS1 was utilized whereby the TRANS4 parameterization was retained and intersubject random effects were added to the TRANS1 parameters such as ka, k23, and k32, to increase the computational stability. The parameter k represented the elimination rate constant and the parameters k23 and k32 were used to represent the inter-compartmental transfer rate constants. The FOCE interaction estimation method of NONMEM was employed. The within-subject variability was modeled with an additive error on the log-transformed concentration and reported as the approximate coefficient of variation (CV [%]).

Prior knowledge of nonlinear PK, and inspection of diagnostic plots by dose, suggested the need for incorporating parameters to account for the dose dependency of apparent bioavailability (F1).

A linear model with respect to logarithmic dose, normalized by the approximate mean dose of 10 mg, was used to describe nonlinear F1 dependent on dose.

$$F_1 = 1 - Slope \cdot \log\left(\frac{Dose}{10}\right)$$

where F1 represents apparent bioavailability in the model, slope is a constant to describe the linear relationship between F1 and logarithmic dose. A positive quantity of slope represents decreased bioavailability with increasing dose."

Random Effects Model Development

Interindividual variability (IIV) and interoccasion variability (IOV) in the pharmacokinetic parameters (ie, k, V2, k23, k32, ka, and F1) were modeled using multiplicative exponential random effects of the form:

$$\theta_{ij} = \theta \cdot \exp(\eta_i + k_{ij})$$

where θij represents the value of the PK parameter (eg, V2) for individual i during occasion j, θ is the typical individual (population mean) value of the parameter, ηi denotes the interindividual random deviation from θ for patient i, and kij denotes the random deviation from individual i's prediction for occasion j. The values for ηi and kij are assumed to have zero means and covariance matrices of Ω and Ψ. The square roots of the diagonal elements of Ω and Ψ can be interpreted as approximate coefficients of variation (CVs). A full block (unstructured) Ω was attempted to be estimated. Alternative reduced structures for Ω were also evaluated to obtain a stable and parsimonious covariance structure. Residual variability was modeled using the log-transformed error model:

ln(Yij) = ln(Fij) + εij

where Yij denotes the observed concentration for the ith individual at time tj, Fij denotes the corresponding predicted concentration based on the PK model, and εij denotes the intraindividual (residual) random effect assumed to have zero mean and variance σ2. Other residual error models were explored when heterogeneity was observed in the WRES versus PRED or IWRES versus IPRED plots.

Full Model Development

Covariates were added to the base model simultaneously to form the full model. Continuous covariates examined in this analysis include age and weight. Continuous covariates were modeled as multiplicative effects of the form:

$\theta = \theta_0 \bullet (x / x_{norm})^{\theta x}$

where θ_0 denotes the population value of the parameter when $x = x_{norm}$ (eg, x_{norm}= 40 years for age and x_{norm} = 70 kg for weight). The parameter θ denotes the population value conditional on the value of x, which is proportional to the power θx. When θx = 1, θ is directly proportional to x.

Dichotomous covariates examined were:

- *Gender (0 for females, 1 for males);*
- *Race (indicator variables for white, black, or Asian for which 1 is for yes and 0 is for no.)*
- *Smoking use (0 for nonsmokers (includes former smokers), 1 for smokers);*
- *Alcohol use (0 for no alcohol consumption, 1 if one or more drinks/week were consumed); and*
- *Patient status (0 for patients, 1 for healthy volunteers).*

The effect of a dichotomous covariate x was modeled as:

$\theta = \theta_0 \bullet (1 + \theta_x \cdot \bullet x)$

where θ_0 denotes the population value of the parameter for the null value of the covariate x (ie, x = 0). The parameter θ_x denotes the fractional change in θ_0 when x = 1.

For Tlag, a high correlation (-0.999) between θ_0 and θ_x was observed, which caused instability in the full model. Since the effect of patient status on lag time was highly significant (OFV decreased by 420.8 with its inclusion to the base model), the effect of patient status was incorporated as structural differences in further covariate testing procedures as follows:

$\theta = \theta_0$ *(for healthy volunteers)*

$\theta = \theta_x$ *(for patients)*

The covariates included in the full model are listed in Table 144.

Table 144 Covariates Included in the Full Model

PK Parameter	***Covariates***
CL/F (ke)	*Age, Gender, Weight, Race, Smoking , Alcohol Use*
F1	*Patient Status*
Ka	*Patient Status*
Tlag	*Patient Status*

When a covariate value was missing for a given visit, the missing value was replaced using a prior reported value, or the average value of all visits for that subject. This was done for all studies.

A full list of the covariates examined is shown in Table 145 on the following page.

Table 145 Covariates Examined

Variable	Definition	Categories / Units
ID	NONMEM Identification Number (unique for the entire dataset)	NA
STUD	Study Number	NA
DOSE	Dose Administered for the dosing period	Mg
AMT	Amount (Dose) for Dosing Event	µg
TIME	Relative Time Since the Very First Dose Within Subject	Hours
RLTM	Relative Time Since the Most Recent Dose	Hours
DV	Dependent Variable: log (asenapine conc)	ng/mL
MDV	Missing Data Value	0 = asenapine observation; 1 = other
EVID	Event Identification Data Item	0 = observation; 1 = dose
HV	Patient Status	0 = patients; 1 = healthy
AGE	Age	Years
WGT	Weight	Kg
SEX	Sex	1 = male; 0 = female
RACE	Race	1=White, Non-Hispanic; 2=Black, Non-Hispanic; 3=Hispanic (White or Black); 4=Asian or Pacific Islander; 6=Other
CLCR	Creatinine Clearance Derived using the following equations: Males: CLcr = (((140-age)*weight)/(72*scr)) Females: CLcr = (((140-age)*weight)/(72*scr))*0.85	mL/min
SMOK	Smoking (Daily Use)	0=no, 1=<1 pack per day, 2=1 to 2 packs per day, 3=>2 packs a day, 4, smoker, but the quantity unknown, 5=unknown
HORM	Hormonal status	2=unknown, 0=pre-menopausal 1=post-menopausal, 3=male
ETH	Ethanol consumption (Past 1 month)	0=none 1= <1 drink per week 2= 1 - 6 drinks per week 3= 7 - 12 drinks per week 4= 13 - 18 drinks per week 5= 19 - 24 drinks per week 6= 25 - 35 drinks per week 7= 36+ drinks per week 8=unknown
ALBU	Albumin concentration	g/dL
BILI	Bilirubin concentration	mg/dL

The characteristics of continuous demographic variables from the phase I/II population PK studies are shown in Table 146.

Table 146 Phase I/II Pop PK Studies Population Characteristics for Continuous Demographic Variables[a] [Mean ± SD]

Treatment	SD / MD	Study Objective	Subjs	Dosage	Duration (days)	N	Age (yr)	Weight (kg)	CLcr[b] (mL/min)	Albumin (g/dL)	Bilirubin (mg/dL)
25537	MD	BE H20	Vol	10 mg qd	28	23	34.3 ± 6.63	78.8 ± 7.97	104 ± 13.3	4.78 ± 0.274	0.701 ± 0.258
25542	MD	MTD	Vol	15 mg	6 - 7	30	23.9 ± 6.91	75.6 ± 9.29	110 ± 16.4	4.82 ± 0.284	0.745 ± 0.461
25545	SD	Smokers	Vol	5 mg		24	32.6 ± 7.86	75.3 ± 6.38	107 ± 14.1	4.81 ± 0.275	0.595 ± 0.241
25546	SD/MD	Race	Vol	10 mg	9	49	24.4 ± 3.39	67.7 ± 7.68	102 ± 15	4.82 ± 0.205	1.03 ± 0.414
A7501001	MD	QTc	Vol	**20 mg**	**16**	76	43 ± 8.63	84.2 ± 15.8	104 ± 43.2	7.21 ± 10.1	**1.26 ± 2.64**
A7501015	SD	BE	Vol	5 mg		38	24.7 ± 6.53	74.5 ± 14.9	118 ± 28	4.51 ± 0.341	0.737 ± 0.331
A7501016	SD	BE	Vol	5 mg		36	26.7 ± 9.08	74.4 ± 11.2	119 ± 22	4.33 ± 0.341	0.833 ± 0.379
041001	MD	MTD	Pxt	0.8 mg	17	24	38.5 ± 6.9	82.5 ± 13	120 ± 16	4.3 ± 0.303	0.717 ± 0.232
041007	MD	MTD	Pxt	4.8 mg	18	20	36.7 ± 7.66	83.7 ± 13.2	140 ± 41.7	4.11 ± 0.335	0.415 ± 0.15
041012	MD	MTD	Pxt	20 mg	10	18	44.3 ± 8.19	87.8 ± 20.8	119 ± 43.2	4.14 ± 0.299	0.5 ± 0.228
041014	MD	MTD	Pxt	15 mg	7	8	39.6 ± 8.16	87.5 ± 19.1	147 ± 40.1	4.3 ± 0.283	0.438 ± 0.16
All Studies (Range)						346	33.0 ± 10.7 (18 - 57)	78.2 ± 14.2 (44.7 - 134.5)	111.9 ± 31.8 (0.78 - 233.8)	5.18 ± 4.99 (1.6 - 50)	0.860 ± 1.32 (0.1 - 11)

a Based on data at screening
b MD is BID unless otherwise noted
c CLcr = Creatinine clearance.

What was noteworthy to this reviewer was that the mean bilirubin and albumin concentrations were elevated and the variability was increased in the thorough QTc study which employed the highest dose for the longest duration. This reviewer then performed identified all bilirubin values in the pop PK dataset that were listed as greater than 1 mg/dL. This resulted in identification of 24 elevated values in 22 individuals. Of these elevated values 6 were 10 or greater and came from the thorough QT study which employed the largest doses for the longest duration in 76 subjects (6/76 = 7.9%). There were also two other bilirubins from other studies listed as > 2X ULN.

Upon checking, this reviewer found that the clinical study report for the thorough QTc study did not include laboratory values. Mean values were reported in the text of the clinical study report, however they were only for pre- and post-treatment values, and the mean and variabilities reported do not indicate any elevated values of bilirubin. In contrast laboratory chemistry values were deteremined during drug adminisation on day 9 per the protocol, however there is no indication that these were reported. Since the bilirubin and other laboratory values could not be checked, it cannot be ascertained whether the elevations are due to hepatic impairment or other mechanisms such as acute hemolytic anemia, and the implication of these values for the pop PK analysis is uncertain. It's also noteworthy that there was a high participation rate of women, blacks, and smokers in this study. Concentrations are expected to be higher in women and blacks, and smaller in smokers. The implications of each of these factors on exposure to asenapine itself and on metabolic shunting is unclear, however they might respectively either increase or decrease risk in a nonadditive manner. In checking other studies this reviewer found that bilirubin values were reported in SI units however, on conversion the values did not match the values in mg/dL reported in the pop PK database. Lastly this reviewer also noted that in the study report for PET study xxx, that

The totality of the information suggests that a dose and treatment duration hepatotoxicity is of real concern with asenapine and there may be greater risk if the drug is swallowed or if children should take an adult dose. Due to these concerns this reviewer requested that the sponsor be asked to provide complete laboratory information and informed the medical reviewer so that this concern could be fully evaluated. A meeting was held with the medical division where the medical division dismissed the concern of hepatotoxcicity. However, this reviewer has been unable to find where the information request for laboratory information was ever forwarded to the sponsor or where it was ever received.

Table 147 shows the number of missing values by study. It's noteworthy that information on alcohol use and smoking is not available from most studies and in particular the degree of tobacco use was not quantified in the smoking study, and was greatest in the thorough QTc study which might skew both the pop PK and the safety results.

Table 148 shows the distribution of categorical variables in the phase I/II pop PK studies. Again it's noteworthy that tobacco use was highest in the patient studies, which is to be expected, however the lack of smokers in other studies may bias the model.

Finally Table 149 shows the degree of tobacco use is highest in the thorough QTc study. Consequently, this may again bias the results resulting in lower exposures with the higher doses used in this study. Although 8 nonsmokers are listed there were only 3 nonsmokers in the highest asenapine dose group.

Table 147 Phase I/II Pop PK Number of Missing Variables by Study

Study	SD / MD[a]	Study Obj	Subjs	Dosage[a]	N	Age (yrs)	Gender	Hormonal Status	Race	Weight (kg)	CLcr (mL/min)	Albumin (g/dL)	Bilirubin (mg/dL)	EtOH	Smoking
25537	MD	BE H20	Vol	10 mg qd	23	0	0	0	0	0	0	0	0	23	23
25542	MD	MTD	Vol	15 mg	30	0	0	0	0	0	0	0	0	30	30
25545	**SD**	**Smokers**	**Vol**	**5 mg**	24	0	0	0	0	0	0	0	0	24	24
25546	SD/MD	Race	Vol	10 mg	49	0	0	0	0	0	0	0	0	49	49
A7501001	MD	QTc	Vol	20 mg	76	0	0	0	0	0	0	0	0	0	0
A7501015	SD	BE	Vol	5 mg	38	0	0	0	0	0	0	0	0	0	0
A7501016	SD	BE	Vol	5 mg	36	0	0	0	0	0	0	0	0	0	0
041001	MD	MTD	Pxt	0.8 mg	**24**	0	0	24	0	0	**18**	**18**	**18**	**24**	**24**
041007	MD	MTD	Pxt	4.8 mg	20	0	0	20	0	1	1	0	0	20	0
041012	MD	MTD	Pxt	20 mg	18	0	0	18	0	0	0	0	0	18	0
041014	MD	MTD	Pxt	15 mg	8	0	0	8	0	0	0	0	0	8	0
Total (%)					346	0 (0)	0 (0)	70 (20.2)	0 (0)	1 (0.29)	19 (5.5)	18 (5.2)	18 (5.2)	196 (56.6)	150 (43.4)

a MD is BID unless otherwise noted

Table 148 Phase I/II Pop PK Population Characteristics for Categorical Variables by Study[a] [N (%)]

Study	SD / MD[b]	Study Obj	Subjs	Dosage[b]	N	Gender		Race				EtOH Use		Smoking Status	
						Male	Female	White	Black	Asian	Other	Yes	No[c]	Yes	No[c]
25537	MD	BE H20	Vol	10 mg qd	23	23 (100)	0 (0)	23 (100)	0 (0)	0 (0)	0 (0)	0 (0)	23 (100)	0 (0)	23 (100)
25542	MD	MTD	Vol	15 mg	30	30 (100)	0 (0)	28 (93.3)	1 (3.33)	1 (3.33)	0 (0)	0 (0)	30 (100)	0 (0)	30 (100)
25545	SD	**Smokers**	Vol	5 mg	24	24 (100)	0 (0)	24 (100)	0 (0)	0 (0)	0 (0)	0 (0)	20 (100)	0 (0)	**24 (100)**
25546	SD/MD	Race	Vol	10 mg	49	49 (100)	0 (0)	25 (51)	0 (0)	24 (49)	0 (0)	0 (0)	49 (100)	0 (0)	49 (100)
A7501001	MD	QTc	Vol	**20 mg**	76	59 (77.6)	**17 (22.4)**	30 (39.5)	37 (48.7)	1 (1.32)	8 (10.5)	**16 (21.1)**	60 (78.9)	**68 (89.5)**	8 (10.5)
A7501015	SD	BE	Vol	5 mg	38	27 (71.1)	11 (28.9)	0 (0)	8 (21.1)	3 (7.89)	27 (71.1)	17 (44.7)	21 (55.3)	13 (34.2)	25 (65.8)
A7501016	SD	BE	Vol	5 mg	36	22 (61.1)	14 (38.9)	0 (0)	4 (11.1)	0 (0)	32 (88.9)	16 (44.4)	20 (55.6)	13 (36.1)	23 (63.9)
041001	MD	MTD	Pxt	0.8 mg	24	21 (87.5)	3 (12.5)	18 (75)	1 (4.17)	0 (0)	5 (20.8)	0 (0)	24 (100)	0 (0)	24 (100)
041007	MD	MTD	Pxt	4.8 mg	20	16 (80)	4 (20)	13 (65)	4 (20)	1 (5)	2 (10)	0 (0)	20 (100)	16 (80)	4 (20)
041012	MD	MTD	Pxt	20 mg	18	17 (94.4)	1 (5.56)	3 (16.7)	15 (83.3)	0 (0)	0 (0)	0 (0)	18 (100)	17 (94.4)	1 (5.56)
041014	MD	MTD	Pxt	15 mg	8	6 (75)	2 (25)	5 (62.5)	1 (12.5)	0 (0)	2 (25)	0 (0)	8 (100)	8 (100)	0 (0)
Total					346	294 (85.0)	52 (15.0)	169 (48.8)	71 (20.5)	30 (8.67)	76 (22.0)	49 (14.2)	297 (85.5)	135 (39.0)	211 (61.0)

a Based on data at screening
b MD is BID unless otherwise noted
c including missing values

Table 149 Smoking Status by Study in Studies used in Phase I/II Pop PK Analyses

Study Number	NONMEM Study Code	N	SD / MD	Study Objective	Subjs	Dosage[a]	Smoking Status Group					
							0	1	2	3	4	5
							Nonsmoker	< 1 PPD	1 - 2 PPD	> 2 PPD	Smoker Unknown Qty	Status Unknown
25537	37	23	MD	BE H_20	Vol	10 mg qd	0	0	0	0	—	23
25542	42	30	MD	MTD	Vol	15 mg	0	0	0	0	—	30
25545	**45**	**24**	**SD**	**Smokers**	**Vol**	**5 mg**	**0**	**0**	**0**	**0**		**24**
25546	46	49	SD/MD	Race	Vol	10 mg	0	0	0	0	—	49
A7501001	**1**	**76**	**MD**	**QTc**	**Vol**	**20 mg**	**8**	**32**	**35**	**1**		**0**
A751015	15	38	SD	BE	Vol	5 mg	25	11	2	0	—	0
A751016	16	36	SD	BE	Vol	5 mg	23	6	7	0	—	0
041001	41	24	MD	MTD	Pxt	0.8 mg	0	0	0	0	—	24
041007	47	20	MD	MTD	Pxt	4.8 mg	4	13	2	1	—	0
041012	12	18	MD	MTD	Pxt	20 mg	1	14	2	1	—	0
041014	44	8	MD	MTD	Pxt	15 mg	0	8	0	0	—	0
Total		**346**					**61**	**84**	**48**	**3**		**150**

a MD is BID unless otherwise noted

The following pages show the sponsor's figures of typical semi-log concentration vs. time profiles predicted using the base structural model, (i.e. a 2 compartment open model with a lag phase and nonlinear first order absorption), developed from the phase I and II data overlaid with observed single dose concentration data in Figure 125 and multiple dose data in Figure 126. Data from healthy volunteers are indicated by red circles and from patients with gray asterixes in these figures.

Figure 127 shows the same data overlaid on the expected typical semi-log concentration vs. time profile with the 95% confidence interval for the population.

Figure 128 shows a QQ plot for observed vs. simulated asenapine concentrations it's clear from this plot that the model begins to break down at concentrations above approximately 11 ng/ml. At the other end of the concentration spectrum examination of Figure 125 shows that at concentrations of around 0.02 ng/ml the concentration vs. profiles indicate a deviation from the model that may be indicative of either a third compartment or cross-over interference in the assay from a metabolite.

Figure 125 and Figure 126 show maximally achieved peak concentrations of around 10 ng/ml after single and multiple 5 mg doses respectively. Figure 126 shows maximally achieved peak concentrations of upwards of 20 ng/ml at multiple dosing of 20 mg, and Figure 127 clearly shows a maximal peak concentration of around 16 ng/ml after multiple dosing of 10 mg. However when the pop PK datafile was checked to determine the actual maximal peak concentrations at various dosages the highest concentration listed at any dose was only 9.58 ng/ml.

This reviewer attempted to double-check the Cmax ranges reported in the individual studies that used the larger doses by examining the summary tables already included in this review, this reviewer noted that ranges were not reported for these studies but only measures of central tendency. Since these reports were done by Pfizer and utilize the type of methodology that is being presently implemented in the FDA, this raises concerns that FDA will not be able to detect problems in the future.

Table 150 Attempt to Verify Cmax Range Across Studies

Study	SD / MD[a]	Study Objective	Subjs	Dosage[a]	Study Report	Data Files with Original Submission	Data Files Provided in Response to OCP Request	Upper Reported Range of Cmax (ng/ml)	Comment
25537	MD	BE H20	Vol	10 mg qd	No	No	Yes[b]		Can't open hyperlink does not work in EDR.
25542	MD	MTD	Vol	15 mg	No	No	Yes[c]		Can't open. Missing header in file.
25545	**SD**	**Smokers**	**Vol**	**5 mg**	No	No	Yes[b]		Can't open hyperlink does not work in EDR.
25546	SD /MD	Race	Vol	10 mg	Yes	No	Yes[b]	13.3	Can't open hyperlink does not work in EDR. Also receive error message in JMP Can't open. Missing header in file.
A7501001	MD	QTc	Vol	20 mg	Yes	No	Yes[c]	15 mg 8.05 (0.672 – 18.0)[d] 20 mg 10.6 (1.58 - 19.8)[d]	Told not to Review Can't open missing header in file. Followup submission of data to QT team. Max reported Conc in datafile was 9.949 ng/ml BP Oct 3, 2007 SN 0004. In addition nearly 1000 samples are listed as But when try to reopen get error msg 25512 then won't even open JMP
A7501015	SD	BE	Vol	5 mg					Told not to Reveiw
A7501016	SD	BE	Vol	5 mg					Told not to Reveiw
041001	MD	MTD	Pxt	0.8 mg		No		Dose normalilzed to 1 mg	
041007	MD	MTD	Pxt	4.8 mg	Yes	No	Yes	5.3	
041012	MD	MTD	Pxt	20 mg	Yes	No	Yes	10 mg 15.5 15 mg 11.8 20 mg 11.4	Can't open missing header in file.
041014	MD	MTD	Pxt	15 mg	Yes	No	Yesb, [c]	13.4	Told not to Review Can't open missing header in file.

a except where noted multiple dosing is BID
b Although data files were submitted in SN 0006 submitted Nov 19, 2007. On March 17, 2009 found that EDR http link does not work. Receive error message that can't find file.

Information for OCP included in Supplement 0006

25545

22 listed as NSR on 15. 20 mg

Information for OCP included in 4month Safety Update

A7501021 PK but what

011

All indiv sub listings

Exploratory Exposure Response to EPS

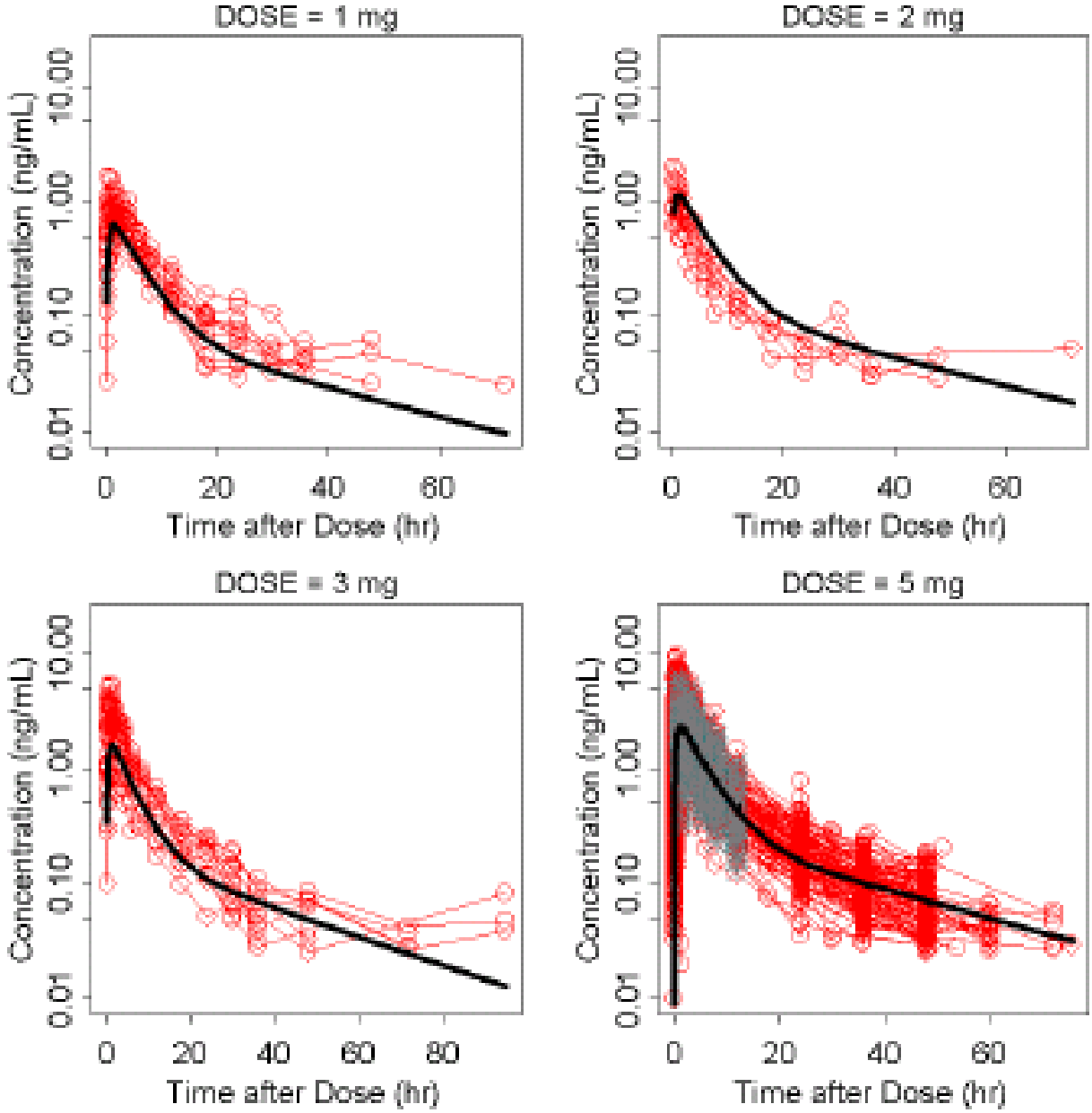
INT000656682

Model Codes

Study 1, the thorough QT study, (i.e. study A7501001), in addition to listing several subjects with bilirubins of 10 and 11 in the pop PK datafile also lists several subjects with albumin concentrations and creatinine clearances that are inconsistent with the units given in the pop PK study report and with the values from all other subjects. For albumin the concentrations listed are 30, 38, 40, 44, and 50 gm/dL and the creatinine clearances are 0.87, 0.96, 0.99, 1.23, 0.78, and 1.25 ml/min. It's possible that the reported values for these measures as well as for bilirubin may be due to misplacement of the decimal point, however this needs to be clarified with the sponsor.[9]

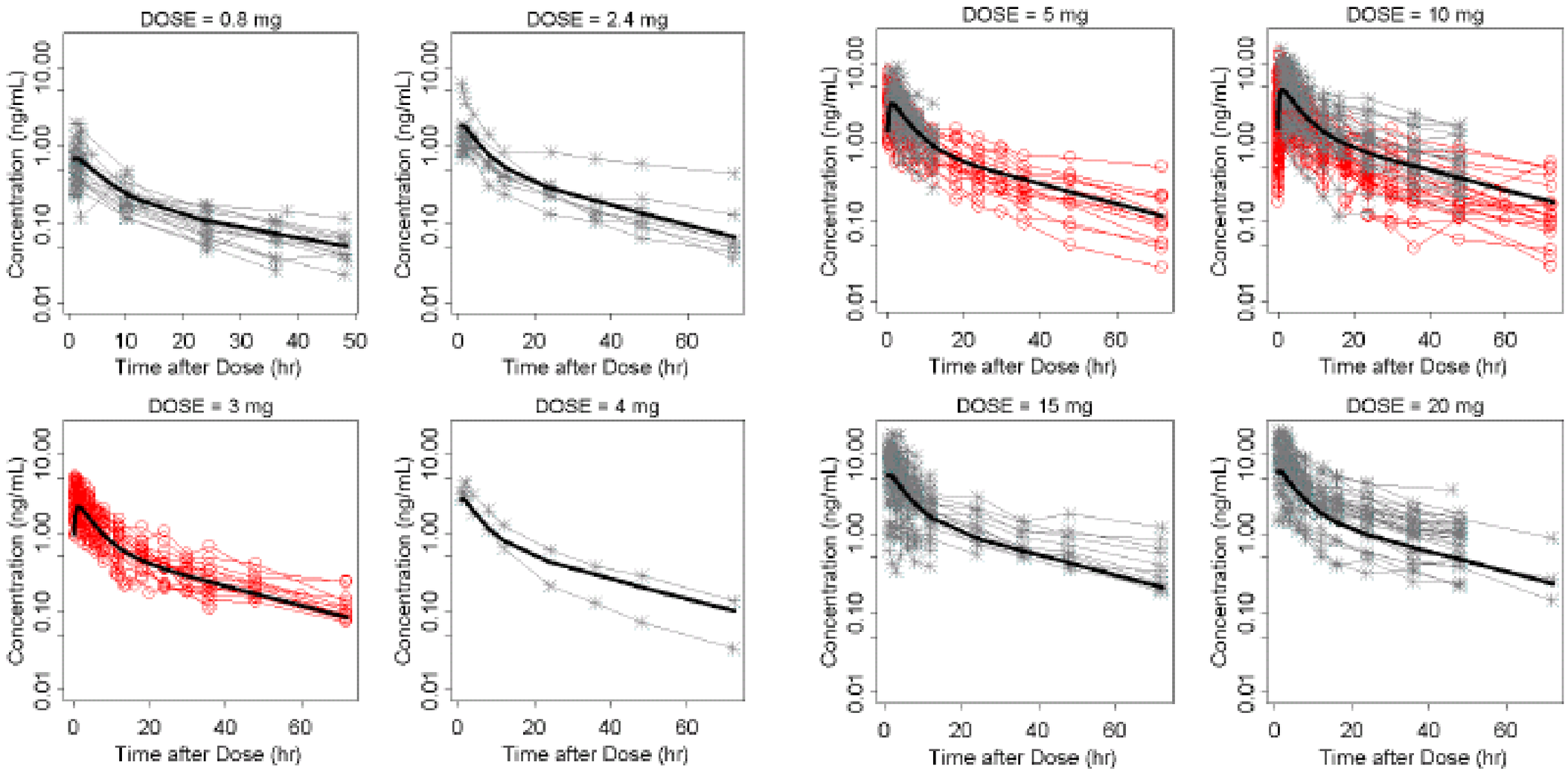
[9] Potential followup issue to be discussed with medical division as necessary.

Figure 125 Single Dose Phase I/II Pop PK Predicted Asenapine Concentration-Time Profile (Base Model) for Selected Doses versus Observed Concentrations



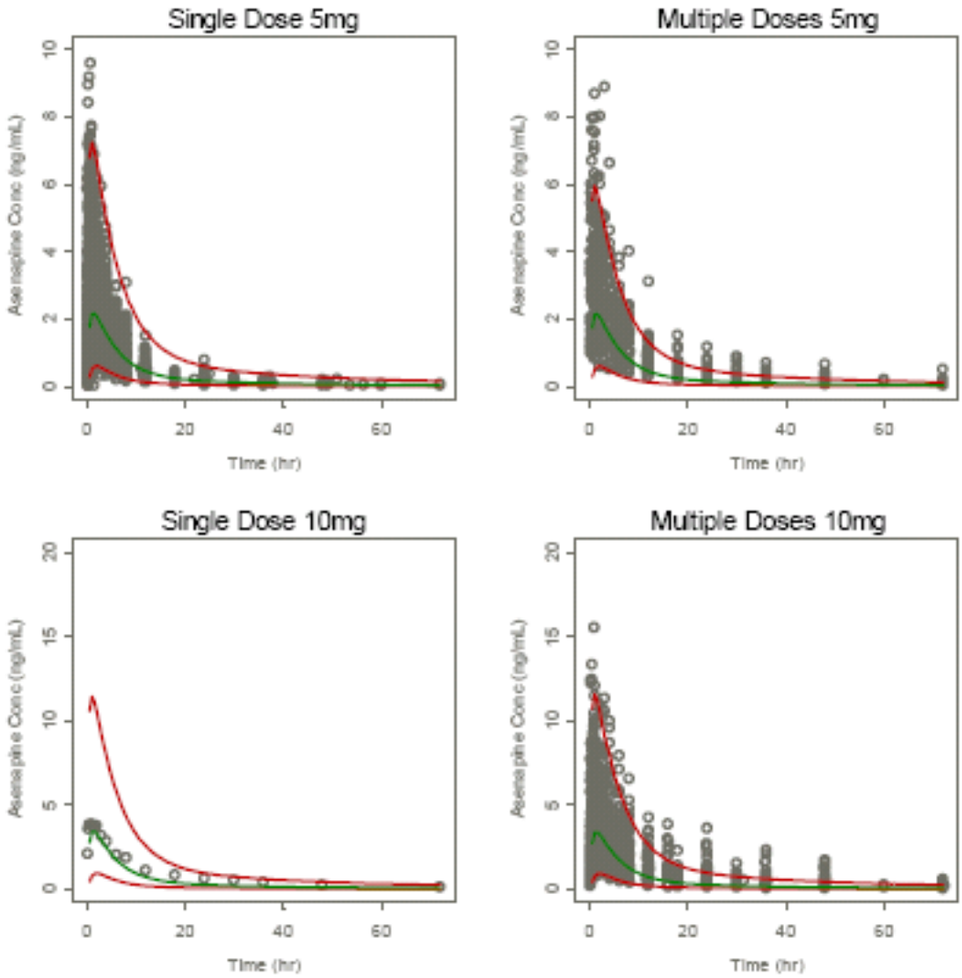
Red circles represent the observed asenapine concentrations from healthy volunteers; gray asterisks represent the observed asenapine concentrations from patients with schizophrenia. Solid lines represent the typical individual (population) predictions obtained from the final base model.

Figure 126 Phase I/II Pop PK Predicted Asenapine Multiple Dose Steady State Concentration-Time Profiles (Base Model) for Selected Doses with Overlaid Observed Concentrations



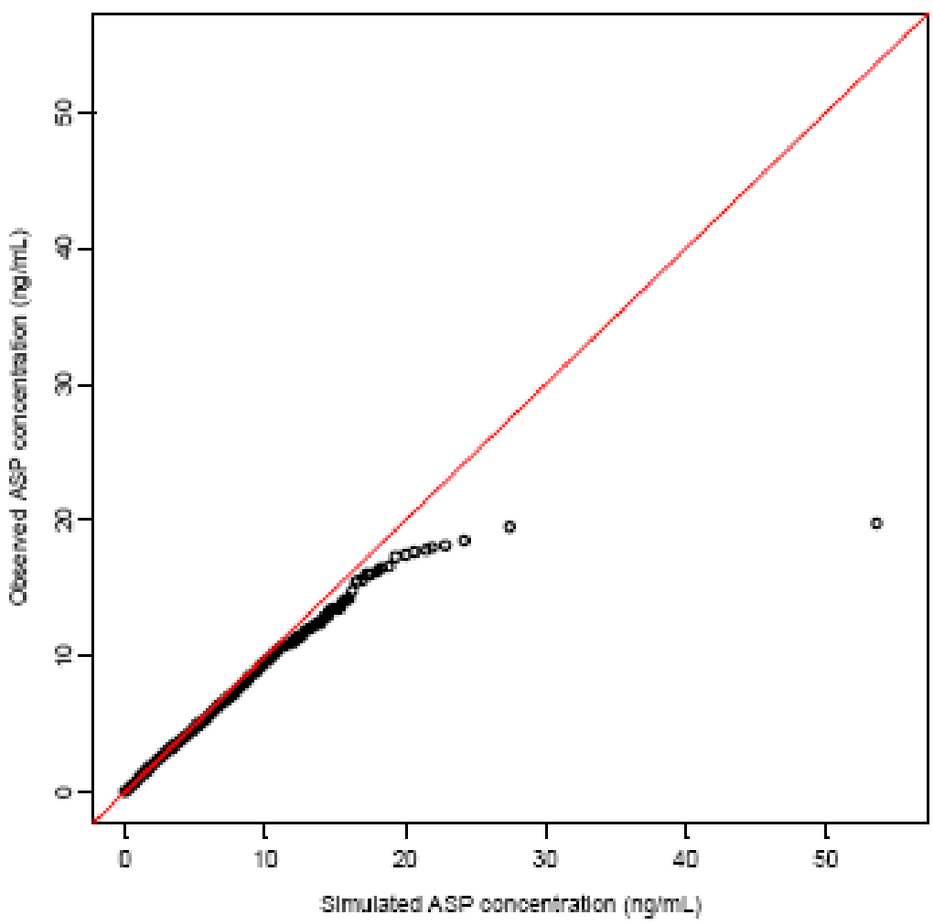
Red circles represent the observed asenapine concentrations from healthy volunteers; gray asterisks represent the observed asenapine concentrations from patients with schizophrenia. Solid lines represent the typical individual (population) predictions obtained from the base model.

Figure 127 Sponsor's Plot of Phase I/II Pop PK Unconditional 95% Prediction Interval with Overlaid Observations



Gray circles represent the observed asenapine concentrations; red lines represent the 0.975th and 0.025th quantiles of simulated asenapine concentrations; green line represents median of simulated asenapine concentrations.

Figure 128 QQ Plot of Observed vs. Phase I/II Pop PK Simulated Asenapine Concentrations



The sponsor makes the following statements in the phase I/II pop PK study report:

'RESULTS:

Asenapine pharmacokinetics both after single dose and at steady state of BID dosing were adequately described by a 2-compartment model with first-order absorption and a lag time on the absorption. The dose-dependent decrease in relative bioavailability was described by a linear function of the logarithm of dose. Inter-individual variability was modeled on the elimination rate constant ke, the apparent central volume of distribution (V2/F), the inter-compartmental transfer rate constants k23 and k32 and the absorption rate constant ka. In the final model for the inter-individual random effects all covariances were fixed to zero to obtain the most parsimonious model. Inter-occasion variability was modeled on ka and relative bioavailability Frel. In the final model apparent clearance estimate was 288 L/h and the overall apparent volume of distribution was 4840 L.

The following covariates were included in the final model: race (Black) on clearance (elimination rate), patient status on ka and patient status on lag time tlag. For black subjects, the estimated elimination rate was 13.8 % smaller than that of other races. In patients, a shorter tlag (0.025 h vs 0.125 h in healthy volunteers) and a lower absorption rate constant (50% of that in healthy volunteers) indicated a different absorption pattern. Most likely these differences can be attributed to the less dense pharmacokinetic sampling scheme in the patient studies. None of the other covariates were found to have an effect.

DISCUSSION

Asenapine is a high extraction ratio drug; therefore elimination may also be dependent on hepatic blood flow. Asenapine is highly protein bound and is widely distributed. As expected with such compounds, no major covariates were identified in this population PK analysis that may warrant dose adjustments.

Large inter-subject and inter-occasion variability was seen in the absorption. Asenapine shows unique characteristics of absorption kinetics for a sublingual formulation. Its individual Tmax values range 0.3 to 4 hours. Nonlinear bioavailability may be due to the solubility limit of asenapine in the mouth. The relationship between relative bioavailability and dose appears to be log-linear rather than an Emax type of relationship.

The different lag times estimated for patients and healthy volunteers as well as the effect on the absorption rate constant between the two groups would indicate a different absorption pattern of sublingual asenapine in patients and healthy volunteers. Most likely these differences can be attributed to the less dense sampling scheme in the patient studies. Race (Black) was identified as a statistically significant covariate on clearance (elimination rate). However, the magnitude of the covariate effect is relatively small compared to intersubject and inter-occasion variability seen with this compound.

CONCLUSION(S)

Asenapine pharmacokinetics after single dose and during BID dosing can be modeled adequately with a 2-compartment model with first order absorption, a lag time on absorption and a dose dependent decrease in relative bioavailability. No clinically meaningful covariates were identified that may warrant dose adjustments.'

Reviewer Comments

Most of the conclusions qualitatively reflect the conclusions drawn from the individual studies themselves. However, the sponsor's statement regarding Tlag is opposite what was reported in the body of the report

where a 1.5 minute Tlag was reported for healthy volunteers and a 7.5 minute Tlag was reported for patients. This degree of difference especially as the sampling schemes would be unable to measure Tlags of these magnitudes, for either population, clearly demonstrate the inappropriateness of the structural model.

The claim regarding the lack of expected effects due to asenapine being a high intrinsic clearance drug is not correct, with the clearest example being the effect of food, as seen in study 41029, which was not even included as acovariate used in this analysis. In addition, the age range was insufficient to detect an effect of age in the elderly or the pediatric populations, and lastly covariates such as smoking were not adequately documented to determine an effect, plus the use of laboratory values obtained prior to dosing may also bias the evaluation of these covariates, if they should change with dosing, e.g. in hepatotoxicity.

5.5.8.2 Phase II and Phase III Efficacy Studies

Validation of the pop PK model developed using the phase I and II data was done utilizing data from the phase II and III acute efficacy studies. The sponsor's description of this validation process follows:

'The final population pharmacokinetic model described above <in the previous section> was utilized, without modification, in this analysis to simulate asenapine concentration data to create unconditional prediction intervals (UPI). The UPI is an uncertainty interval that reflects model predicted variability at the individual observation level. The UPI was used to assess whether the observed data were consistent with the population PK model developed previously. Consistency between the model and the data can be determined by comparing the percentage of observations below or above the UPI distribution percentiles (e.g., a 90% UPI should contain 90% of the observed data). Since the UPI addresses data at the observation level, residual variability (as well as between patient variability) is included in its calculation. The term 'unconditional' is utilized in the name of this prediction interval to indicate that uncertainty in the residual variability estimate is incorporated within the interval unlike the prediction interval typically computed for regression analyses. Since a closed form expression for the UPI is not available for nonlinear mixed effects models, it is computed using simulation. To this end, a parametric bootstrap procedure was implemented, which is described below.

Each simulation dataset contained 1000 subjects and 500 replicates of simulated dataset per dose were generated to create unconditional prediction intervals. The simulations consisted of the following three steps.

1. Simulation Data Shell Generation: Using Splus 6.2, 1000 subjects records were created with missing DV for steady state. Time after dose in hours as a predictor variable were created ranging from 0 to 48 hours in an increment of 0.5 hours for every subject. As black race on ke was a significant covariate, uniform random numbers were used to generate 34% (observed black race population proportion in Phase 2/3 datasets) of black race patients among the 1000 subjects in the shell dataset.

2. Simulation: Using PERL scripts, the NONMEM output of the Phase 1/2 was parsed and multivariate normal random sampling was performed with mean of parameters estimates and variance of the variance-covariance matrix (N=500). Then each sample parameter vector was replaced into the NONMEM script and changed estimation into simulation with a different seed resulting in a simulated dataset for all 500 replicates.

3. Post Processing: All the simulated concentrations were combined and at each time point 5th, median, and 95th percentiles were calculated. The unconditional prediction intervals based on the previous population PK model were generated to assess similarities/differences in the results from the Phase 2/3 studies versus the Phase 1/2 studies.'

A listing of the studies utilized is shown in Table 151 and demographic characteristics are shown in Table 152. Although the sampling was not intensive Table 151 shows that sampling was adequate and better than is usually seen.

Figure 129, Figure 130, Figure 131, and Figure 132 on the following pages show observed asenapine concentrations from phase II and III studies overlaid on simulated 90% confidence intervals based on the phase I / II pop PK model. Figure 129 shows all phase II and phase III data from the acute efficacy studies by dose. Figure 130 shows data by dose and indication. Figure 131 shows data from the thorough QT study, and Figure 132 shows data from each individual acute efficacy study by indication and dose.

Again maximal peak concentrations appear to be around 20 ng/ml however inspection of the datafile reveals a maximum concentration of 9.99 ng/ml with a dose of 10 mg and on two concentrations at a dose of 20 mg with the highest reported concentration being 2.64 ng/ml. In addition, there are listings for lithium and valproate concentrations and the data definition file includes these in the phase I/ II data sets also even though these drugs were not coadministered in the phase I and II studies modeled.

Table 151 Phase II and III Acute Efficacy Studies included in Population Pharmacokinetic Modeling

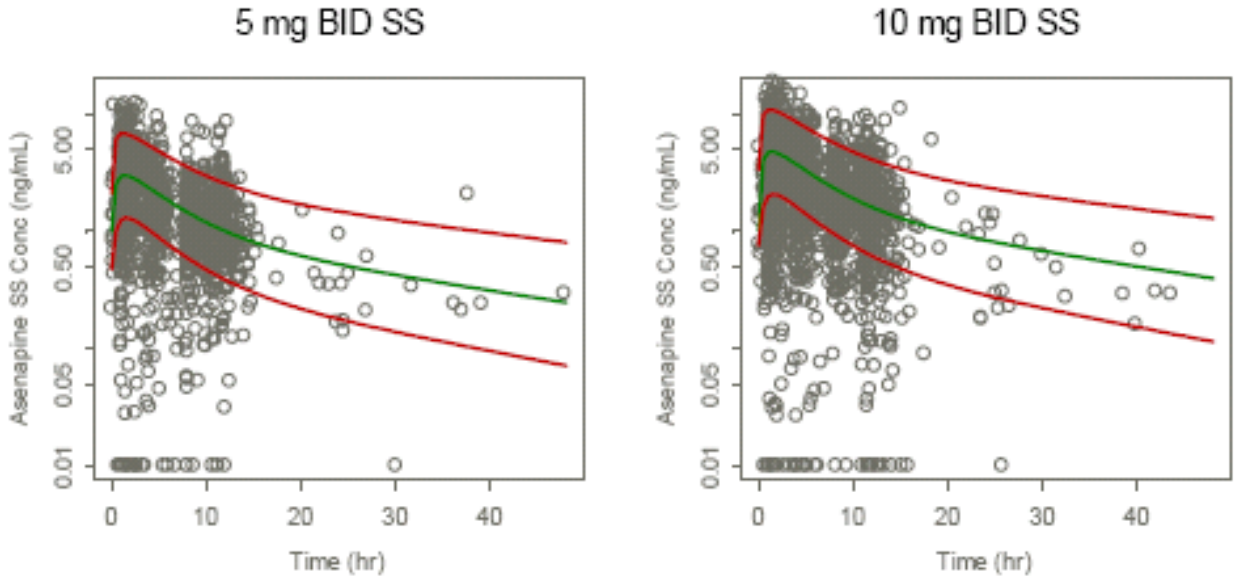
Study # (Phase)	SD / MD	Study Title	Subject Population	Treatment	Analytic Method	LLOQ (ng/mL)	PK Sampling Times
041004 (2b)	MD	Rand DB fixed-dose 6-week efficacy and safety trial of Asenapine, risperidone and placebo in acute exascerbation of schizophrenia	Acute Schizophrenia	Day 1: 1 mg BID Day 2: 2 mg BID Day 3: 3 mg BID Day 4: 4 mg BID Day 5-42: 5 mg BID	GC-MS	0.020	***Days 0, 7 & 21:*** 1-2 hours before AM dose. ***Day 7:*** 1-3, 4-6, and 8-12 hours postdose. ***Day 42:*** postdose
041021 (3)	MD	Rand DB fixed-dose 6-week efficacy and safety trial of Asenapine,olanzpaine, and placebo in acute exascerbation of schizophrenia	Acute Schizophrenia	5 or 10 mg BID up to 42 days	LC-MS	0.025	***Screening. Day 14:*** predose, 1-3, 4-6, 8-12 hours. ***Day 28:*** 1-8 hours. ***Day 42:*** Within 24 hours postdose.
041022 (3)	MD	Rand DB fixed-dose 6-week efficacy and safety trial of Asenapine,olanzpaine, and placebo in acute exascerbation of schizophrenia	Acute Schizophrenia	5-10 mg BID up to 42 days	LC-MS	0.025	***At screening. Day 14:*** predose, 1-3, 4-6, 8-12 hours. ***Day 28:*** 1-8 hours. ***Day 42:*** Within 24 hours postdose.
041023 (3)	MD	Rand DB fixed-dose 6-week efficacy and safety trial of Asenapine,haloperidol, and placebo in acute exascerbation of schizophrenia	Acute Schizophrenia	5 or 10 mg BID up to 42 days	LC-MS	0.025	***At screening. Day 14:*** predose, 1-3, 4-6, 8-12 hours. ***Day 28:*** 1-8 hours. ***Day 42:*** Within 24 hours postdose.
A7501004 (3)	MD	Rand DB fixed-dose 6-week efficacy and safety trial of Asenapine,olanzpaine, and placebo in inpatiens with an acute manic episode	Acute Mania	5-10 mg BID for 21 days	LC-MS	0.025	***Day 1, 7, 14 and 21:*** predose. ***Day 7:*** 1-3, 4-6, 8-12 hours postdose.
A7501005 (3)	MD	Rand DB fixed-dose 6-week efficacy and safety trial of Asenapine,olanzpaine, and placebo in inpatiens with an acute manic episode	Acute Mania	5-10 mg BID for 21 days	LC-MS	0.025	***Day 1, 7, 14 and 21:*** predose. ***Day 7:*** 1-3, 4-6, 8-12 hours postdose.

Table 152 Population Demographic Characteristics for Categorical Variables from Phase II/III Population PK Studies[a] [N (%)]

Study	N	Gender		Race				Alcohol Consumption		Smoking Status	
		Male	Female	White	Black	Asian	Other	Yes	No	Yes	No
14	45	36 (80)	9 (20)	21 (46.7)	20 (44.4)	0 (0)	4 (8.89)	0 (0)	45 (100)	40 (88.9)	5 (11.1)
21	187	135 (72.2)	52 (27.8)	94 (50.3)	81 (43.3)	8 (4.28)	4 (2.14)	186 (99.5)	1 (0.5)	133 (71.1)	54 (28.9)
22	79	59 (74.7)	20 (25.3)	39 (49.4)	34 (43)	1 (1.27)	5 (6.33)	79 (100)	0 (0)	57 (72.2)	22 (27.8)
23	199	129 (64.8)	70 (35.2)	123 (61.8)	49 (24.6)	21 (10.6)	6 (3.02)	199 (100)	0 (0)	118 (59.3)	81 (40.7)
4	67	32 (47.8)	35 (52.2)	43 (64.2)	21 (31.3)	1 (1.49)	2 (2.99)	67 (100)	0 (0)	51 (76.1)	16 (23.9)
5	79	51 (64.6)	28 (35.4)	56 (70.9)	19 (24.1)	0 (0)	4 (5.06)	79 (100)	0 (0)	63 (79.7)	16 (20.3)
Total	656	442 (67.4)	214 (32.6)	376 (57.3)	224 (34.1)	31 (4.73)	25 (3.81)	610 (93)	46 (7.0)	462 (70.4)	194 (29.6)

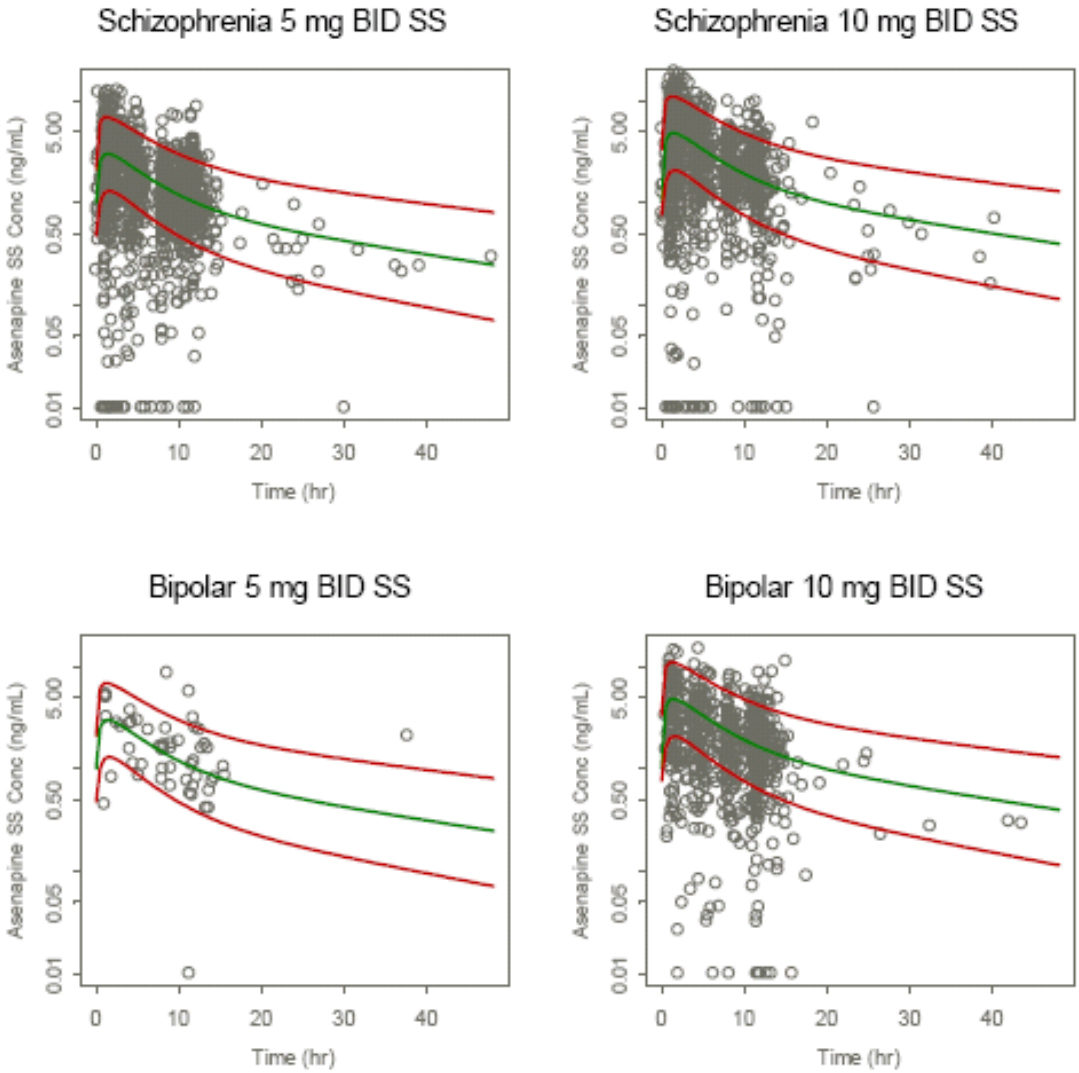
a Based on data at screening

Figure 129 Observed Asenapine Concentrations from All Phase 2/3 Studies by Dose Overlaid on Unconditional 90% Prediction Interval



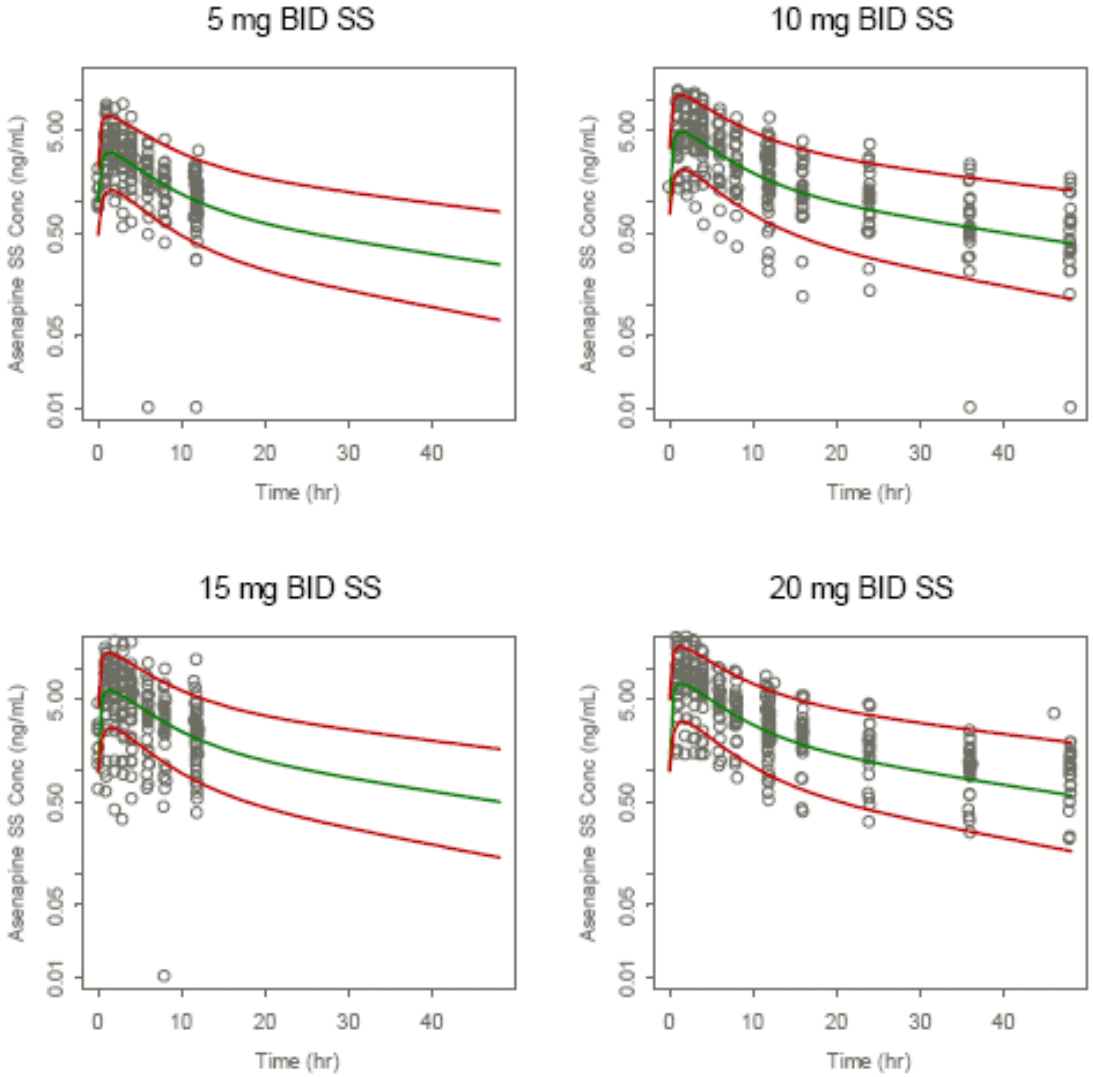
Grey circles represent the observed asenapine concentrations; red lines represent the 95th and 5th quantiles of simulated asenapine concentrations; green line represents median of simulated asenapine concentrations.

Figure 130 Observed Asenapine Concentrations from Phase 2/3 Studies by Indication and Dose Overlaid on Unconditional 90% Prediction Interval



Grey circles represent the observed asenapine concentrations; red lines represent the 95th and 5th quantiles of simulated asenapine concentrations; green line represents median of simulated asenapine concentrations.

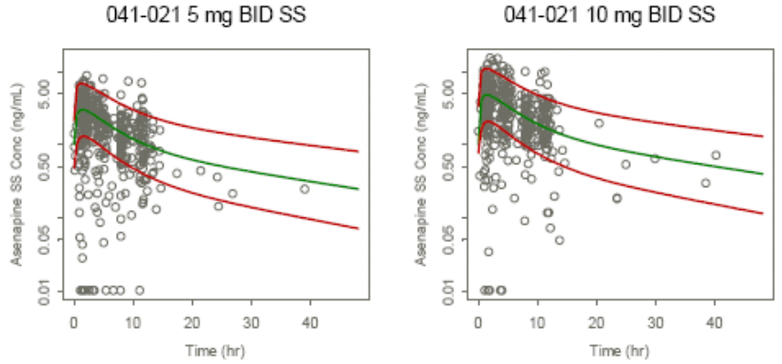
Figure 131 Observed Asenapine Concentrations from the Thorough QTc Study Overlaid on the Unconditional Prediction Interval for Model Validation - Study A7501001

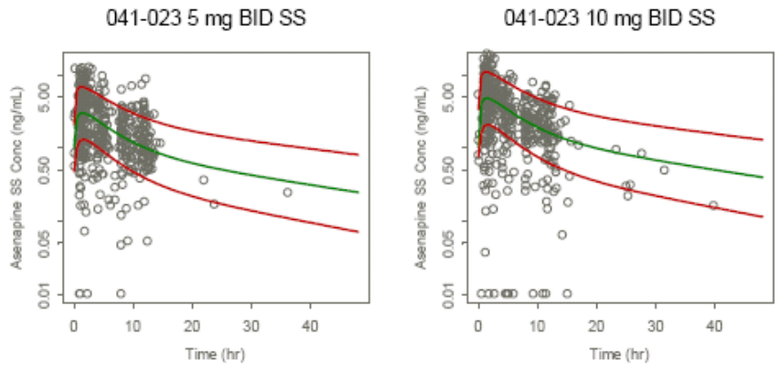


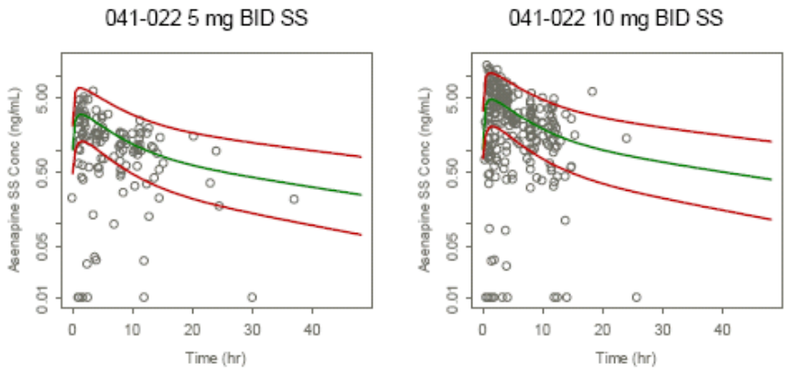
Grey circles represent the observed asenapine concentrations; red lines represent the 95th and 5th quantiles of simulated asenapine concentrations; green line represents median of simulated asenapine concentrations.

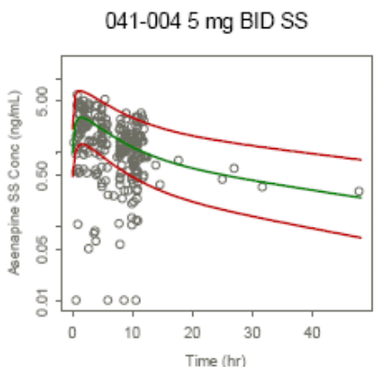
Figure 132 **Observed Asenapine Concentrations from Individual Phase 2/3 Studies Overlaid on Unconditional 90% Prediction Interval by Indication, Study, and Dose**

Phase II / III Efficacy Studies in Schizophrenia

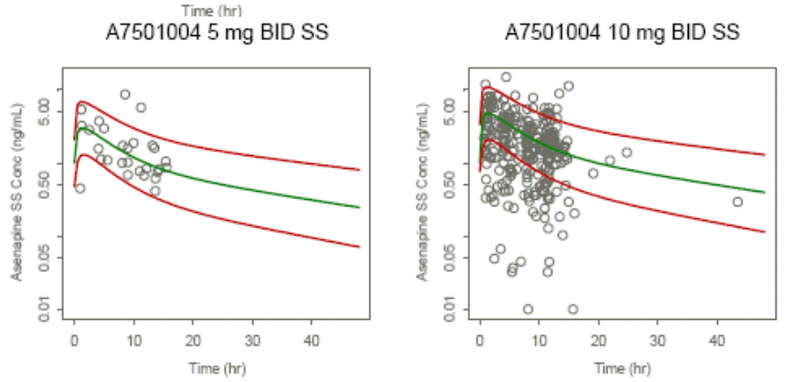








Phase II / III Efficacy Studies in Acute Mania



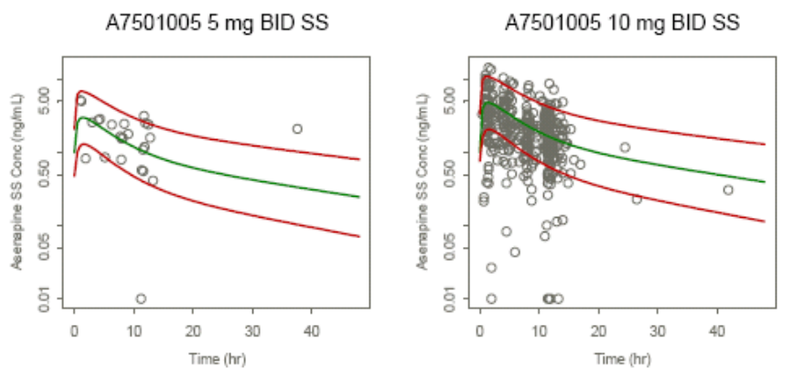


Table 153 shows the percent of the observations above and below the predicted median, 5th, and 95th, percentiles for the phase II / III studies. It's clear that the model overpredicts however, the large percent of concentrations that are below the 5th percentile and are even zero suggests that this may be in part due to noncompliance although it's also likely that a large percentage of this is due to the effect of smoking that has not been adequately captured in the model. In addition, the underprediction of variability, especially on the high end may indicate that not all covariates have been adequately identified.

Table 153 Percent (%) of Observations from Phase II/III Population PK Studies Above and Below the 5th, Median, and 95th Percentiles for the Simulated Unconditional Prediction Intervals

Study Number	5 mg				10 mg			
	Below 5th	Below Median	Above Median	Above 95th	Below 5th	Below Median	Above Median	Above 95th
A7501001 (Phase 1 in Patients)	4.8	40.9	59.1	3.9	9.3	44.9	55.1	8.6
All Phase 2/3	20.1	57.3	42.7	6.5	22.9	58.4	41.6	5.7
All Schizophrenia	20.6	57.9	42.1	6.5	21.9	56.5	43.5	6.0
All Bipolar	7.4	42.6	57.4	7.4	24.7	61.4	38.6	5.3
041-021	18.1	54.2	45.8	3.6	20.1	58.0	42.0	5.6
041-023	19.0	53.5	46.5	13.2	19.7	53.2	46.8	7.7
041-022	29.3	72.4	27.6	0.8	29.3	60.8	39.2	3.4
041-004	23.9	65.7	34.3	3.2	—	—	—	—
A7501004	3.6	50.0	50.0	7.1	28.2	61.3	38.7	4.9
A7501005	11.5	34.6	65.4	7.7	21.8	61.4	38.6	5.6

5.6 Pharmacodynamics

5.6.1 PK/PD

5.6.1.1 Biomarker - PET Studies

Two PET studies after oral administration of asenapine were conducted in 1989 and 1990, and two studies after sublingual administration of asenapine were conducted in 1996 and 1997.

Little binding to D_2 receptors and no binding to D_1 receptors was detected at Tmax after 10 mg oral doses of asenapine in studies 86033 and 25503.

After sublingual administration of a single 100 mcg dose in study 25510, and multiple doses of asenapine 300 mcg in study 25516, low levels of binding to dopamine D_2 receptors in the caudate nucleus and putamen were detected.

Based upon the observed plasma concentrations and binding values, and assuming a simple Bmax model, this reviewer estimated that Cmaxs of around 3 – 9 ng/ml are needed to achieved 90% D_2 receptor blockade. Based on the phase I pharmacokinetic studies this appears to be achievable with doses of 5 – 10 mg SL BID in young healthy male volunteers.

5.6.1.1.1 Oral Administration

In 1989 and 1990 the sponsor conducted PET studies of orally administered 10 mg doses of asenapine to determine the receptor binding to D_2 and D_1 receptors respectively. In study 86033, conducted in 1989, asenapine 10 mg was administered to 2 healthy male volunteers and D_2 binding by ^{11}C - raclopride in the putamen and cerebellum was measured at 2 hours and 5.5 hours post dose. No binding was detected at 5.5 hours post - dose although at 2 hours post - dose binding was 24%.

According to the introduction section of this study report 1.5 mg 5 mg, 10 mg, and 15 mg PO BID dosing for 14 days resulted in dose dependent increases in transaminases in the 5 – 15 mg dose groups in 3 of 6 subjects, (see Figure 223 in Appendix §**Error! Reference source not found.**). This was a safety study and plasma samples for pharmacokinetics were not obtained. In addition hepatotoxicity was seen in the dog studies.

In study 25503, conducted in 1990, asenapine 10 mg was administered to 2 healthy male volunteers and D_1 binding by ^{11}C - SCH - 23390 in the putamen and cerebellum was measured at 2 hours and 3 hours post dose. No binding was detected at either time.

5.6.1.1.2 Sublingual Administration

5.6.1.1.2.1 PET Study 25510

Three healthy male volunteers were administered a single dose of placebo on day 1 and asenapine 100 mcg sublingually one week later.

PET ligands to measure binding affinities to D_2 and 5 - HT_{2A} receptors *in vivo* were guided by the pharmacokinetic characteristics of asenapine. Information on the administration of these ligands and the timing of their scans are shown in Table 154Table 154 PET Scans Employed in Study 25510

Table 154 PET Scans Employed in Study 25510

Scan No.	Time of PET Scan	Receptor of Interest	Positron Emitter
PET 1	2.5 hrs post dose	D_2	^{11}C - raclopride
PET 2	4.5 hrs post dose	5 - HT_{2A}	^{11}C - N - Methyl - spiperone (NMSP)

Figure 133 shows the *in vitro* receptor binding affinities for asenapine reported in this study.

Figure 133 Asenapine *In Vitro* Receptor Binding Affinities per Study Report 25510

Receptor	Radioligand	ORG 5222 (K_i in nM)
D_1	[3H]SCH 23390	4
D_2	[3H]spiperone	3.1
D_2	[3H]NPA	0.6
α_1	[3H]prazosin	0.6
α_2	[3H]rauwolscine	7.9
5-HT_{1A}	[3H]8-OH-DPAT	10
5-HT_{1B}	[3H]5-HT (rat)	40
5-HT_{1D}	[3H]5-HT (calf)	79
5-HT_{2A}	[3H]ketanserin	0.06
5-HT_{2C}	[3H]5-HT (pig)	0.08
H_1	[3H]mepyramine	7.9
ACh/m	[3H]QNB	5000

From de Boer et al. 1993

Figure 134 shows the asenapine concentration time profiles and Figure 135 and Figure 136 show the degree of radionuclide receptor binding to D_2 in the putamen and $5HT_{2A}$ in the frontal cortex compared to the cerebellum in the presence and absence of asenapine. From these 3 figures it's easy to see that asenapine peak concentrations of around 110 pg/ml in subject #3 are associated with around 10% binding to $5HT_{2A,}$ and around 25% binding to D_2. This suggests that a concentration of around 1 ng/ml is needed to achieve 75% D_2 binding, and concentrations of 3 ng/ml or more is needed to achieve around 90 % D_2 binding.

Figure 134 Asenapine Plasma C vs.T Profiles in Subjects Undergoing PET Scans – Study 25510

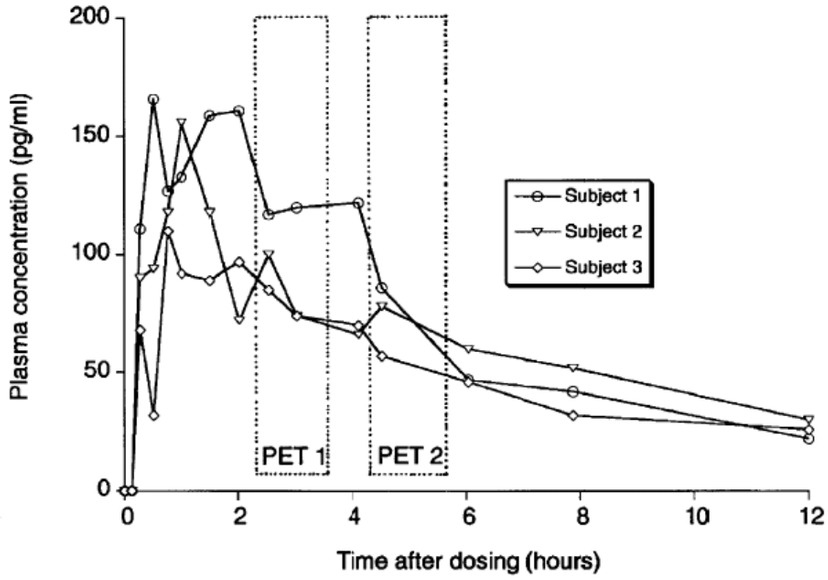


Figure 135 Radionuclide Receptor Binding to $5HT_{2A}$ in the Frontal Cortex and Cerebellum in the Presence and Absence of Asenapine 100 mcg – Study 25510

Figure 4 Regional radioactivity versus time in man (subject 3 in this study), before and 4.5 hours after sublingual administration of 100 µg Org 5222 with the ligand [^{11}C]NMSP. 19

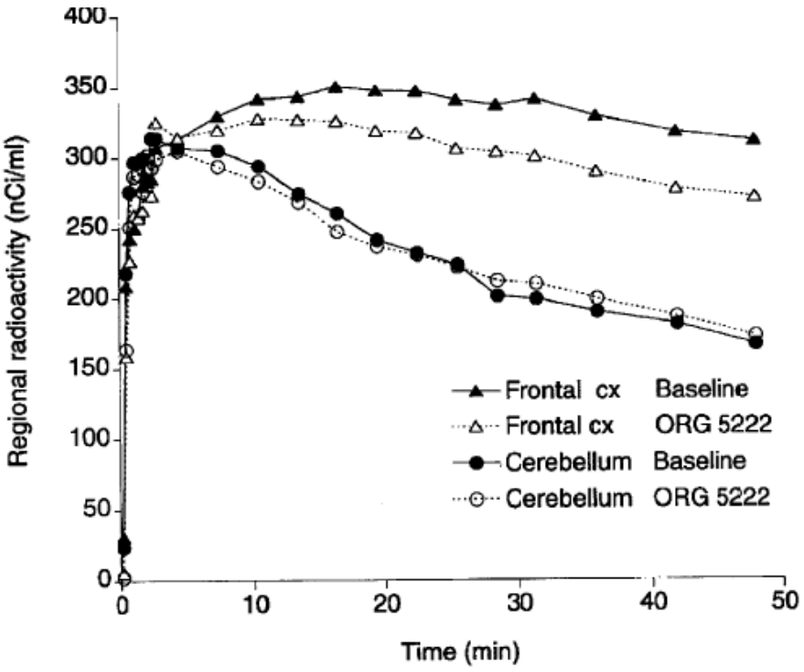


Figure 136 Radionuclide Receptor Binding to D_2 in the Putamen and Cerebellum in the Presence and Absence of Asenapine 100 mcg – Study 25510

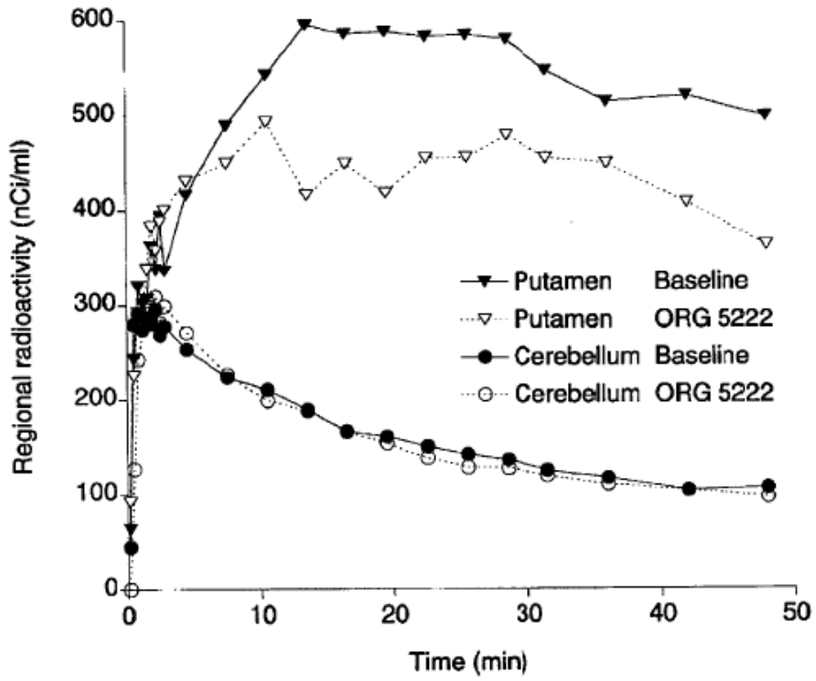


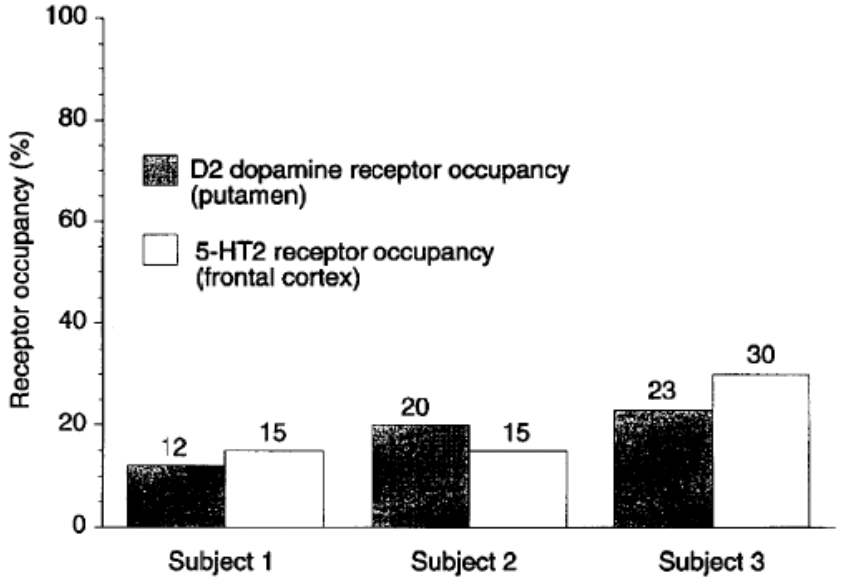
Figure 137 and Figure 138 show the actual pharmacokinetic metrics and the sponsor's calculated % binding to D_2 and $5HT_{2A}$ associated with these metrics in these 3 subjects.

Figure 137 Asenapine Pharmacokinetic Metrics from Healthy Volunteers in PET Ligand Binding Study 22510

Subject #	AUC_{0-12} (pg·h/mL)	$AUC_{0-\infty}$ (pg·h/mL)	CL/f (l/h)	C_{max} (pg/mL)	t_{max} (h)	$t_{½}$ (h)
1 (1st occasion)	570*	785	127	140	0.75	4.5
2	776	1028	97	156	1	5.7
3	609	850	118	110	0.77	6.8
1 (2nd occasion)	905	1023	98	166	0.5	3.9
Mean	715	922	110	143	0.8	5.2
S.D.	155	123	15	24	0.2	1.3

* AUC given is AUC_{0-8} ,because at t=12 the concentration was below the lower limit of quantification.

Figure 138 Asenapine D_2 and $5HT_{2A}$ Receptor Binding in Healthy Volunteers after Asenapine 100 mcg SL in PET Ligand Study 22510



Based upon these values and assuming a simple Bmax model we can estimate that Cmaxs of around 3 – 9 ng/ml are needed to achieved 90% D2 receptor blockade, (see Table 155).

Table 155 Reviewer's Estimation of Cmax needed for 90% D_2 Binding based on Study 25510 Data

Subject	Cmax (pg/ml)	% D2 Binding	Ki_{app} (pg/ml)	Estimated Cmax needed for 90% D_2 Binding[a]	
				(pg/ml)	(ng/ml)
1	140	12	650	6000	6
2	156	15	1000	9000	9
3	110	23	375	3500	3.5

a Reviewer's estimate based on simple Bmax model.

Based on the results of multiple dose PK study 25542, (conducted June 2004 – Aug 2004 at doses of up to 15 mg BID SL for safety), as well as multiple other PK studies this suggests a dose of around 5 - 10 mg SL BID is needed and in smokers the dose may possibly need to be even higher.

Even at the time of this this PET study this dose should have been predictable, not only based on the pharmacokinetics from this PET study, study 25510, but also based on the pharmacokinetics from an earlier study, study 25509 conducted from November 1994 to April 1995 with single sublingual doses of 100 mcg. Table 156 shows the individual peak concentrations seen in this study.

Table 156 Peak Concentrations with Single Sublingual Dose of Asenapine 100 mcg - Study 25509

Subject	Tmax (hours)	Cmax (pg/ml)
53	3	75.2
54	3	76.1
55	1	85.6
56	1	85.6
57	1	98.1
58	1	100.9
59	2	83.8
60	1	68.7
Average	—	84.2 ± 11.1 (13.2)

Assuming linear kinetics a 100 fold higher dose of 10 mg should product average peak concentrations of 8400 pg/ml, (8.4 ng/ml) with a range of 6.9 – 10.1 ng/ml. This is consistent with a dosage of 10 mg daily assuming no decrease in bioavailability.

The sponsor's conclusion from this PET study was that doses greater than 100 mcg were needed, and in the introduction to their follow - up confirmatory PET study, 25516, states that this data suggested an efficacious dose range of only 400 – 800 mcg.

5.6.1.1.2.2 PET Study 25516

PET study 25516 was intended both to be a confirmatory study and to follow the time course of asenapine caudate nucleus and putamen D_2 receptor occupancy in 7 healthy male volunteers over a 24 hour period after 4 doses of asenapine 300 mcg SL BID.

shows the observed mean plasma concentrations and mean observed % D_2 occupancy in the Putamen and Caudate Nucleus over a 24 hour period after dosing with asenapine.

Table 157 Asenapine Plasma Concentrations and Mean D_2 Occupancy in the Putamen and Caudate Nucleus over Time – Study 25516

Time (hours)	n	Mean Plasma concentration Org 5222 (pg/ml)	Putamen Occupancy (%)	N. Caudatus Occupancy (%)
2	4	217.7	31	29
3.5	2	166.2	25	31
6	6	108.9	16	18
12	6	54.5	5	7
24	6	30.2	5	3

Using a simple Bmax model and these values, this reviewer calculates a concentration of 5 ng/ml is needed to achieve 90% D_2 receptor occupancy with asenapine which is similar to what this reviewer calculated with the data from study 25510. The sponsor also used a Bmax model (model 1) as well as an exponential model. However the sponsor instead of using a Bmax of 100% used Bmax's of 97% (based on the PET ligand itself) and a target D_2 occupancy of 61% based on reports with clozapine. It appears that they chose this 61% as their maximum target based on this study and PET study reports for other atypical antipsychotics where subtherapeutic doses were used. However it does not appear that they corrected for time postdose in these studies. Consequently they estimated a dose of only 600 – 800 mcg as shown in Table 158.

To this reviewer is seems readily apparent that these would be inefficacious doses based both on the maximum binding and the expected binding over a 12 hour dosage interval.

Table 158 Sponsor's Estimated D2 Receptor Binding with Two Proposed Biferpunox Dosages – Study 25516

Org 5222 [µg]	Estimated Plasma Level, (2h post-dosing) [pg/ml]	Model 1, 97 %			Model 1, 61 %		
		2 h	12 h*	24 h*	2 h	12 h*	24 h*
600	430	45	19	7	38	16	6
800	580	52	22	8	42	18	6

* Values were calculated from the receptor occupancy at 2 hours, assuming a receptor binding half-life of 8.1 hours.

5.6.1.2 PK / PD Modeling and Simulation

On September 28, 2001 Pharsight, on contract to Organon, issued a modeling and simulation report, INT00039259, for dose-finding.

According to the report:

'The revised objectives of Aim 1 were:

- Predict mean week 6 Last Observation Carried Forward (LOCF) PANSS change from placebo for the ongoing study (041-013)[1], and the uncertainty around these predictions (including uncertainty and variability).

- The underlying predicted mean LOCF PANSS true dose response curve for Org5222 and the uncertainty around that prediction.

- Simulations giving the predicted likelihood of the treatments in study 041-013 being significantly different from placebo.

- An evaluation of the effect of dropout on the LOCF predictions.

- Predicted doses of Org5222 corresponding to clinically used doses of atypical antipsychotics.'

To achieve this Pharsight did the following:

- Developed population pharmacokinetic models for 4 antipsychotics in addition to asenapine
- Fit models to D2 occupancy vs. plasma concentration data
- Simulated D2 receptor occupancy time profiles with steady-state dosing and performed a covariate analysis
- Developed a model to convert BPRS scores to PANSS scores for inclusion in the PK/PD model
- Developed a pharmacodynamic link model for the influence of D2 occupancy biomarker on PANSS score
- Explored other Potential Co-Factors
    - Evaluated the potential of a Bell (or U) shaped dose response
    - Developed a mixed effects model to incorporated the influence of dropouts on PANSS scores
- Developed a Final Model
- Simulated the effect of asenapine under conditions used in study 41013 at doses of 1.6 mg and 2.4 mg BID

5.6.1.2.1 Development of Population Pharmacokinetic Models for 4 Antipsychotics in addition to Asenapine

The following pharmacokinetic data was used per the report:

'Pharmacokinetic data for Org5222 was provided by Organon. A three-compartment population pharmacokinetic model provided by Organon as the most suitable model was used for Org5222 pharmacokinetics. For Olanzapine, Risperidone, Ziprasidone and Quetiapine, public domain regulatory

[1] DB PBO controlled fixed dose study of Asenapine 1.6 mg and 2.4 mg SL BID.

documents including the Summary Basis of Approval (SBA's), Advisory Committee documents, and clinical expert reports were used. A thorough literature review was also performed and provided additional information about these compounds, as well as information on the pharmacokinetics of Haloperidol.'

The final pharmacokinetic models and parameters used in the modelling are shown in Table 159. It's interesting that the sponsor used a 3-compartment model for asenapine here but a 2 compartment model in the Pop PK analysis.

Table 159 Sponsor's Table 5 Population mean PK parameters used in simulations, and associated fractional SEs.

Compound	Haloperidol	Olanzapine	Asenapine	Risperidone	Ziprasidone
Model	1 compartment	1 compartment	3 compartment	2 compartment	1 compartment
Ka (h^{-1})	0.36 (26%)	0.54 (30%)	2.31	2.19 (6%)	0.147 (5%)
Cl (L/h)	26 (10%)	20.6 (4.5%)	159 (11%)	5.64 (4%)	31.5 (5%)
Vc (L)	672 (8%)	1121 (12%)	1080 (18%)	75 (3%)	105 (10%)
Vp (L)			4340 (16%)	73 (3%)	
V3 (L)			846 (16%)	2.64 (4%)	
Q1 (L/h)			29.6 (56%)		
Q2 (L/h)			311 (56%)		
F (%)	60 (13%)	*	*	*	60 (15%)
Reference	YF Cheng et al, 1987	SBA, page A 63	Internal report	Expert report, page 134	Drug label
Comments	Corrected for average study population of 74% men, 64% smokers			active moiety (risperidone + 9-OH-risperidone)	Ka derived from tmax

*parameters are corrected for F (i.e. CL/F, V/F, etc.)

5.6.1.2.2 Fit of D2 Occupancy vs. Plasma Concentrations

The sponsor fit the following models to the data:

- Linear
- Emax
- Quadratic
- Cubic
- Quartic
- Sine Functions (Fourier Series)
- Splines

For the Emax model both a common Emax model was fit as well as individuals Emax models for each drug. Parameter estimates for the common Emax model are shown in Table 160, and parameter estimates for individual drug Emax models are shown in Table 161.

Table 160 Sponsor'sTable 7 Parameters of model with common Emax

	Value	SE
Emax	93%	1.8
	EC50	
Haloperidol	0.548	*0.106
Org5222	0.437	*0.082
Olanzapine	6.75	*0.127
Risperidone	4.78	*0.112
Ziprasidone	13.3	*0.173

* SE of logs

Table 161 Sponsor's Table 6. Parameters of model with separate Emax for each compound

Drug	Emax	SE	EC50	SE
Haloperidol	92.0	4	0.532	*0.16
Olanzapine	87.5	3	5.29	*0.14
Org5222	101.8	6	0.528	*0.14
Risperidone	91.2	3	4.43	*0.14
Ziprasidone	98.0	10	15.4	*0.29

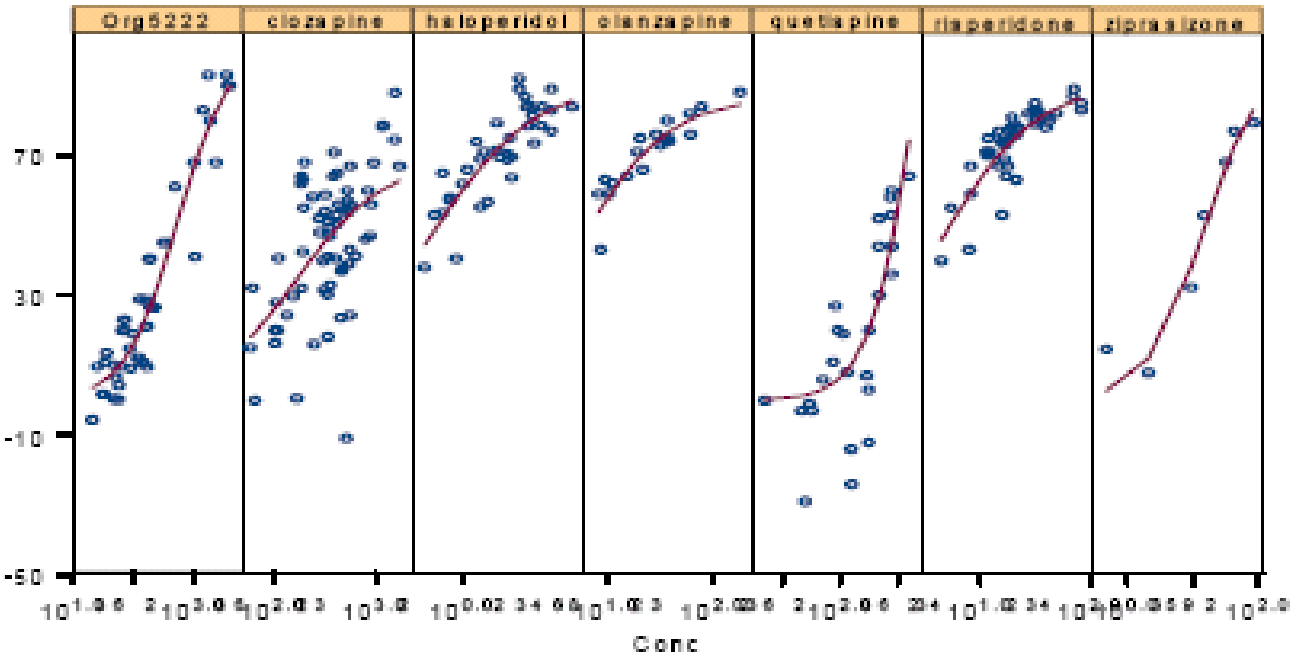
*SE of logs

According to the sponsot both models gave reasonable fits as assessed graphically, and the precision of all parameter estimates was high.

The final model selected was the separate Emax model for each compound.

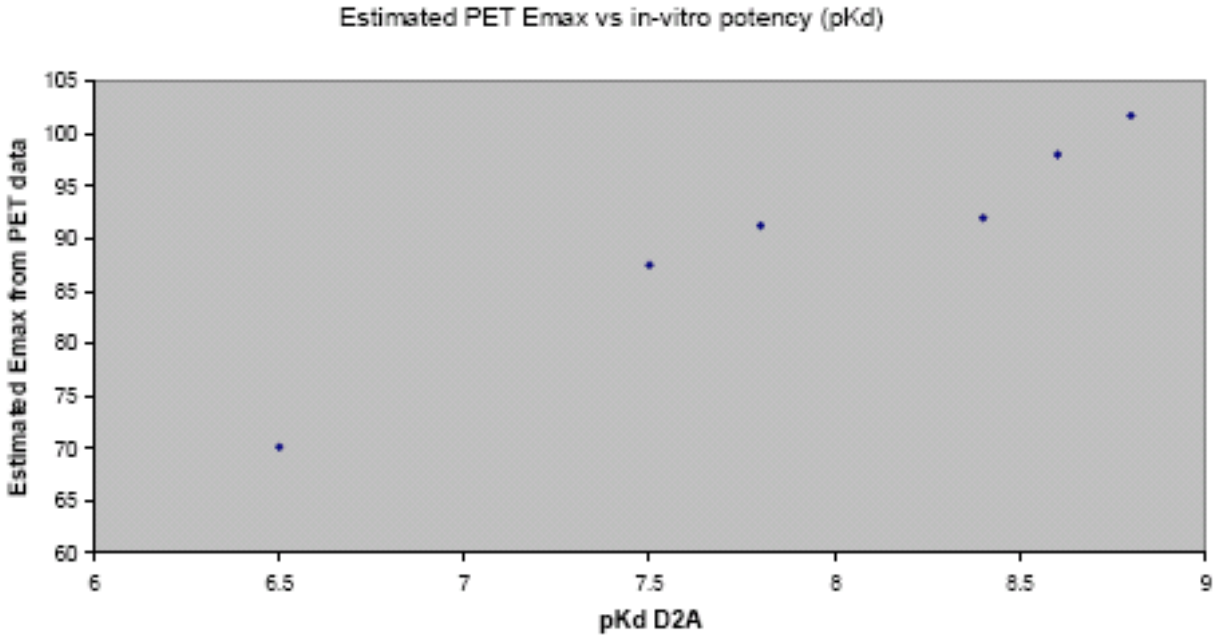
The sponsor's fits of individual Emax models to data for the various drugs is shown in Figure 139.

Figure 139 Sponsor's Figure 2 of the fit of separate Emax models to drug concentration / D2 occupancy data for antipsychotics.



Since the Emaxs in Figure 139 are less than 100%, it's possible the sponsor limited the fit to the data range. However, Figure 140 indicates that this apparent Emax might also be due to the binding affinity relative to the radioligand or another ligand.

Figure 140 Sponsor's Figure 3 Emax from fitting of concentration-D2 occupancy data, plotted against in-vitro receptor affinity estimates.



In either event, both the sponsor's Emaxs and EC_{50}s shown in Table 162 are apparent values are suspect.

Table 162 Sponsor's Table 3 Parameters from fitting of Emax model to PET data.

Drug	Clozapine	Haloperidol	Olanzapine	Org5222	Quetiapine	Risperidone	Ziprasidone
Emax	70.1	92.0	87.5	101.8	75.1	91.2	98.0
EC_{50}	136	0.532	5.29	0.528	301	4.43	15.4

Table 163 shows a comparison of relative *in vivo* EC_{50}s to *in vitro* Kds. The table shows the best concordance with asenapine and haloperidol, and worse concordance with clozapine and quetiapine which did not have adequate coverage of the the entire binding range. However, as these are corrected values which can't be checked and as the relationship with Risperidone isn't available the reliability of this analysis is unknown.

Table 163 Sponsor's Table 4. Comparison of relative EC50s derived from human in-vivo PET data to relative Kds derived from in-vitro data. Haloperidol is used as the reference.

Drug	Clozapine	Haloperidol	Olanzapine	Org5222	Quetiapine	Risperidone	Ziprasidone
Relative PET EC_{50}*	258	1	10	1	17	1200	0.5
Relative Kd	79-100	1	8-10	0.4-0.8	3-4	—	0.6-8

*Corrected for molecular weight and plasma protein binding.

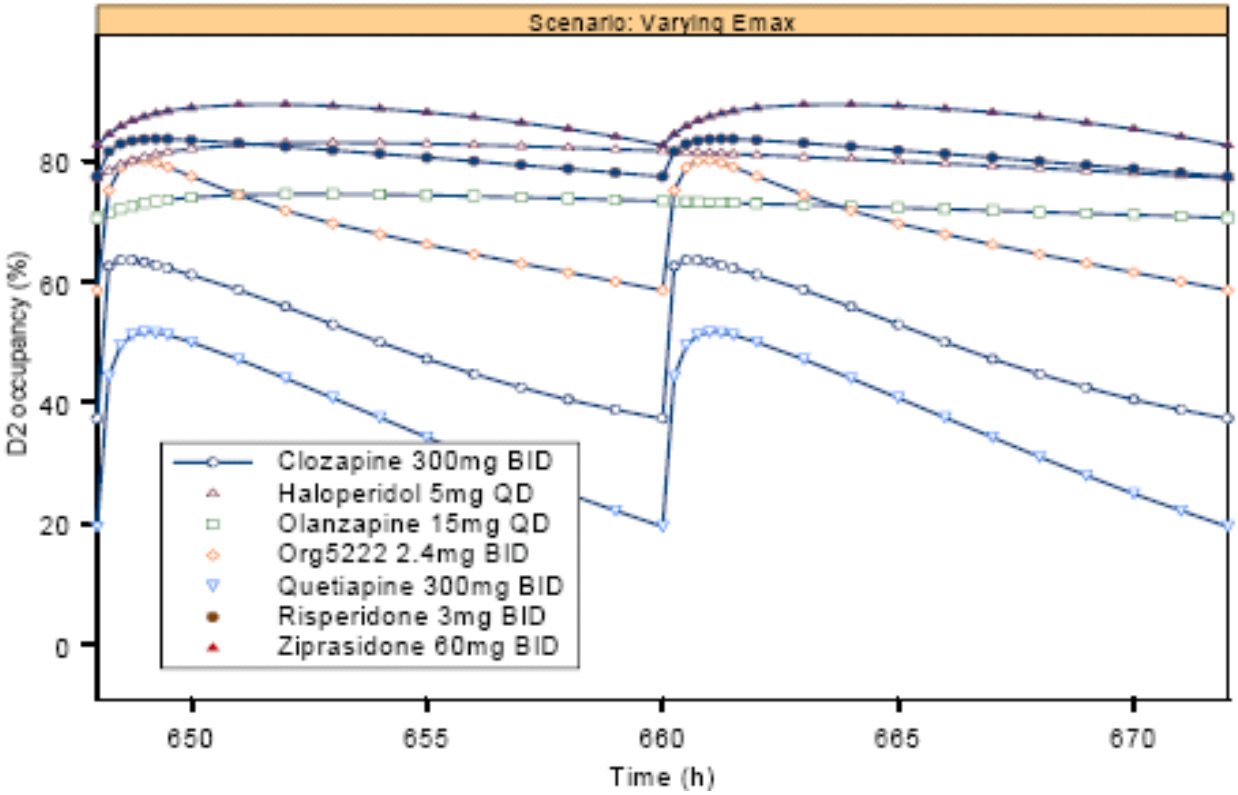
The sponsor to an extent came to a similar conclusion as shown by the following and excluded clozapine and quetiapine data from further analysis.

'After discussions with the project team and with Dr Kapur, the consensus was that clozapine and quetiapine, with their far lower receptor affinity, may not be similar to the other atypical antipsychotics, and that it is currently impossible to say whether they truly have a lower Emax, and thus act at far lower occupancies than other atypicals, or whether this is an artefact of the PET methodology. Thus, as these differences make data from clozapine and quetiapine difficult to interpret, it was decided not to include data from these drugs in the final analyses. It was decided to examine two scenarios regarding the Emax in the final analysis, one where a common estimate was achieved across compounds, and one which allowed separate estimates to be used for all compounds, see Section 10.2.'

5.6.1.2.3 Simulation of D2 Cccupancy vs. Time Profiles and Covariate Analysis

Figure 141 shows predicted Mean D_2 occupancy at steady-state based on their estimated metrics. The D2 occupancy is likely low except for ziprasidone. Consequently, excluding clozapine and quetiapine whose binding metrics are likely off by large amounts the extent of D2 occupancy over the entire dosage interval is in the range of 70% – 90% and is likely higher. Based on this figure alone an asenapine dose of 2.4 mg BID is subtherapeutic.

Figure 141 Sponsor's Figure 4 Predicted mean D2-occupancy – time profiles for antipsychotics given in commonly used dosage regimens. Separate Emax values estimated for each compound.



5.6.1.2.3.1 Convariate Analysis

The sponsor also performed a covariate analysis using data from study 41002.

In addition to a center effect, the following covariates were investigated, for the main endpoint LOCF PANSS week 6, and the effect on time of dropout.

Smoking; Age; Sex ;Weight; Race; Prior olanzapine drug use; Prior risperidone drug use; Prior haloperidol drug use ;Any prior psycholeptic use ;Prior anti-epileptic drug use; Prior anti-Parkinson drug use; Prior anti-analeptic drug use.

The sponsor made the following conclusions: 'In short, none of the above had any major impact on either the absolute PANSS score and, more importantly, none were associated with a clear treatment by covariate interaction. That is, the size of the treatment effect was reasonably consistent across the various levels of each covariate.

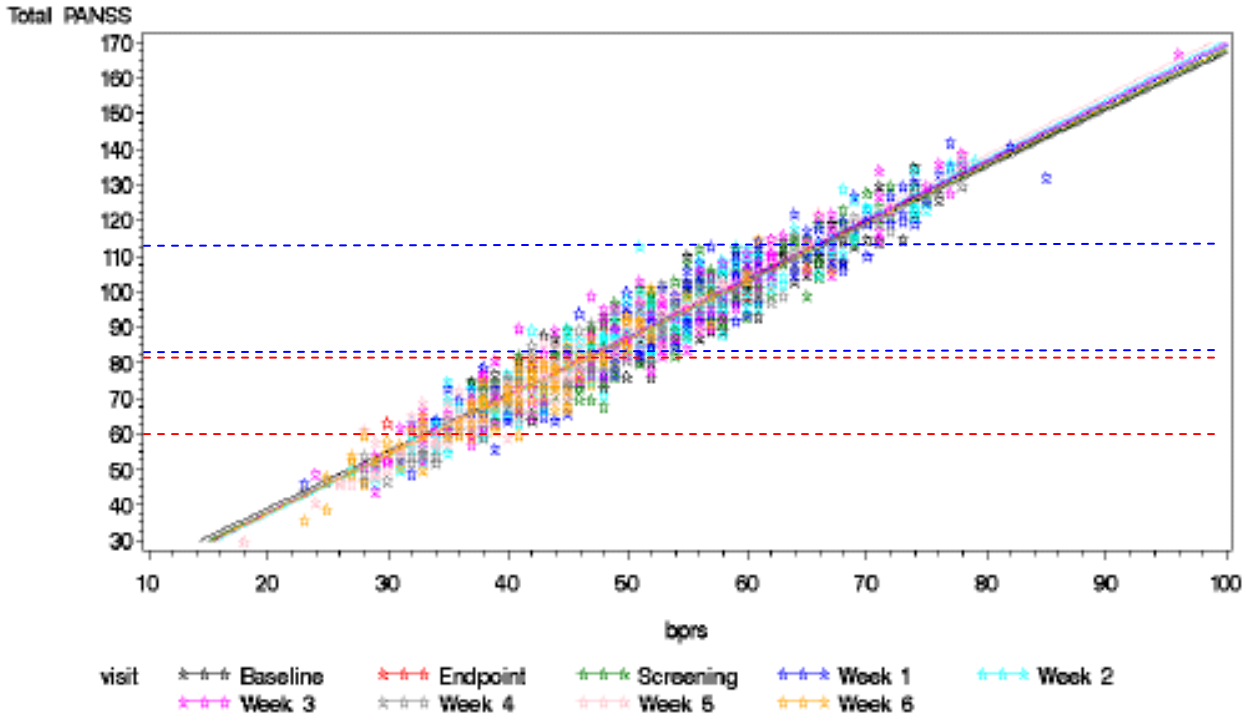
In the analysis looking at time of dropout, there was no evidence that any subgroup were significantly more likely to stay in or withdraw from the study. This result must be taken with caution, as subtle effects may be difficult to detect with this relatively small sample size.'

However, no store can be placed in these conclusions as the maximum dose used in study 41002 was only 0.8 mg BID which is clearly an inadequate dose.

5.6.1.2.4 Conversion of BPRS Scores to PANSS Scores

The sponsor also examined the relationship of Total PANSS score and BPRS so that they could use data from trials that did not have PANSS scores. Figure 142 shows the correlation of Total PANSS scores with BPRS scores although the relationship might seem to be quite good to get a true idea of the acceptability the variability at a single BPRS score needs to be assessed. Consequently, we can see that a BPRS score of 52 at week 2 can mean a PANSS score of between 82 and 112 a spread of 30 units. Since that is the typical degree of change over time in a typical efficacy study it appears that this conversion may not be sufficiently reliable. Although this is the maximum difference we can also see that for the six week data at a BPRS score of 41 the range in PANSS scores is still 20 units.

Figure 142 Plot of Total PANSS score vs. BPRS for All Data by Duration of Treament.



5.6.1.2.5 Pharmacodynamic Link Model of PANSS vs. D2 Occupancy

Full details of the model development, are included by the sponsor in Appendix 3 of the report. The investigation of the modelling resulted in the following conclusions by the sponsor:

- A transformation of the predictor variable was appropriate.
- A cubic polynomial fit the data well.
- Only placebo controlled data would be used.
- A weighting based on the sample size was appropriate.

The transformation of the %D2 scale used was Log (100-%D2). This made the scale more concordant with parametric modelling.

The relationship between the treatment effect and %D2 receptor occupancy was modelled as a cubic polynomial, as shown below.

$$Y = \beta_0 + \beta_1 X + \beta_2 X^2 + \beta_3 X^3 + \xi$$

Where:

Y = Response = change from placebo, week 6 PANSS LOCF value.
X = Log (100 – %D2) = Log transformed (100 – Mean %D2 Receptor Occupancy)

The data and model prediction with 95% Confidence Interval is shown in Figure 10. Each symbol represents a treatment arm in a clinical study. The change from placebo for this treatment arm observed in the study is plotted against the (transformed) expected %D2 receptor occupancy for the corresponding drug and dose level. Clearly, as %D2 receptor occupancy increases, clinical effect (change from placebo) increases.

Figure 143 Sponsor's Figure 10 Mean PANSS LOCF at 6 weeks versus D2 occupancy Overlaid with Mean model prediction and 95% CI

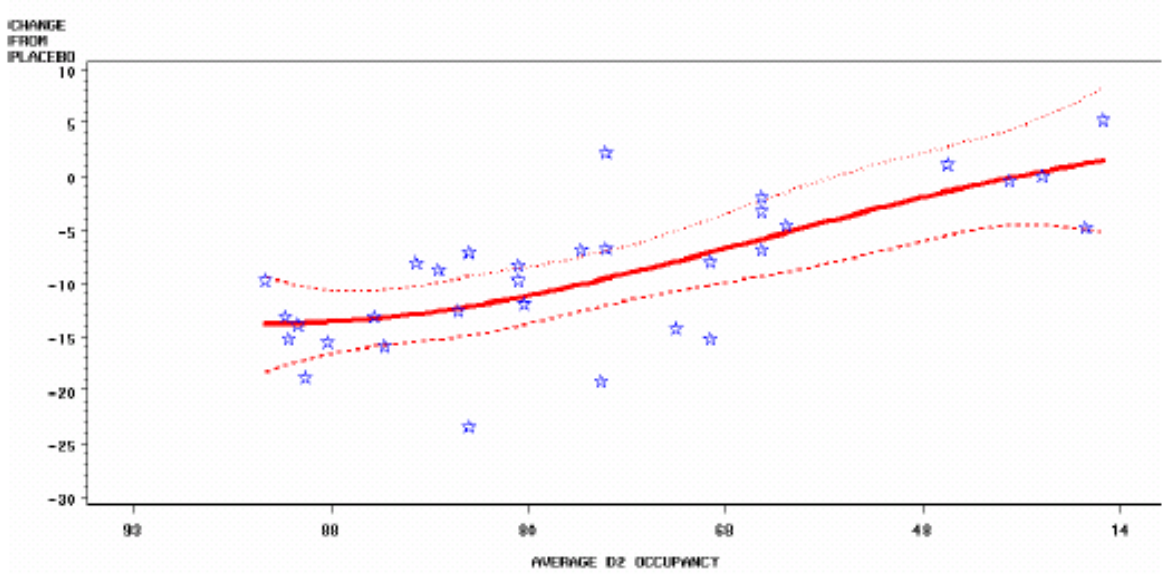
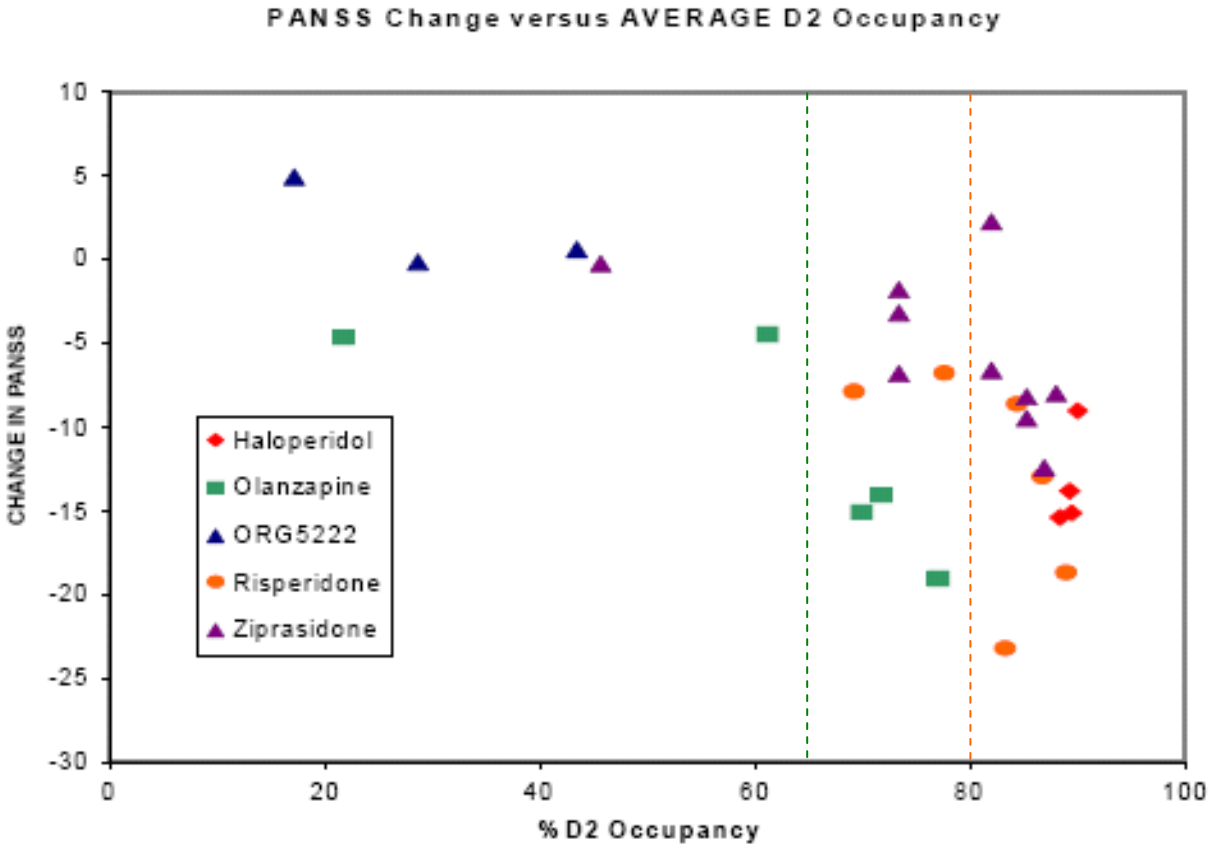


Figure 141 shows the sponsor's plot for Change in PANSS vs. predicted mean D2 occupancy. Interpretaion of this graph must be done cautiously, as we don't know for which data points the PANSS scores were estimated based on BPRS and thereby may introduce excessive variability. Also the D2 occupancy is a mean value and is based on predictitions. In spite of this the graphs indicates that a mean D2 occupancy of greater than 80% is likely needed to achieve a clinically significant change in PANSS score based on 3 of the 4 active controls. Figure 143 demonstrates this even more clearly as below 80% D2 occupancy the variability is excessively high.

Figure 144 Sponsor's Figure 7 Observed clinical response (PANSS LOCF change from placebo), plotted against the mean predicted D2 occupancy for each dose level.



5.6.1.2.6 Exploration of Other Potential Co-Factors

5.6.1.2.6.1 U-Shaped Dose Response

This was allowed initially but then rejected.

5.6.1.2.6.2 Mixed Effect Model of Drop-outs on LOCF

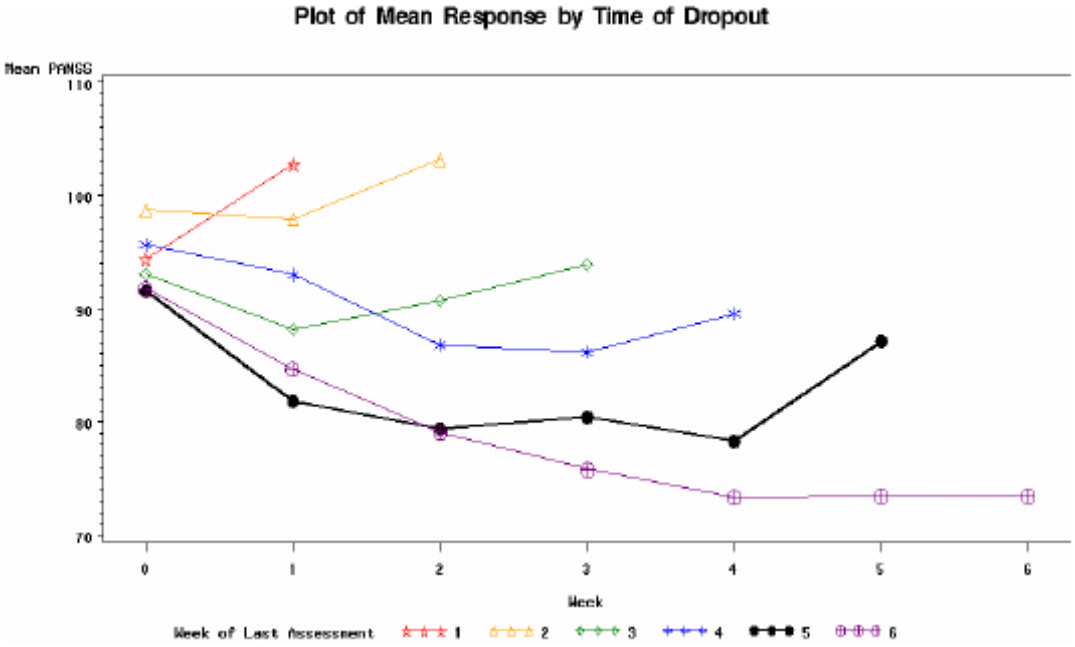
This was explored but eventually dropped from the model. The lack of a relationship may have been due to evaluating the effect on LOCF rather than OC, due to an inadequate model, or other reasons. The sponsor's discussion follows:

'Dropout is a very important factor during clinical studies of antipsychotics. The level of dropout is generally high in this area, ranging from 9% to 91 % in the analysed studies, over a 6 week study duration. To try to avoid bias because of the high and often treatment related dropout, PANSS scores are

mostly analysed as Last Observation Carried Forward (LOCF) values. The interaction between dropout and LOCF PANSS scores is complex. On one hand, data from study 041-002 indicate that patients with higher or increasing PANSS scores tend to drop out earlier in the study (Figure 8), which likely reflects drop out due to lack of sufficient efficacy.

A mixed effects model was applied to the relationship between D_2 occupancy and LOCF PANSS scores. Using this model, a highly significant relationship between dropout and LOCF PANSS change from baseline could be detected. However, the effect of dropout on the change from placebo in LOCF PANSS was not significant. This may be due to the high variability in the placebo effect, which increases over time in some studies, but decreases in others. Thus, even as the PANSS score at a given week may influence dropout, there may be no clear correlation between dropout and LOCF PANSS that is not better explained by differences in D_2 occupancy.

Figure 145 Sponsor's Figure 8 Mean PANSS scores at weeks 0-6 of study 041-002, grouped by the week of dropout



Initially, it was also assumed that a relationship exists between PANSS scores or change in PANSS and likelihood of dropout. However, after further examination this was not found to impact the results, as shown above in Section 6.7.'

5.6.1.2.7 Modeling and Simulation

In summary the final model included:

- POP PK models of several individual antipsychotics as shown in Table 159, excluding clozapine and quetiapine
- Emax models of D2 occupancy vs. plasma concentration for each individual antipsychotic as shown in Table 161
- A pharmacodynamic link model of PANSS vs. D2 Occupancy as shown in §5.6.1.2.5.

5.6.1.2.7.1 Simulation of Study 041-013

Pharsight TrialSimulator TS2.1 was used for simulations. According to the sponsor The simulation used the following algorithm:

"Response" is defined as Change from Placebo in LOCF PANSS Score at Week 6.

Effect is defined as log transformed (100 – %D_2 occupancy).

1) Fit the model of Response versus Effect.

2) From the PK-PET model, the mean and SD of %D_2 occupancy were derived for an N=60 study, for each Org5222 dose level.

3) Sample from the above distribution, to obtain 1000 replicates of the %D_2 occupancy for each dose.

4) For each replicate, obtain from equations 4 and 5 the expected mean and SD of Response corresponding to that specific Effect (derived from %D_2 occupancy).

5) Sample once from distribution from 4) to obtain Response for each replicate.

6) For each replicate, sample an N=60 study, based on mean from 5), and SD of 20. This reflects variability at the subject level.

7) Obtain estimate of Response from each N=60 study, and summarise responses across all 1000 replicates. This provides the distribution of results incorporating model uncertainty, D_2 uncertainty and study uncertainty.

8) For each replicate in 5), simulate 1000 corresponding placebo data, each with expected mean zero, and SD 20. Empirical power calculated by simple t-test of mean and SD from 5) versus simulated placebo. Significance level set at $p < 0.05$.

Figure 146 shows the expected D2 distribution with an asenapine dose of 1.6 mg BID and its' predicted effect on difference in PANSS score from Placebo. From the graph this appears to result in a mean D2 occupancy rate of ~60% and a difference from placebo of a change in PANSS of -5 from baseline. Extrapolating visually, a D2 occupancy rate of greater than 80% is need for a change of -10 which is low for an active agent.

Figure 147 shows the distribution of simulated mean responses (Change in LOCF PANSS score) with the asenapine doses of 1.6 g BID and 2.4 mg BID employed in study 41013 assuming a scenario with the Same Emax and average D2 occupancy and incorporating the combined model and interindividual uncertainty. It's clear that at these doses that the predicted response included a difference in PANSS score of zero.

Table 164 shows the sponsor's mean predicted response and the 95% confidence limits for the doses employed in study 41013 for all 4 scenarios, and Table 165 shows the sponsor's predictions of the success of study 41013 for each of the 4 scenarios. Overall the chance of success from study 41013 is estimated as only 50% and with the most likely scenario the chance of success is only slightly greater than 1 in 3. Thus modeling indicates that this was a poor business decision.

Figure 146 Sponsor's Figure 11 Expected Mean Fit and Distribution of D2 occupancies and Corresponding Effects on PANSS, following Asenapine 1.6 mg SL BID

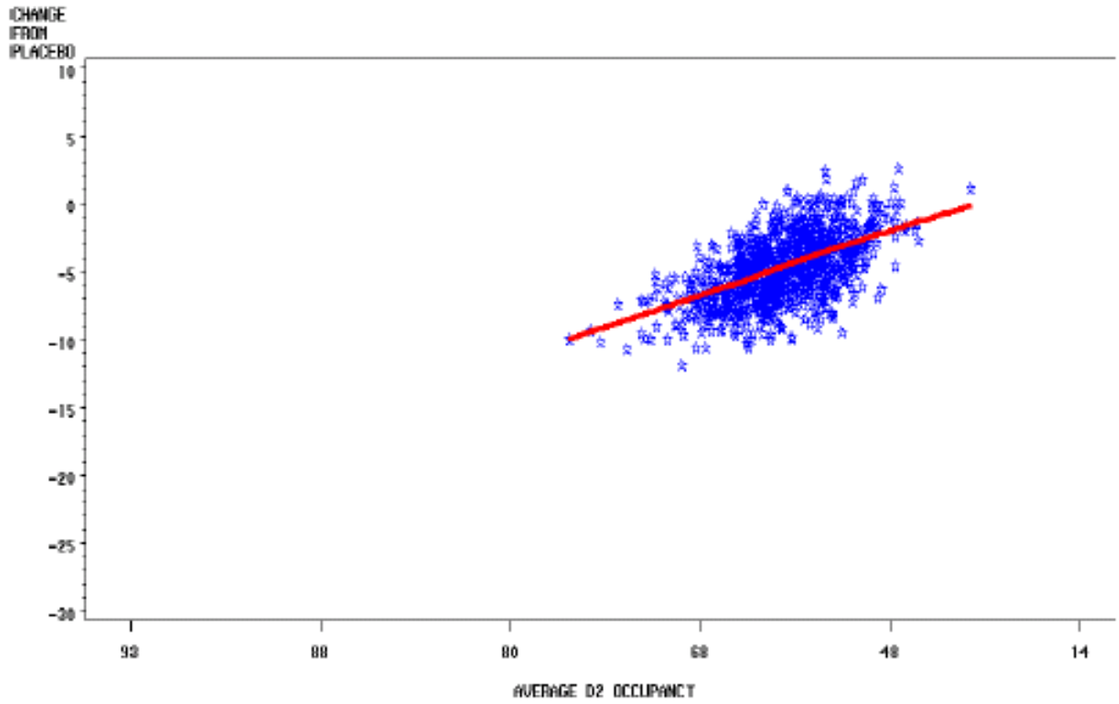


Figure 147 Sponsor's Figure 12 Distribution across 1000 simulated replicates showing predicted mean LOCF PANSS change from placebo after administration of 1.6 and 2.4mg Org5222 b.i.d to 60 subjects. Distribution incorporates model uncertainty and interindividual variability.

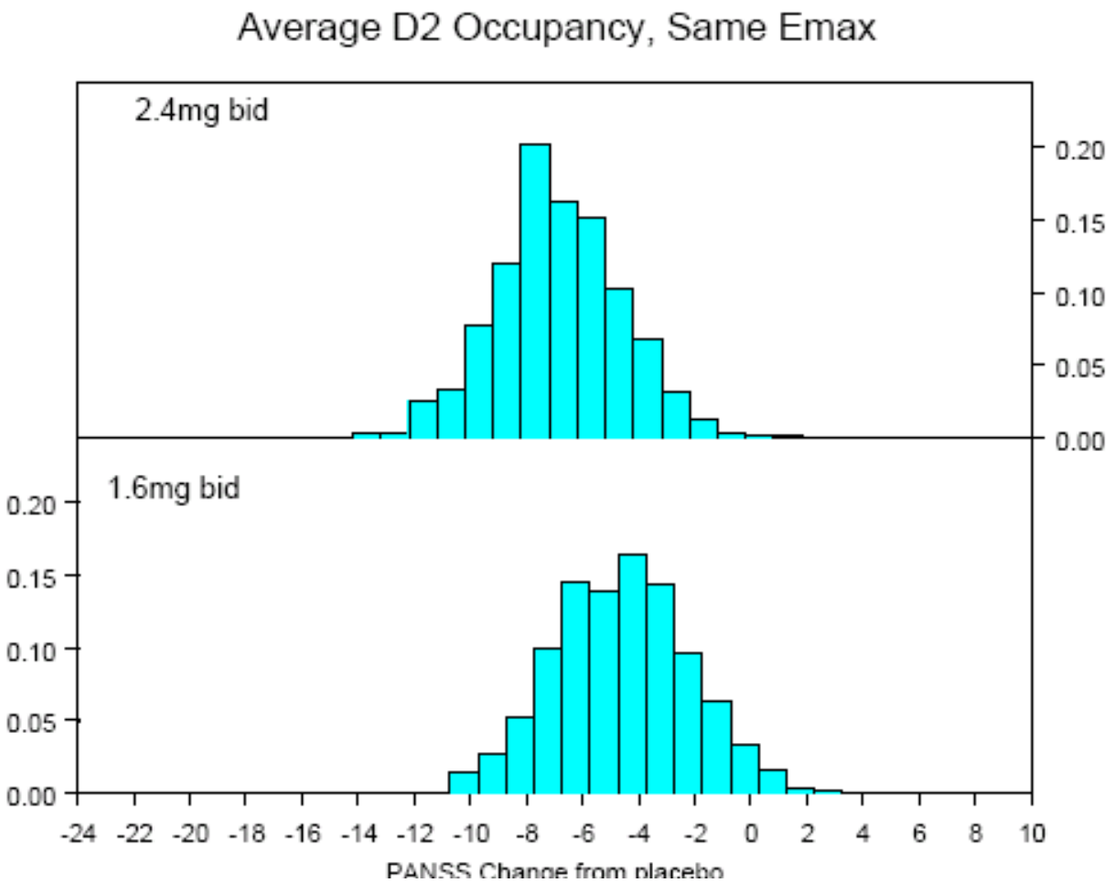


Table 164 Sponsor's Predicted mean PANSS LOCF change from placebo at 6 weeks for Org5222 given at the doses of 1.6 and 2.4mg in study 041-013 for 4 different simulation scenarios.

Scenarios	Assumptions		Dose (mg)	Mean	Confidence Limits	
	Emax	Average or Mean D2 Occupancy			Lower 95%	Upper 95%
1	Same Emax	Average	1.6	-4.6	3.2	-13.2
			2.4	-6.8	2.2	-15.2
2	Same Emax	Max	1.6	-6.7	0.9	-15.1
			2.4	-9.0	-0.3	-17.3
3	Different Emax	Average	1.6	-5.1	3.4	-14.2
			2.4	-8.1	1.7	-16.8
4	Different Emax	Max	1.6	-8.5	-0.2	-17.3
			2.4	-10.7	-0.7	-19.6

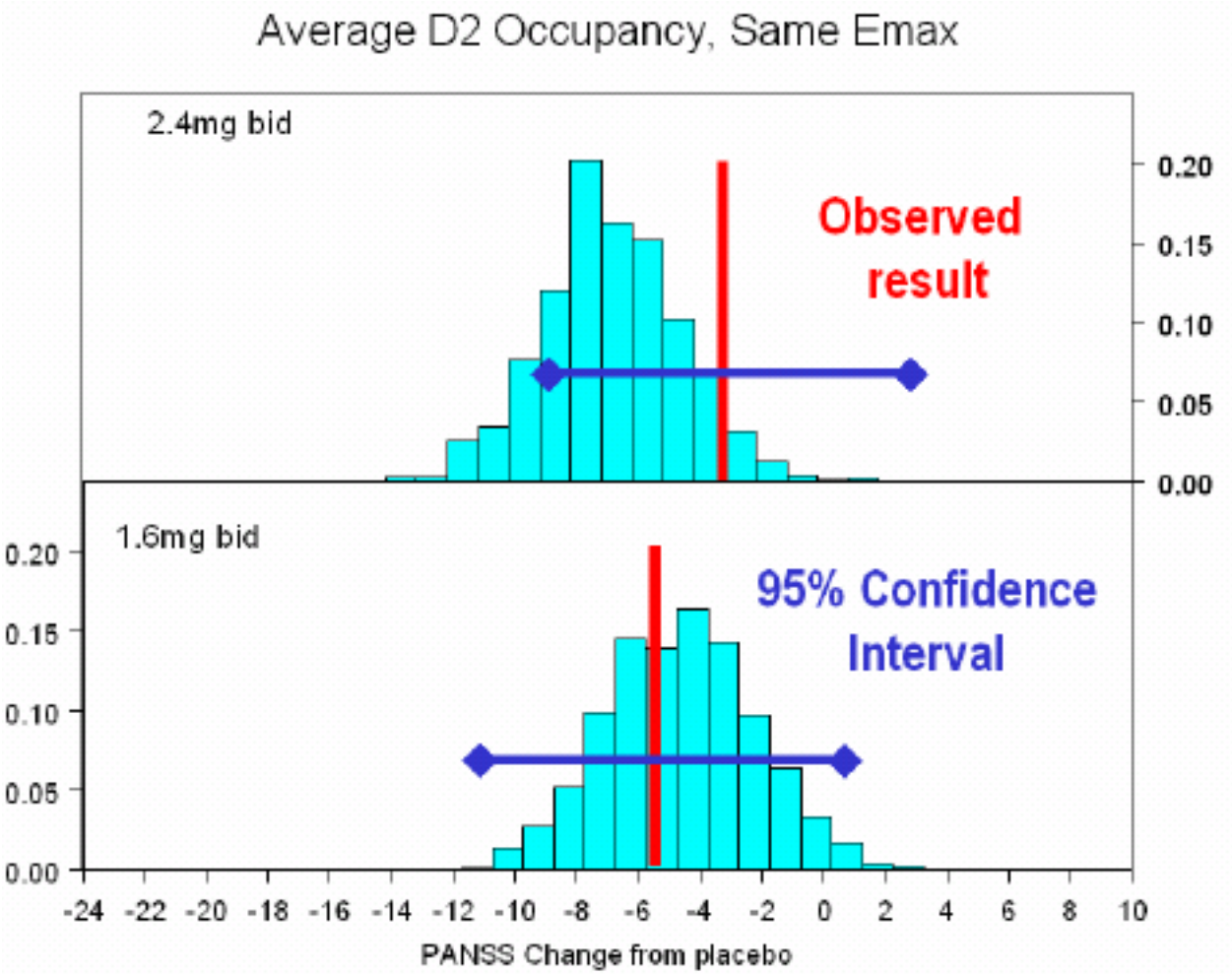
Table 165 Sponsor's Table 11. Predicted likelihood of showing a significant difference from placebo for each of the two doses in study 041-013, for the four different simulation scenarios.

Scenarios	Assumptions		Dose (mg)	Likelihood of Success
	Emax	Average or Mean D2 Occupancy		
1	Same Emax	Average	1.6	27%
			2.4	46%
2	Same Emax	Max	1.6	44%
			2.4	67%
3	Different Emax	Average	1.6	33%
			2.4	58%
4	Different Emax	Max	1.6	60%
			2.4	81%
Overall Average				52%

5.6.1.2.7.2 Validation

Figure 148 shows the actual results from study 41013 and the 95% CI overlaid on the predictions based on the most likely scenario clearly showing the failure of the study and the inability to differentiate from placebo for both doses. Consequently this is a poor test of the validity of the model.

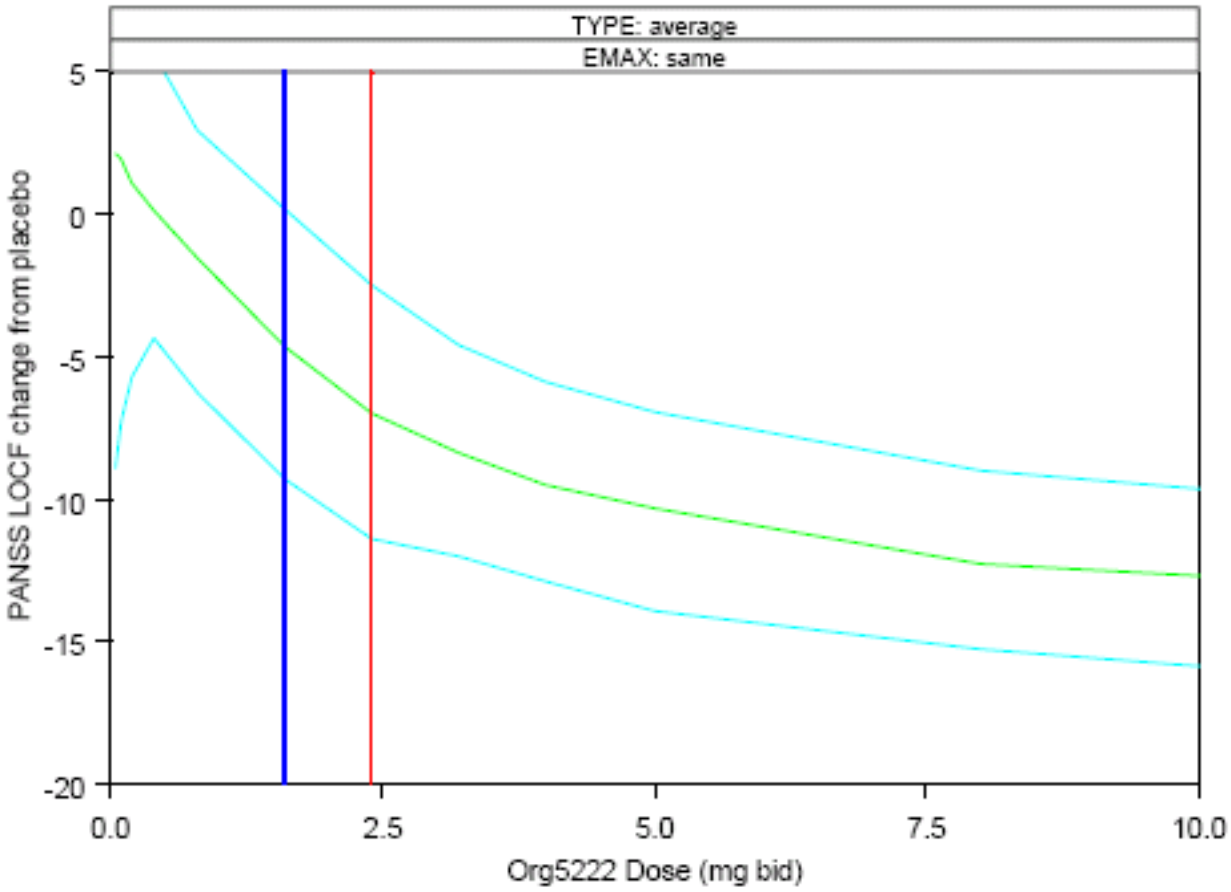
Figure 148 Sponsor's Figure 14 Actual results from study 041-013 shown with estimate and 95% CI, in comparison to distribution across 1000 simulated replicates showing predicted mean LOCF PANSS change from placebo.



5.6.1.2.7.3 Dose Prediction

Figure 149 shows the exposure response curve of the difference from Placebo in change in LOCF PANSS score vs. dosage, with the simulated 95% confidence interval indicating that a dose of 5 – 10 mg BID is needed for a clinically significant response. However the overlay of the response seen with the 1.6 and 2.4mg doses indicate that the 2.4 mg should have definitely differentiated from placebo, however in actuality it didn't. Consequently, the model is clearly flawed in some manner.

Figure 149 Sponsor's Figure 13 Dose response curve showing the predicted mean PANSS LOCF change for placebo vs dose of Org5222. Predictions for Scenario 1: Average D2 occupancy, same Emax, are shown. The green line represents the mean predicted response while the light blue lines represent the 5th and 95th percentiles. The vertical lines indicate the response seen with the 1.6 and 2.4 mg doses.

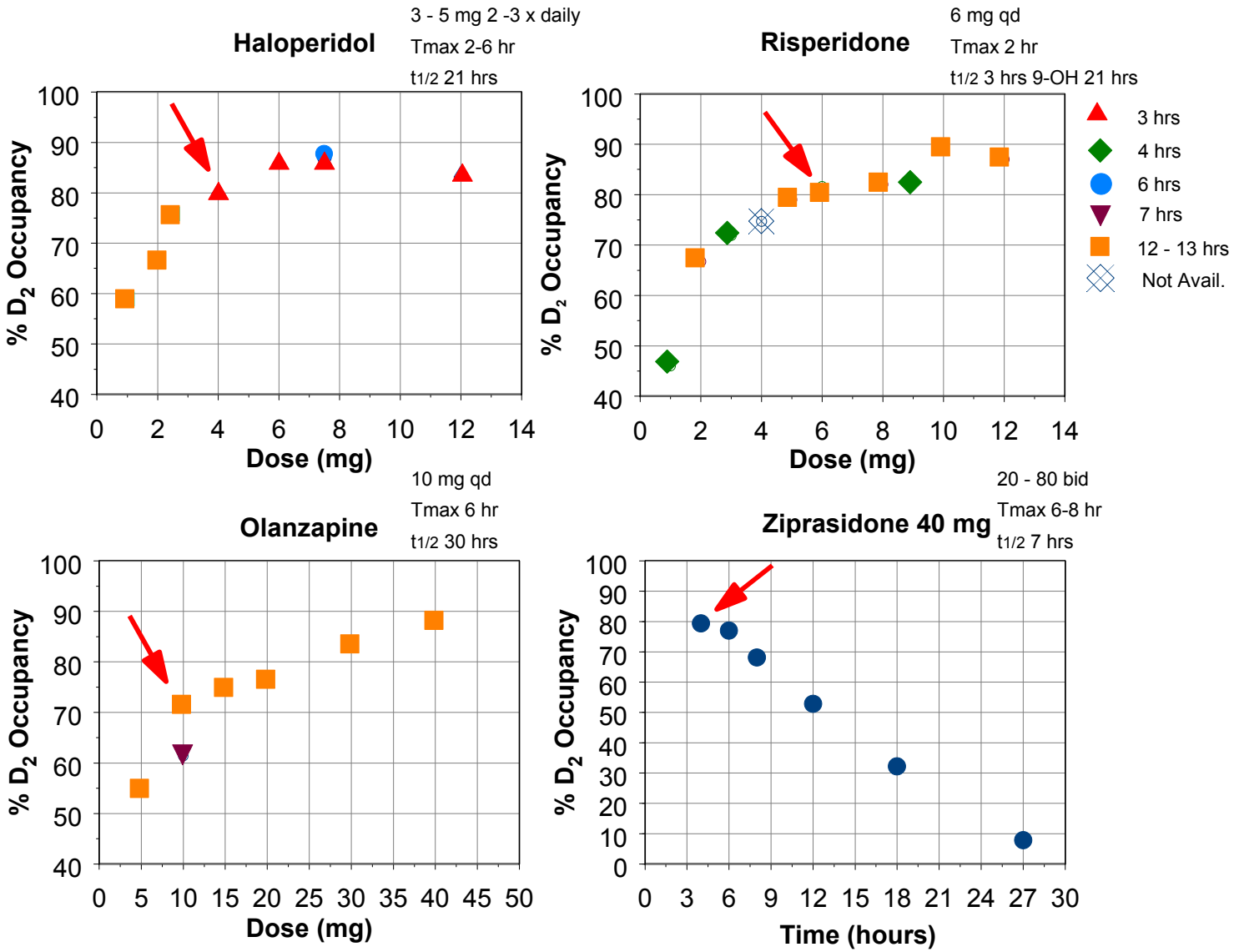


5.6.1.2.8 Reviewer's Dose Estimates Based on Analysis of PET Studies

Figure 150 shows graphs of average D2 receptor cccupancy by dose and time post administration for the four antipsychotics that did not have low apparent Emaxs. For 3 of the 4 drugs typical clinical doses result in 80% receptor occupancy. Since there is variability, peak receptor occupancy may be closer to 85% - 90% in many individuals.

As previously stated in §5.6.1.1.2.1 and §5.6.1.1.2.2 that respectively reviewed PET studies 25510 and 25516, fitting an Emax model to the asenapine D2 occupancy data indicates that a peak concentration of 3 – 9 ng/ml is needed to achieve 90% occupancy and that extrapolation of the data available at the time of the study indicates that a daily dosage of 10 mg is necessary to achieve this assuming dose linearity.

Figure 150 D2 Receptor Occupancy by Dose and Time of Administration for Four Antipsychotics



5.6.1.2.8.1 Conclusions

In summary, the modeling and simulation did not result in a better dose estimate than simply fitting and Emax model to the PET data and eyeballing doses needed to achieve these concentrations. However, the quantitative estimations of having a positive or failed study under various scenarios would be quite useful for business decisions, although additional model refinement is clearly needed as shown by the poor predictability of the current model.

Source: Clinical Summary

There are 63 trials in the asenapine schizophrenia and bipolar mania clinical development programs that were conducted with the sublingual formulation of asenapine as of the database cut-off of 15 January 2007. The safety information from the completed Phase 2/3 trials was analyzed in five cohorts. As of the January 15, 2007 database cutoff date, there were 11 deaths in the all asenapine group, 1 death in the placebo group, and 3 deaths in the olanzapine group.

One subject in the long-term schizophrenia trial (study 25517) died from aspiration during a *seizure*. The subject, a 33 year old Caucasian female had received asenapine 5-10 mg for one month during the study and was discontinued due to a *seizure*. Three months later, she had another seizure that resulted in death. This death is not included in the tables and listings because it occurred more than 30 days after the last dose. The most common adverse event leading to death was suicide (6 asenapine 5-10 mg b.i.d. [0.3%], 2 olanzapine [0.2%]). In addition, there were 2 drug overdoses that led to death, 1 in the asenapine 5-10 mg b.i.d. group (accidental overdose) and 1 in the olanzapine group (overdose) neither of the overdose cases was due to asenapine overdose. One subject died of cardiac failure in an ongoing trial

The most common cardiac AEs were bradycardia (3.6%) and tachycardia (2.8%) A 27 year old male Caucasian healthy volunteer (study 25506), collapsed 15 minutes after the end of a 30 minute intravenous infusion of asenapine (0.7 mg). Just prior to collapse, the subject reported feeling dizzy and unwell and then fell back on the bed. The event was reported as *asystole*; however, this event was considered to be due to neurally mediated reflex bradycardia. The subject recovered.

A 22 year old Caucasian male (resting heart of 58 bpm), received a 30 mg oral dose of asenapine in study 25501. Approximately 2.5 hours after the dose, the subject sat up in bed and felt dizzy and nauseated. The ECG telemetry strip showed heart rate slowing and an *8.7 second pause. This was followed by heart block with nodal bradycardia*, which spontaneously converted to sinus rhythm. He had another episode 2 hours later. Both episodes resolved spontaneously without intervention while the subject remained in the supine position

Vomiting, *syncope*, hypotension were experienced by a 23 year old female (study 25504), following asenapine (4 mg dose) on Day 13, which led to discontinuation from the study (considered related to study drug). Subject recovered the same day. Grand mal *convulsion* occurred in a 59 year old male (study 25505), following asenapine (2 mg dose) on Day 6, which led to discontinuation from the study. Subject recovered the same day. According to the investigator, the grand mal convulsion was due to hyponatraemia (sodium: 114 mmol/L) secondary to polydipsia and was not related to study drug (see Section 2.7.4.2.1.5.7 on hyponatraemia).

In the long-term schizophrenia study 25517, ECGs were performed at Screening, Weeks 3, 6, 24, and endpoint, and the tracings were read by a central laboratory. Analyses included interval changes from baseline (descriptive statistics), categorical changes, outlier analysis, and post-baseline markedly abnormal changes in morphology. The most frequently reported ECG related AE in the asenapine group (1.2%) was Electrocardiogram QT corrected interval prolonged (0.6% in the olanzapine treatment group).

Reviewers Comment: QT prolongation was also noted in clinical studies. Seizures can be expected in this population due to lowering of seizure threshold due to drug, polydipsia/substance abuse. However, syncope/asystole and an 8.7 sinus pause were noted in young healthy subjects.

Oral ORG 5222 (1-50 mg/kg) administered to conscious dogs induced dose-dependent negative inotropic and positive chronotropic effects, accompanied by shortening of the PR interval, less marked hypotensive effects and dose-dependently prolonged QTc. The QRS interval was shortened but only at the higher dose. Moderate orthostatic hypotension was observed on tilt which was accompanied by marked and dosedependent tachycardia. Behavioral excitation was observed at dose levels from 2.5 mg/kg onwards. Sublingual administration of ORG 5222 (0.01-1 mg/kg) induced dose dependent tachycardia in the absence of negative inotropy and hypotension. QTc was only markedly prolonged by the highest dose used which also lengthened QRS. A similar moderate orthostatic hypotension was seen upon tilt but the accompanying tachycardia was considerably less than after oral administration. Sublingually given Org 5222 caused minor and transient behavioral excitation at the highest dose only, but induced long lasting tranquilization especially at the mid and high doses.

Reviewer's Comment: Non clinical data are suggestive of dose-and concentration dependent QT prolongation.

3.2 PRECLINICAL INFORMATION

Source: nonclinical summary

ORG 5222, tested at 0.1, 0.3, and 1 μM concentrations using HEK-293 cells transfected with HERG produced statistically significant and concentration-dependent decreases in hERG current amplitude (30.9 ± 4.3%, 51.2 ± 5.7%, and 69.8 ± 5.8%, respectively) when compared to vehicle control. The IC50 for ORG 5222, the concentration computed from the concentration-response relationship at which 50% of total current was suppressed, was 0.3 μM.

The results of a study in isolated canine Purkinje fibers indicate that asenapine induced mainly decreases in action potential duration, in particular on APD_{50}. These effects were associated with a decrease in the plateau of action potential involving mainly calcium channel current. Decreases in action potential duration were dose-dependent and were more pronounced under low stimulation rate (0.33Hz) than under normal stimulation rates (1Hz). N-desmethylasenapine induced comparable effects (decreased action potential duration, particularly APD_{50}) but at approximately 10 times higher concentrations.

FDA Analysis: The Point Estimates and 90% CI Corresponding to the Largest Upper Bounds for Asenapine by Dose Group

Treatment	N	Time, h	Mean ΔΔQTcF, ms	90% CI, ms
Asenapine 5 mg b.i.d.	30	3	5.0	-1.5, 11.4
Asenapine 10 mg b.i.d.	27	2	10.5	4.5, 16.5
Asenapine 15 mg b.i.d.,	33	3	8.7	3.0, 14.4
Asenapine 20 mg b.i.d.,	29	4	4.9	-1.9, 11.6

An exposure-response analysis conducted by both the sponsor and FDA reviewers showed that asenapine prolonged the QTcF interval in a concentration-dependent manner (described in section 5.2.1.2). The model predicted mean ΔΔQTcF at a mean C_{max} of 10.6 ng/mL, which corresponds to an asenapine dose of 20 mg b.i.d., is 6 ms (8 ms, 90% upper confidence limit). Asenapine 20 mg b.i.d., the maximum tolerated dose in patients with schizophrenia, provides a 2-fold increase in exposure over the highest clinical dose (10 mg b.i.d.) and adequately covers the plasma concentrations observed in phase 2b/3 clinical studies (Figure 1). We note, however, that subjects with severe hepatic impairment have 7-fold increase unbound AUC. The magnitude of QT prolongation in these subjects is not known.

Because asenapine belongs to a pharmacological class of compounds associated with QT/QTc prolongation, the sponsor used quetiapine 375 mg b.i.d. as the positive control. The magnitude of quetiapine effects on the QTc interval is not well characterized. In this study, the difference from placebo in LS mean time-matched QTcF change from baseline at T_{max} was 7 ms (90% CI: 1, 13) on Day 10 and 10 (90% CI: 3, 17) ms on Day 16. The exposure-response relationship for quetiapine was similar to the observed relationship in Study R076477-SCH-1014 in NDA 21,999 (Table 13). Therefore, assay sensitivity with quetiapine could be established.

4.2.7.3 Safety Analysis There were no deaths reported in this trial. Three subjects experienced serious adverse events- a 51-year-old man, experienced severe atrial fibrillation on Day 1 after receiving a 5 mg dose of asenapine. He required hospitalization and was withdrawn from the trial. A 40-year-old woman, experienced a change in intensity of sinus tachycardia from mild to moderate on Study Day 9, and she was hospitalized. She was receiving quetiapine 375 mg b.i.d.. Study drug was discontinued and she was withdrawn from the trial. A 38-year-old woman experienced the adverse event of severe schizoaffective disorder 1 day after completing screening and starting to taper off her antipsychotic medication. Nine subjects, including 2 who experienced serious cardiac adverse events, discontinued from the trial due to adverse events. One of these subjects discontinued from the trial due to laboratory abnormalities (elevated LFT). Five discontinued due to psychiatric adverse events . The adverse events, other than oral adverse events (dry mouth, dysgeusia), experienced by 3 or more asenapine-treated subjects and reported for a higher percentage of asenapine-treated subjects than quetiapine- or placebo- treated subjects were somnolence, restlessness, anxiety and dizziness, constipation and fatigue, akathisia, gait disturbance, nasal congestion, loose stools, and dysarthria.

5.6.1.3 Effect on QTc

Asenapine prolonged QTc.

There were four study reports associated with the sponsor's evaluation of the effect of asenapine on QTc and they are listed in Table 166. Three of these study reports were located under eCTD section 5.3.5.4 (Reports of Efficacy and Safety Studies [Indication] – Schizophrenia – Other Study Reports), that this reviewer was advised not to examine.

Table 166 Study Reports Associated with the Sponsor's Evaluation of QTc

Study Report #	Study Report Title	Report Date
A7501001	A Double-Blind, Parallel, Multicenter Study to Assess the Effect of Asenapine, Quetiapine (Seroquel®), and Placebo on the QTc Interval in Patients With Schizophrenia	June, 2005
754-0046	Exposure-Response Analysis to Assess the Effect of Asenapine, Quetiapine (Seroquel®), or Placebo Administration on the QTc Interval in Patients with Schizophrenia	31 May 2006
INT00036960	Exposure-Response analysis to assess the Effect of Asenapine Administration on the QTc Interval in Patients with Schizophrenia (Phase 3 ACTAMESA study)	May, 2007
INT00036719	Population pharmacokinetic analysis using Phase 2/3 asenapine concentration data from patients with schizophrenia or bipolar disorder	May, 2007

The QT team performed the QT review and this may be found in the DFS file. Consequently this section of this review takes the most important graphs and tables from that review[11] and adds additional critiques when warranted. It should be noted that the QT review contains the sponsor's background information on clinical safety (with respect to cardiac effects) and preclinical *in vivo* and *in vitro* evaluations of cardiotoxicity, all of which are consistent with clinically significant arrhythmigenic potential.

Independent analyses by the QT team include selected data in Table 168, plus Figure 152 and Figure 153. Otherwise the QT team incorporates the sponsor's analyses into their review. This reviewer found that the manner in which the QT team wrote their review did not clearly indicate when analyses and discussions were taken directly from the sponsor's reports and when the QT did independent analyses and made independent assessments. In fact it is not even clearly stated that that report 754-0046 was reviewed and that figures were taken from that report.

Study A7501001 was a double-blind, placebo and active controlled parallel design, multicenter PK/PD study to assess the effect of asenapine on the QTc interval in male and female patients with schizophrenia.

Treatments are shown in Table 167. The study was designed to have 30 completers per group. It's readily apparent from Table 167 that not only is this a parallel design with respect to the test drug and the active comparator but also with respect to placebo which results in additional intersubject variability with respect to subtraction of baseline drug ΔQTc from time matched placebo ΔQTc.

[11] Except for Figure 157and Figure 158 which this reviewer took from the sponsor's study report as the QT review included them as black and white graphics rather than in color.

Table 167 Treatment Groups and Dosing in TQTc - Study A7501001

Group	Drug	Period 1: Target Dose (post Titration)	Period 2: Target Dose (post Titration)
1	Asenapine	5 mg BID 10 days	10 mg BID 6 days
2	Asenapine	15 mg BID 10 days	20 mg BID 6 days
3	Quetiapine	375 mg BID 10 days	375 mg BID 6 days
4	Placebo	BID 10 days	BID 6 days

Table 168 on the following page shows the statistical reviewer's analysis at each time point post-dosing for the various asenapine dosing regimens. The study is clearly positive with a maximum upper limit of the 90% CI for the mean change in ΔΔQTc of 16.5 mSec (i.e. above 10 mSec) at 4 hours after dosing of 10 mg BID. It's noteworthy that the change in ΔΔQTc is greater with proposed clinical dose of 10 mg BID than with the higher doses of 15 mg and 20 mg BID. Although there is a signal for a clinically significant QT effect for asenapine at even 5 mg SL BID.

It's also noteworthy that the sponsor's analysis has an even greater upper limit of 17.5 mSec based on manually read ECGs which are typically considered more reliable than machine read ECGs which I'm assuming was what was used in the statistician's analysis, (see Table 168).

Table 168 Difference in Least Square Means from Placebo of Time Matched Change from Baseline in QTcF (ΔΔQTcF) – Study A7501001

Treatment Day	Treatment Comparison	Statistical Reviewer's Analysis					Sponsor's Analysis of Manually Read ECGs				
		N	Time Post-Dose (hour)	Difference (SE)	Lower Limit 90% CI	Upper Limit 90% CI	N	Time Post-Dose (hour)	Difference (SE)	Lower Limit 90% CI	Upper Limit 90% CI
Day 10	Asenapine 5 mg b.i.d. vs Placebo	30	1	0.9 (4.2)	-6.0	7.9	30	1	0.9	-5.0	6.9
		30	2	2.6 (3.4)	-3.0	8.2	30	2	2.6	-3.3	8.6
		30	3	5.0 (3.9)	-1.5	**11.4**	30	3	5.0	-1.0	**10.9**
		30	4	5.8 (3.0)	0.8	**10.8**	30	4	5.8	-0.2	**11.7**
		30	6	4.1 (3.0)	-0.8	8.9	30	6	4.1	-1.9	**10.0**
		29	8	5.8 (3.4)	0.3	**11.3**	29	8	5.9	-0.1	**11.9**
		29	12	0.8 (3.6)	-5.1	6.6	29	12	0.9	-5.1	6.8
	Asenapine 15 mg b.i.d. vs Placebo	33	1	5.6 (3.7)	-0.6	**11.7**	33	1	5.6	-0.2	**11.4**
		33	2	6.4 (3.4)	0.9	**12.0**	33	2	6.4	0.6	**12.3**
		33	3	8.7 (3.5)	3.0	**14.4**	33	3	8.7	2.9	**14.5**
		33	4	8.0 (3.4)	2.5	**13.6**	33	4	8.0	2.2	**13.8**
		33	6	5.1 (2.5)	0.9	9.2	33	6	5.1	-0.8	**10.9**
		33	8	6.2 (3.2)	0.9	**11.3**	33	8	6.1	0.3	**12.0**
		32	12	1.2 (3.2)	-4.1	6.5	32	12	1.0	-4.8	6.9
Day 16	Asenapine 10 mg b.i.d. vs Placebo	27	1	3.4 (3.3)	-2.0	8.8	27	1	3.4	-3.13.9	**10.0**
		27	2	10.5 (3.6)	4.5	**16.5**	27	2	10.5		**17.1**
		27	3	-0.4 (3.8)	-6.6	5.9	27	3	-0.4	-6.9	6.2
		27	4	9.3 (4.4)	2.0	**16.5**	27	4	9.3	2.7	**15.9**
		26	6	6.0 (3.8)	-0.3	**12.3**	26	6	6.2	-0.4	**12.8**
		26	8	5.0 (4.3)	-2.0	**12.1**	26	8	5.2	-1.4	**11.9**
		26	12	0.2 (4.9)	-7.8	8.3	26	12	0.4	-6.2	7.1
	Asenapine 20 mg b.i.d. vs Placebo	29	1	2.6 (3.5)	-3.2	8.4	29	1	2.6	-3.8	9.1
		29	2	5.2 (3.6)	-0.7	**11.2**	29	2	5.2	-1.2	**11.7**
		29	3	-1.1 (4.3)	-8.1	5.9	29	3	-1.1	-7.5	5.4
		28	4	4.9 (4.1)	-1.9	**11.6**	28	4	5.1	-1.4	**11.6**
		29	6	-1.3 (3.8)	-7.5	4.9	29	6	-1.3	-7.8	5.1
		29	8	-1.8 (4.1)	-8.5	5.0	29	8	-1.8	-8.2	4.7
		29	12	-1.4 (4.6)	-9.0	6.2	29	12	-1.4	-7.9	5.0

Figure 151 shows the positive results for the positive control quetiapine and the similar degree of maximal ΔΔQTc seen with the dosage used.

Figure 151 Sponsor's Table 4 of Manually Read ECG Double-Delta QTcFs for Quetiapine

Table 4: Difference in Least Square Means of Quetiapine from Placebo of Time Matched Change from Baseline in QTcF (Manually Read)

Treatment Comparison	Time Post-Dose (hour)	N	Difference	90% Lower	90% Upper
Day 10					
Quetiapine 375 mg b.i.d. vs Placebo	1	30	2.5	-3.5	8.4
	2	30	6.7	0.8	12.7
	3	30	7.5	1.5	13.4
	4	30	7.9	1.9	13.8
	6	30	2.7	-3.2	8.7
	8	30	10.9	4.9	16.8
	12	30	3.1	-2.8	9.0
Day 16					
Quetiapine 375 mg b.i.d. vs Placebo	1	27	4.1	-2.5	10.7
	2	27	9.9	3.3	16.5
	3	27	6.9	0.4	13.5
	4	27	6.8	0.3	13.4
	6	27	3.1	-3.4	9.7
	8	27	4.9	-1.7	11.5
	12	27	-0.6	-7.2	6.0

Sponsor's Section 11.1.2.01.01.01, pages236-239 of CSR for A750-1001

Figure 152 and Figure 153 are the only independent data analysis that appears to have been performed by the QT team. They show linear-log plots of the linear model of mean ΔΔQTcF vs. drug concentration with a 90% CI for asenapine and quetiapine respectively. In addition, the QT team pharmacometricians divided the reported drug concentrations into 10% quartiles, which is shown at the bottom of the graphs. They then calculated the mean and 90% CI for the ΔΔQTc at the median concentration for each quartile and overlaid this on the linear plot. What is interesting about these are, a) there appears to possibly be a nonlinear relationship in particular with quetiapine that suggests a threshold effect, b) the 90% upper limit for asenapine barely breaks the 10 mSec threshold in contrast to the analysis by time post-dose, whereas it appears more similar quetiapine, c) the upper range of the measured asenapine concentrations only goes slightly above 10 ng/ml (possible 14 ng/ml) whereas Figure 154 on the following page clearly shows that asenapine concentrations clearly go up to 20 ng/ml in this study with a dose of 20 mg SL BID. In addition Figure 155 shows that concentrations of 20 ng/ml were commonly seen with sparse sampling with the phase IIb/III efficacy studies at the maximum studied clinical dose of 10 mg SL BID

Figure 152 Linear Model of ΔΔQTcF vs. Asenapine Concentration Overlaid with Mean QT Prolongation with 90% CIs at the Median-of the 10% Quantiles for Asenapine Concentration

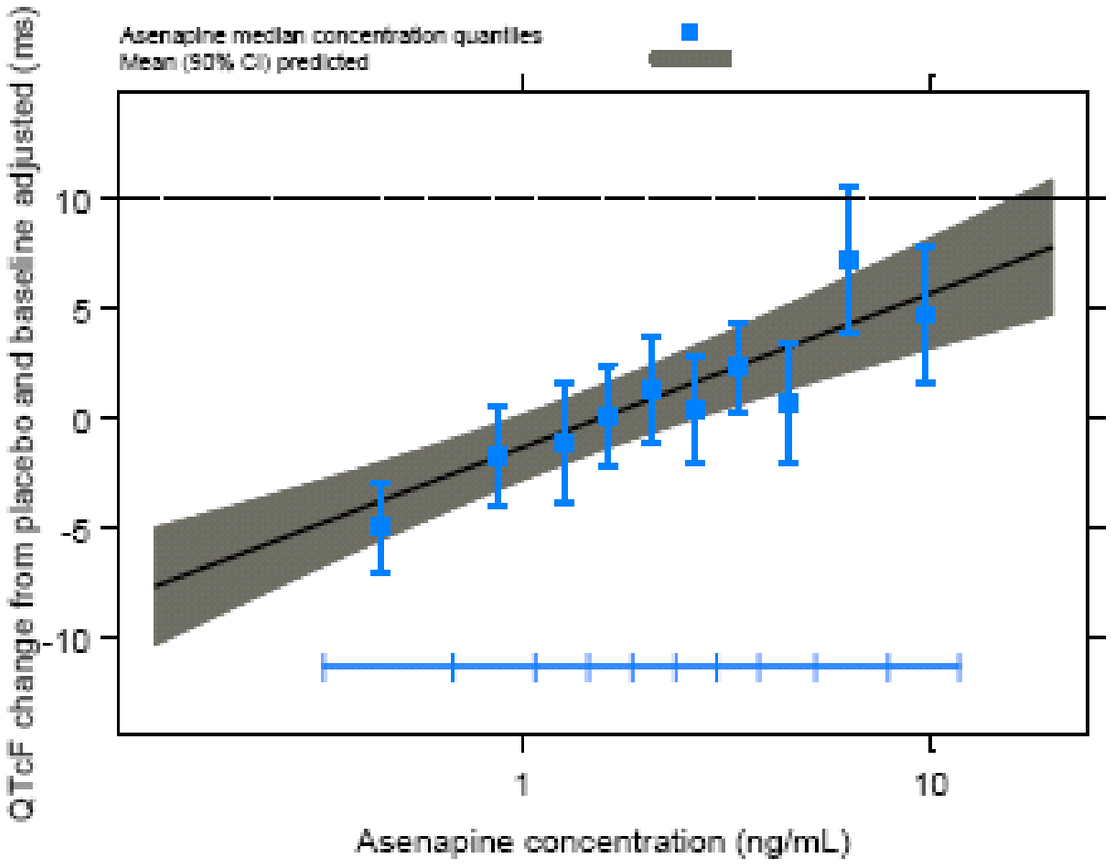


Figure 153 Linear Model of ΔΔQTcF vs. Quetiapine Concentration Overlaid with Mean QT Prolongation with 90% CIs at the Median-of the 10% Quantiles for Quetiapine Concentration.

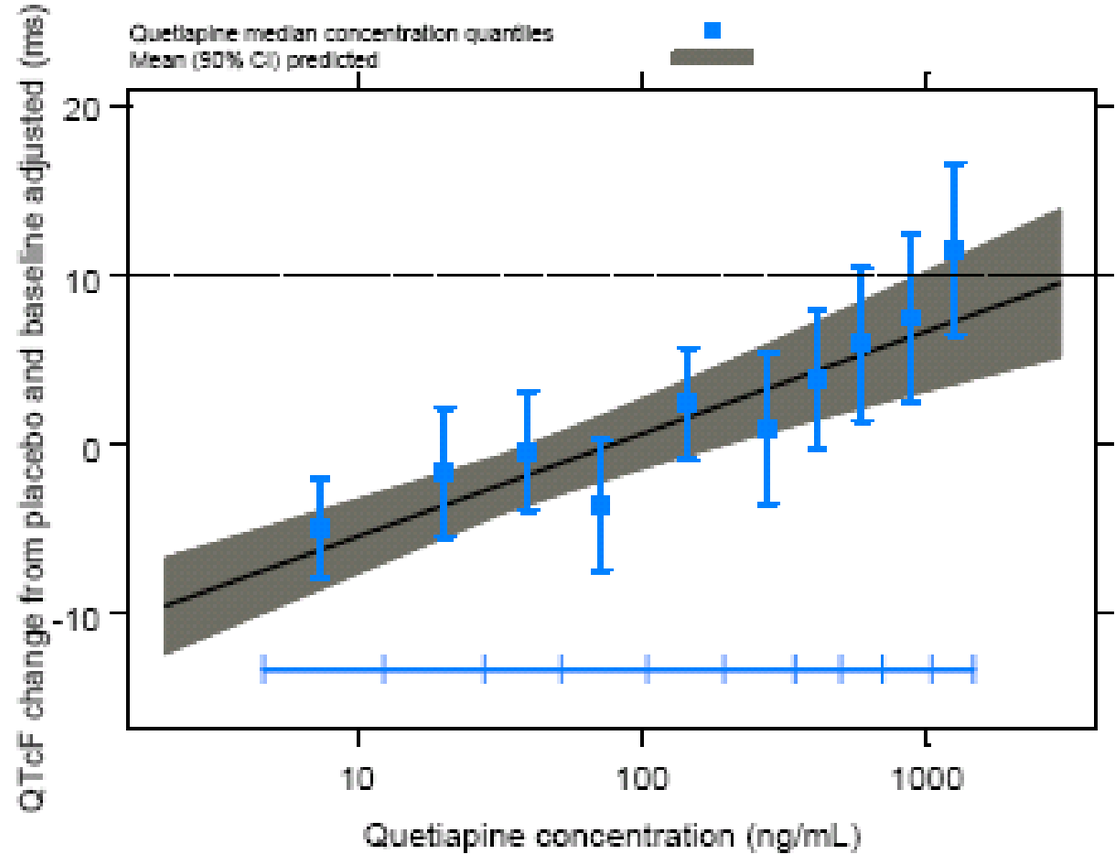


Figure 154 Steady State Asenapine Concentrations with Overlaid Mean Concentration vs. Time Profile Prediction with 90% CIs for Asenapine 20 mg SL BID. Data from Thorough QT study – A7501001

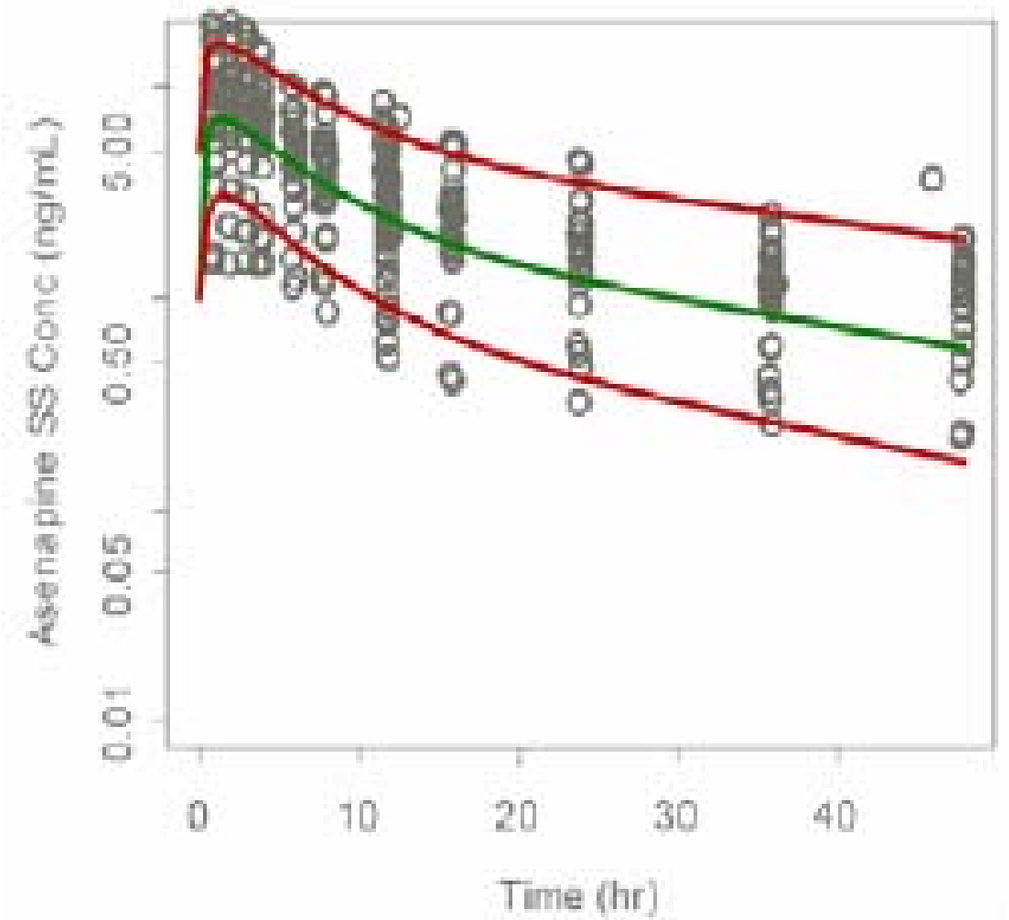
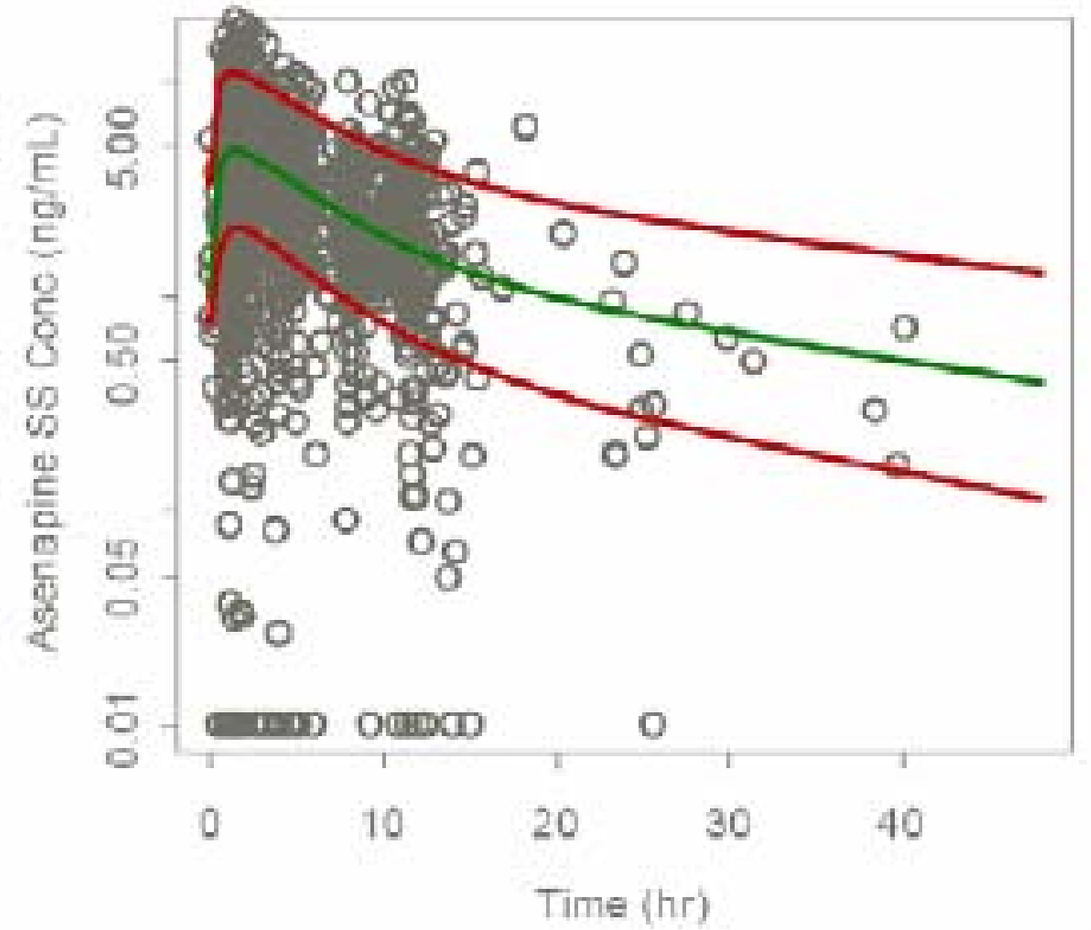


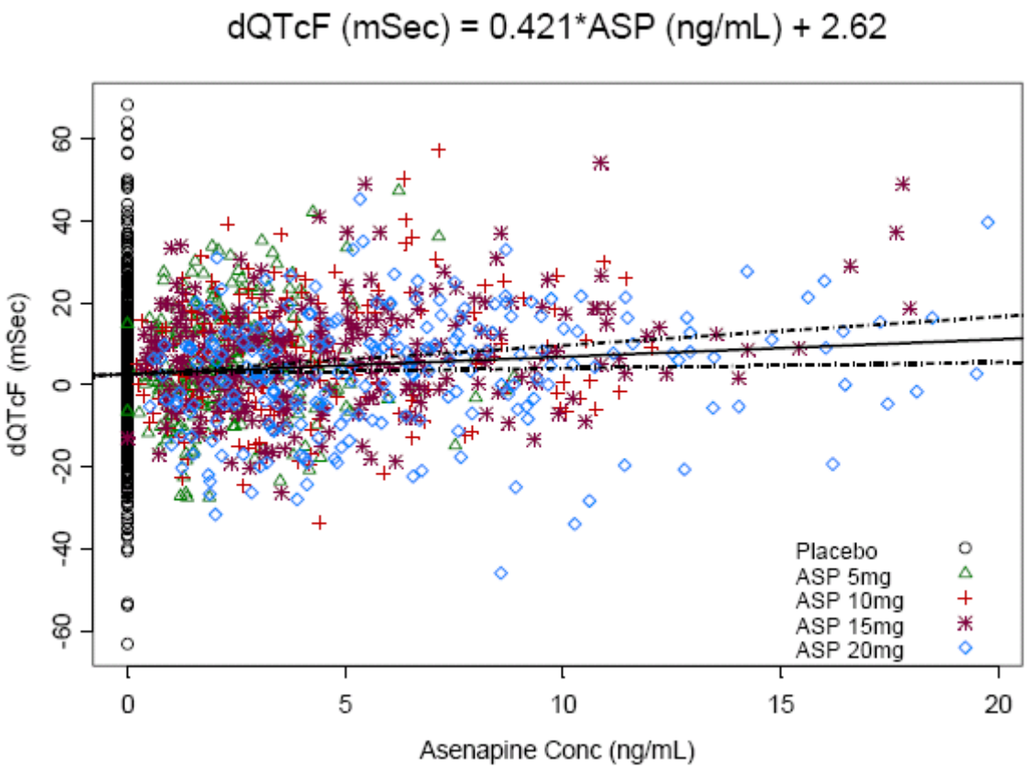
Figure 155 Steady State Asenapine Concentrations with Overlaid Mean Concentration vs. Time Profile Prediction with 90% CIs for Asenapine 10 mg SL BID. Data from TQT and phase IIb/III Studies



Although this reviewer when evaluating the data files submitted for the pop PK study found that there were no asenapine concentrations greater than 10 ng/ml.

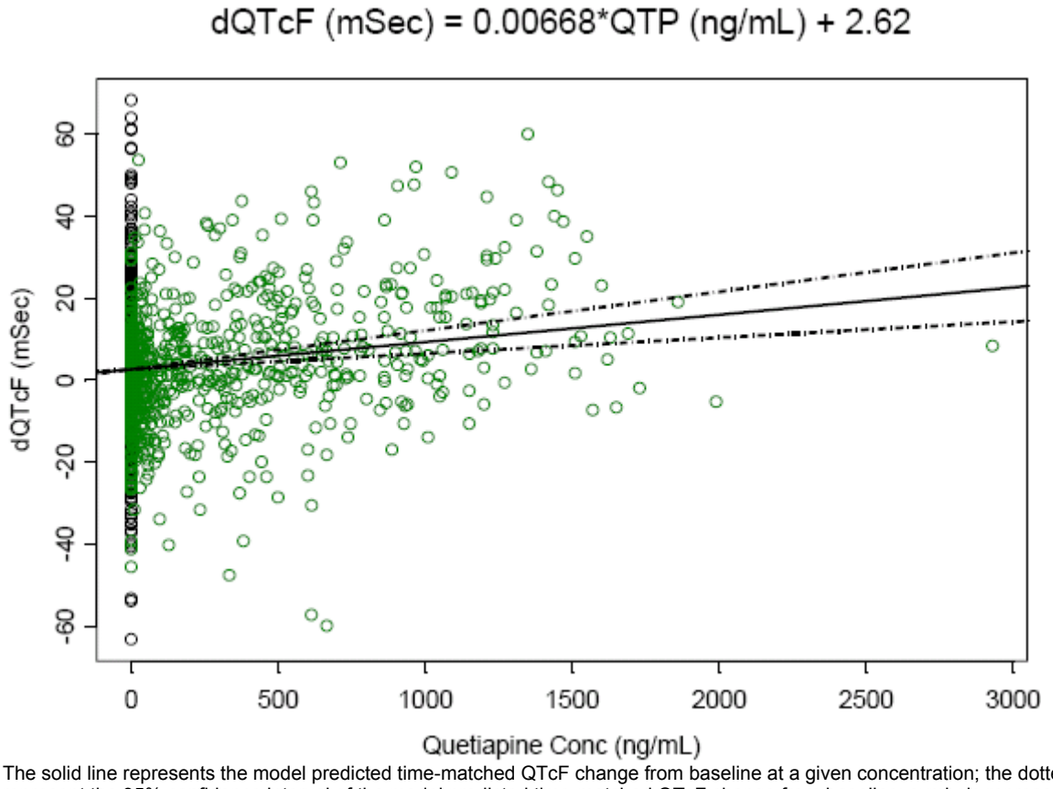
Figure 156 and Figure 158 shows the sponsor's linear models of ΔΔQTcF vs. plasma asenapine and quetiapine concentrations. It's clear that asenapine concentrations do go up to 20 ng/ ml and that most concentrations between 10 and 20 ng/ml are achieved by a dose of 20 mg BID followed by a dose of 15 mg BID, although the mean and upper limits of the CI are much lower than the values seen with the post-administration time dose data. In addition, most Quetiapine concentrations are below 2000 ng/ml at a dose of 375 mg BID which is within the therapeutic dose range of 400 – 800 mg daily. Assuming the highest concentration seen with quetiapine is 2750 ng/ml the maximum dose may result in concentrations of nearly 6000 ng/ml in some individuals. This translates into a ΔΔQTc of over 35 mSec in spite of this quetiapine is not generally considered to have a higher than normal incidence for arrhythigenic potential.

Figure 156 Sponsor's Plot of ΔΔQTcF vs. Plasma Asenapine Concentration for A7501001



The solid line represents the model-predicted time-matched QTcF change from baseline at a given concentration; the dotted lines represent the 95% confidence interval of the model-predicted time-matched QTcF change from baseline; color-coded symbols represent individual patient observations.

Figure 157 Sponsor's Plots of ΔΔQTcF vs. Plasma Quetiapine Concentrations for Study A7501001



The solid line represents the model predicted time-matched QTcF change from baseline at a given concentration; the dotted lines represent the 95% confidence interval of the model predicted time-matched QTcF change from baseline; symbols represent individual patient observations.

Figure 158 shows that when the percent of subjects with changes of 30 – 60 mSec are considered asenapine is no worse than Quetiapine. However when the maximal absolute QTcF is examined women appear to achieve higher QTcFs than males, (see Figure 159). This may be due to lower body mass and higher concentrations in women. This may also help to partly explain the higher ΔΔQTcF seen with the 10 mg SL BID dose, (see Table 169).

Figure 158 Sponsor's Table 6 of Categorical Changes in ΔQTcF by Treatment Group

Table 6: Categorization of QTcF maximum increase from baseline by treatment group

		N (%) of Subjects by Maximum QTcF Increase from Baseline		
Study Day		<30 msec	30-<60 msec	≥60 msec
Treatment	N	n (%)	n (%)	n (%)
Day 1[a] through Day 10				
Placebo	35	27 (77.1%)	6 (17.1%)	2 (5.7%)
Asenapine 5 mg	38	31 (81.6%)	7 (18.4%)	0 (0.0%)
Asenapine 15 mg	38	28 (73.7%)	10 (26.3%)	0 (0.0%)
Quetiapine 375 mg	37	22 (59.5%)	14 (37.8%)	1 (2.7%)
Day 11 through Day 16				
Placebo	32	27 (84.4%)	3 (9.4%)	2 (6.3%)
Asenapine 10 mg	28	20 (71.4%)	8 (28.6%)	0 (0.0%)
Asenapine 20 mg	30	23 (76.7%)	7 (23.3%)	0 (0.0%)
Quetiapine 375 mg	29	20 (69.0%)	9 (31.0%)	0 (0.0%)

Source: 11.1.2.01.01.06
[a] Post dose

Sponsor's Table 38, page 95 of CSR for A750-1001

Figure 159 Sponsor's Table 5 of Categorical QTcFs by Gender and Treatment

Table 5: Categorization of QTcF Data by Gender and Treatment Group

		Number (Percent) of Subjects by Maximum Post-dose QTcF (msec)								
		Males				Females				
		<430	430-<450	450-<500	≥500		<450	450-<470	470-<500	≥500
Treatment	N	n(%)	n(%)	n(%)	n(%)	N	n(%)	n(%)	n(%)	n(%)
Baseline										
Placebo	28	27 (96.4)	1 (3.6)	0 (0.0)	0 (0.0)	7	7 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asenapine 5 mg	33	33 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	5	5 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asenapine 15 mg	26	26 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	12	12 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Quetiapine 375 mg	27	27 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	10	10 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Day 1[a] through Day 10										
Placebo	28	27 (96.4)	0 (0.0)	1 (3.6)	0 (0.0)	7	6 (85.7)	0 (0.0)	1 (14.3)	0 (0.0)
Asenapine 5 mg	33	29 (87.9)	4 (12.1)	0 (0.0)	0 (0.0)	5	5 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asenapine 15 mg	26	24 (92.3)	1 (3.8)	1 (3.8)	0 (0.0)	12	9 (75.0)	2 (16.7)	1 (8.3)	0 (0.0)
Quetiapine 375 mg	27	26 (96.3)	1 (3.7)	0 (0.0)	0 (0.0)	10	9 (90.0)	1 (10.0)	0 (0.0)	0 (0.0)
Day 11 through Day 16										
Placebo	27	26 (96.3)	1 (3.7)	0 (0.0)	0 (0.0)	5	5 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asenapine 10 mg	24	21 (87.5)	3 (12.5)	0 (0.0)	0 (0.0)	4	4 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asenapine 20 mg	20	20 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	10	8 (80.0)	1 (10.0)	1 (10.0)	0 (0.0)
Quetiapine 375 mg	22	22 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	7	6 (85.7)	1 (14.3)	0 (0.0)	0 (0.0)

Source: 11.1.2.01.01.05
[a] Post dose

Sponsor's Table 36, page 93 of CSR for A750-1001

In contrast the QT team reports that: *'In the long-term schizophrenia study 25517, ECGs were performed at Screening, Weeks 3, 6, 24, and endpoint, and the tracings were read by a central laboratory. Analyses included interval changes from baseline (descriptive statistics), categorical changes, outlier analysis, and post-baseline markedly abnormal changes in morphology. The most frequently reported ECG related AE in the asenapine group (1.2%) was Electrocardiogram QT corrected interval prolonged (0.6% in the olanzapine treatment group).'*

This was a flexible dose study of asenapine 5 – 10 mg BID vs. Olanzapine 10 – 20 mg QD with randomization in a 3:1 ratio to the lower to higher doses. Dosage adjustments and exposures were similar however EPS was nearly doubled in the asenapine group, elevations in LFTs were lower, by worsening psychosis and dropoutw were worse in the asenapine arms.

The percentage of women treated with asenapine ranged from 13.2% of the asenapine 5/10 mg group (5 of 38 subjects) to 31.6% of the asenapine 15/20 mg group (12 of 38 subjects).

Table 169 Sponsor's Table 15 Summary of subject characteristics: safety analysis group

Characteristic	Placebo	Asenapine BID		Quetiapine 375 mg BID	All Subjects
		5/10 mg	15/20 mg		
N	35	38	38	37	148
Male	28 (80.0%)	33 (86.8%)	26 (68.4%)	27 (73.0%)	114 (77.0%)
Female	7 (20.0%)	5 (13.2%)	12 (31.6%)	10 (27.0%)	34 (23.0%)
Premenopausal	6 (85.7%)	4 (80.0%)	6 (50.0%)	7 (70.0%)	23 (67.6%)
Postmenopausal	1 (14.3%)	1 (20.0%)	6 (50.0%)	3 (30.0%)	11 (32.4%)
Race, n (%)					
Caucasian	16 (45.7%)	12 (31.6%)	18 (47.4%)	11 (29.7%)	57 (38.5%)
Black	13 (37.1%)	19 (50.0%)	18 (47.4%)	21 (56.8%)	71 (48.0%)
Asian	1 (2.9%)	1 (2.6%)	0 (0.0%)	1 (2.7%)	3 (2.0%)
Other	5 (14.3%)	6 (15.8%)	2 (5.3%)	4 (10.8%)	17 (11.5%)
Age	44.8 ± 8.4 19 - 57 [45.0]	42.4 ± 9.5 23 - 57 [43.5]	43.6 ± 7.7 28 - 56 [44.0]	39.6 ± 7.6 26 - 53 [39.0]	42.6 ± 8.5 19 - 57 [43.0]
Weight (kg)	83.8 ± 14.8 52 - 114 [83.6]	82.1 ± 17.4 48 - 127 [81.5]	86.4 ± 14.0 55 - 113 [85.5]	84.9 ± 17.0 56 - 126 [82.7]	84.3 ± 15.8 48 - 127 [83.6]
BMI	27.5 ± 5.0 18 - 35 [27.1]	26.5 ± 4.5 17 - 35 [26.7]	29.2 ± 4.2 20 - 36 [29.4]	28.0 ± 4.4 20 - 35 [27.0]	27.8 ± 4.6 17 - 36 [27.7]
Alcohol Use (drinks per week)	1.8 ± 4.55 0 - 22 [0.0]	0.6 ± 1.43 0 - 6 [0.0]	0.6 ± 1.39 0 - 6 [0.0]	0.2 ± 0.72 0 - 3 [0.0]	0.8 ± 2.50 0 - 22 [0.0]

Other factors that may have biased the results are that virtually all subjects were smokers, (see Table 147), which induces asenapine's metabolism and would decrease exposure, and Subjects were to have had their meals before dosing and to be finished eating at least 15 minutes before each dose which would also decrease exposures, (see). Consequently, those who don't smoke, those with smaller body mass, and more typical administration not in combination with a meal would all result in higher exposures even

with the 5 mg dose and the 10 mg dose than seen in the present study. All of these factors point to a greater risk for cardiotoxicity in patients with bipolar illness, as they are likely to include more nonsmokers, and children.

The QT data in women as well as the higher exposures seen in mild hepatic impairment and the elderly indicate that these groups may be at increased risk as well.

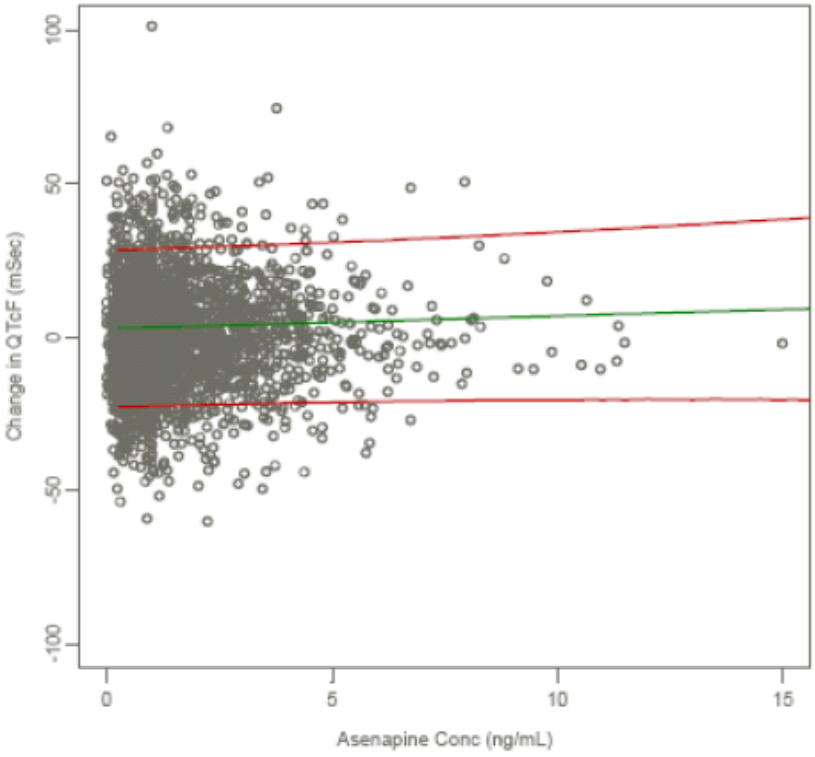
Figure 160 is claimed to be plot of observed ΔΔQTcF from the TQTc study vs. individual predicted concentrations based on a population pharmacokinetic model for a phase 3 schizophrenia trial of Asenapine 5 mg or 10 mg BID with sparse sampling.

Interpretation is difficult as it's not clear how you can even reasonably plot this information from two different studies with two different subject populations. Also the variability in ΔΔQTc is so wide even at zero concentration there is a positive QT effect with and upper limit of approximately 30 mSec.

However upon further review of the original study report it was realized that this is intended to not show the 90% CIs on the mean data, but rather the 90% CIs on all QTc changes in the population. Consequently we can see that we expect a significant amount of ΔΔQTcF of 30 – 60 mSec with clinical dosing and 4 values of greater than 60 mSec even with concentrations less than 5 ng/ml. Unfortunately the data files did not include ΔΔQTcF so the proportion of subjects at each dose that had significant changes could not be assessed. However examination of absolute QTcFs revealed that 1.1% of subjects had QTcF values of greater than 450 mSec.

Figure 160 Sponsor's Figure 4 from INT00036960 Plotting Observed ΔΔQTcF from Study A7501001 vs. Population PK individually Predicted Asenapine Concentrations from Phase III Efficacy Study 25517

Figure 4: Unconditional Prediction Interval Overlaid with Observed ΔΔQTcF vs. Individual Predicted Asenapine Concentrations from Study 25517, A Phase 3 Study



Sponsor's Figure 4, page 20 from Study INT00036960

5.6.2 Exposure Response

5.6.2.1 Schizophrenia

5.6.2.1.1 Acute Treatment of Psychosis

Table 170 and Table 171 show the sponsor's summary of the statistical analysis of 4 phase IIB and phase III active and placebo controlled trials of the efficacy of asenapine in the short term treatment of an acute psychotic episode in patients with schizophrenia as assessed by total PANSS score. These tables are from the sponsor's summary of clinical efficacy and only include those trials that utilized dosages that are proposed for marketing. Table 170 shows analysis by LOCF, where as Table 171 shows analyses using mixed models of repeated measures, (MMRM). No summary tables were provided for analyses by OC. As expected the mixed model of repeated measures shows a greater degree of statistical significance and this will be discussed later.

Even based on simple inspection of these data tables immediately reveal concerns with the studies, including:

- Of 4 studies only 2, the smaller initial phase IIb study 41004 and the last phase III study 41023, were positive. The other 2 phase III studies were negative.

- The active control risperidone failed to show efficacy in the positive phase IIb study 41004 in spite of adequate dosing and is therefore a 'failed' study.

- Only the lower dose of asenapine 5 mg BID and not the higher dose of 10 mg BID showed efficacy in the second positive study 41023.

- Although the most efficatious available antipsychotics were used at therapeutic doses, i.e. risperidone 3 mg BID, olanzapine 10 – 20 mg QD, and haloperidol 4 mg BID, the difference from placebo was minimal, i.e. ~5.6, -5.4 and -2.3, and -5.7 respectively. Whereas the difference from placebo expected with each of these compounds is on the order of at least -10 and closer to -15 units.

Due to the size and complexity of the submission, this reviewer's lack of skill in the new computer programs and CDISC data files and need for training, lack of assistance from the pharmacometrics group[12], lack of prior experience in analyzing antipsychotic ER data, and the insufficient time available for the present review, this reviewer in the time available simply undertook an exploratory evaluation of the exposure response relationships for efficacy for the two 'positive' studies 41004 and 41023.

[12] The pharmacometrics group was represented at the scoping meeting. The clinical division asked whether swallowing drug from the sublingual formulation would effect efficacy. This reviewer replied that on an individual basis this is possible however there would be variability from day to day and since the clinical studies were claimed to be positive this would have shown up as negative results or decreased efficacy in the clinical studies with the active comparator showing activity. No questions were asked by the clinical division regarding toxicity.

Table 170 Sponsor's Inferential Analysis of Change from Baseline in PANSS Total Score (LOCF, ITT group) for Short-Term Schizophrenia Trials 041004, 041021, 041022, and 041023

Study		041004			041021			
Treatments		Placebo	Asenapine 5 mg BID	Risperidone 3 mg BID	Placebo	Asenapine 5 mg BID	Asenapine 10 mg BID	Olanzapine 15 mg QD
Rx Arm (tcaf)		3	2	1	1			
N		60	58	56	93	102	96	95
Baseline		92.4 (1.9)	96.5 (2.2)	92.2 (2.1)	93.7 (1.1)	90.8 (1.0)	93.2 (1.1)	92.6 (1.1)
Δ to:	Day 4				-3.9 (.8)	-4.0 (0.8)	-5.5 (0.8)	-3.3 (0.8)
	Day 7	-3.9 (1.5)	-6.2 (1.7)	-5.6 (1.8)	-6.5 (1.0)	-7.8 (1.0)	-8.8 (1.0)	-7.1 (1.0)
	Day 14	-5.5 (1.6)	-11.3 (2.0)*	-8.3 (2.4)	-9.8 (1.3)	-13.1 (1.3)	-11.5 (1.3)	-11.6 (1.3)
	Day 21	-6.4 (2.1)	-16.9 (2.4)*	-10.8 (2.8)	-10.5 (1.4)	-12.9 (1.4)	-11.9 (1.4)	-12.8 (1.4)
	Day 28	-6.6 (2.3)	-16.9 (2.5)*	-10.3 (2.7)	-10.7 (1.5)	-14.0 (1.5)	-12.0 (1.5)	-14.6 (1.5)
	Day 35	-4.7 (2.2)	-16.0 (2.6)*	-10.5 (2.7)	-10.2 (1.6)	-14.5 (1.5)*	-13.1 (1.6)	-15.8 (1.6)*
	Day 42	-5.3 (2.3)	-15.9 (2.6)*	-10.9 (2.7)	-11.1 (1.6)	-14.4 (1.6)	-13.5 (1.6)	-16.5 (1.6)*
	Endpoint	—	—	—	-11.1 (1.6)	-14.5 (1.6)	-13.4 (1.6)	-16.5 (1.6)*

Study		041022			041023			
Treatments		Placebo	Asenapine 5/10 mg BID	Olanzapine 10-20 mg QD	Placebo	Asenapine 5 mg BID	Asenapine 10 mg BID	Haloperidol 4 mg BID
Rx Arm (tcaf)								
N		89	85	85	122	109	105	112
Baseline		84.7 (1.1)	86.8 (1.1)	86.5 (1.1)	89.0(0.9)	88.9 (1.0)	89.4 (1.0)	88.5 (1.0)
Δ to:	Day 4	-2.9 (0.7)	-4.2 (0.7)	-3.7 (0.7)	-3.4 (0.7)	-2.9 (0.8)	-4.4 (0.8)	-3.4 (0.8)
	Day 7	-4.8 (1.2)	-4.9 (1.2)	-5.0 (1.1)	-5.9 (0.9)	-7.2 (1.0)	-7.7 (1.0)	-7.3 (1.0)
	Day 14	-7.1 (1.5)	-8.7 (1.5)	-9.2 (1.5)	-8.3 (1.1)	-10.5 (1.2)	-10.4 (1.2)	-11.0 (1.2)
	Day 21	-8.8 (1.6)	-9.5 (1.6)	-9.9 (1.6)	-9.1 (1.3)	-13.2 (1.4)*	-11.6 (1.4)	-13.8 (1.4)*
	Day 28	-8.9 (1.6)	-10.0 (1.6)	-10.7 (1.6)	-9.4 (1.4)	-14.2 (1.5)*	-11.7 (1.5)	-14.4 (1.5)*
	Day 35	-9.3 (1.7)	-10.1 (1.7)	-11.2 (1.7)	-10.2 (1.5)	-15.3 (1.6)*	-13.3 (1.6)	-14.7 (1.5)*
	Day 42	-10.1 (1.7)	-9.1 (1.7)	-11.4 (1.7)	-10.8 (1.6)	-16.2 (1.7)*	-14.7 (1.7)	-15.6 (1.6)*
	Endpoint	-9.9 (1.7)	-9.4 (1.7)	-11.5 (1.7)	-10.7 (1.6)	-16.2 (1.7)*†	-14.9 (1.7)	-15.4 (1.6)*

Source: Table 16 in CTR 041004, Table 15 in CTR 041021; Table 16 in CTR 041022; Table 16 in CTR 041023.
All values are mean (SE)
*indicates p≤0.05. In the Phase II trials, p-values were based on a two-sided t-test comparing each active treatment group with the placebo group; an ANOVA model with fixed effects for treatment and pooled investigative site was used. In the Phase III trials, an ANCOVA model with treatment and pooled investigative site as fixed effects and baseline as a covariate was used; p-values are based on the difference in the LS mean change for active treatment versus placebo.
† indicates adjusted p≤0.05. Adjusted p-values were determined in Trials 041021 and 041023 using Hochberg method for testing 2 asenapine groups versus the placebo group.

Table 171 Sponsor's Mixed Model for Repeated Measures (MMRM) Analysis of Change from Baseline in PANSS Total Score (ITT Group)

Study		041004			041021			
Treatments		Placebo	Asenapine 5 mg BID	Risperidone 3 mg BID	Placebo	Asenapine 5 mg BID	Asenapine 10 mg BID	Olanzapine 15 mg QD
Rx Arm (tcaf)		3	2	1	1			
N		60	58	56	93	102	96	95
Baseline		92.4 (1.9)	96.5 (2.2)	92.2 (2.1)	93.7 (1.1)	90.8 (1.0)	93.2 (1.1)	92.6 (1.1)
Δ to:	Day 4	NA	NA	NA	93.7 (1.1)	90.8 (1.0)	93.2 (1.1)	92.6 (1.1)
	Day 7	-4.8 (1.5)	-6.0 (1.6)	-6.3 (1.6)	-3.9 (0.8)	-4.0 (0.8)	-5.5 (0.8)	-3.3 (0.8)
	Day 14	-6.5 (2.0)	-12.3 (2.0)*	-9.6 (2.0)	-6.4 (1.0)	-7.6 (1.0)	-8.9 (1.0)	-7.2 (1.0)
	Day 21	-8.0 (2.4)	-20.1 (2.4)*	-13.7 (2.4)	-10.0 (1.4)	-13.1 (1.3)	-11.9 (1.4)	-11.8 (1.4)
	Day 28	-9.1 (2.9)	-20.8 (2.9)*	-12.4 (2.8)	-11.1 (1.6)	-13.3 (1.5)	-13.7 (1.6)	-14.0 (1.6)
	Day 35	-7.0 (3.3)	-20.1 (3.2)*	-15.5 (3.2)	-11.4 (1.7)	-15.2 (1.6)	-14.2 (1.7)	-16.7 (1.7)*
	Day 42	-8.5 (3.4)	-19.8 (3.3)*	-16.2 (3.3)	-11.6 (1.8)	-16.3 (1.7)	-16.3 (1.8)	-18.7 (1.8)*

Study		041022			041023			
Treatments		Placebo	Asenapine 5/10 mg BID	Olanzapine 10-20 mg QD	Placebo	Asenapine 5 mg BID	Asenapine 10 mg BID	Haloperidol 4 mg BID
Rx Arm (tcaf)								
N		89	85	85	122	109	105	112
Baseline		84.7 (1.1)	86.8 (1.1)	86.5 (1.1)	89.0 (0.9)	88.9 (1.0)	89.4 (1.0)	88.5 (1.0)
Δ to:	Day 4	-2.9 (0.7)	-4.1 (0.7)	-3.7 (0.7)	-3.4 (0.7)	-2.9 (0.8)	-4.4 (0.8)	-3.4 (0.8)
	Day 7	-5.5 (1.1)	-5.3 (1.2)	-5.8 (1.2)	-6.2 (0.9)	-7.3 (1.0)	-8.0 (1.0)	-7.7 (1.0)
	Day 14	-8.6 (1.5)	-10.4 (1.5)	-11.1 (1.5)	-9.4 (1.2)	-11.5 (1.3)	-12.0 (1.3)	-12.3 (1.2)
	Day 21	-12.2 (1.7)	-12.3 (1.7)	-12.6 (1.7)	-10.9 (1.3)	-15.7 (1.4)*	-13.9 (1.4)	-16.1 (1.4)*
	Day 28	-13.9 (1.7)	-13.9 (1.7)	-14.5 (1.7)	-12.0 (1.4)	-17.9 (1.5)*	-14.5 (1.5)	-17.2 (1.5)*
	Day 35	-14.2 (1.9)	-14.0 (2.0)	-15.2 (2.0)	-13.3 (1.5)	-19.7 (1.6)*	-17.4 (1.6)	-18.0 (1.6)*
	Day 42	-15.6 (2.0)	-11.6 (2.1)	-15.9 (2.1)	-14.6 (1.6)	-21.3 (1.7)*	-19.4 (1.7)*	-20.0 (1.7)*

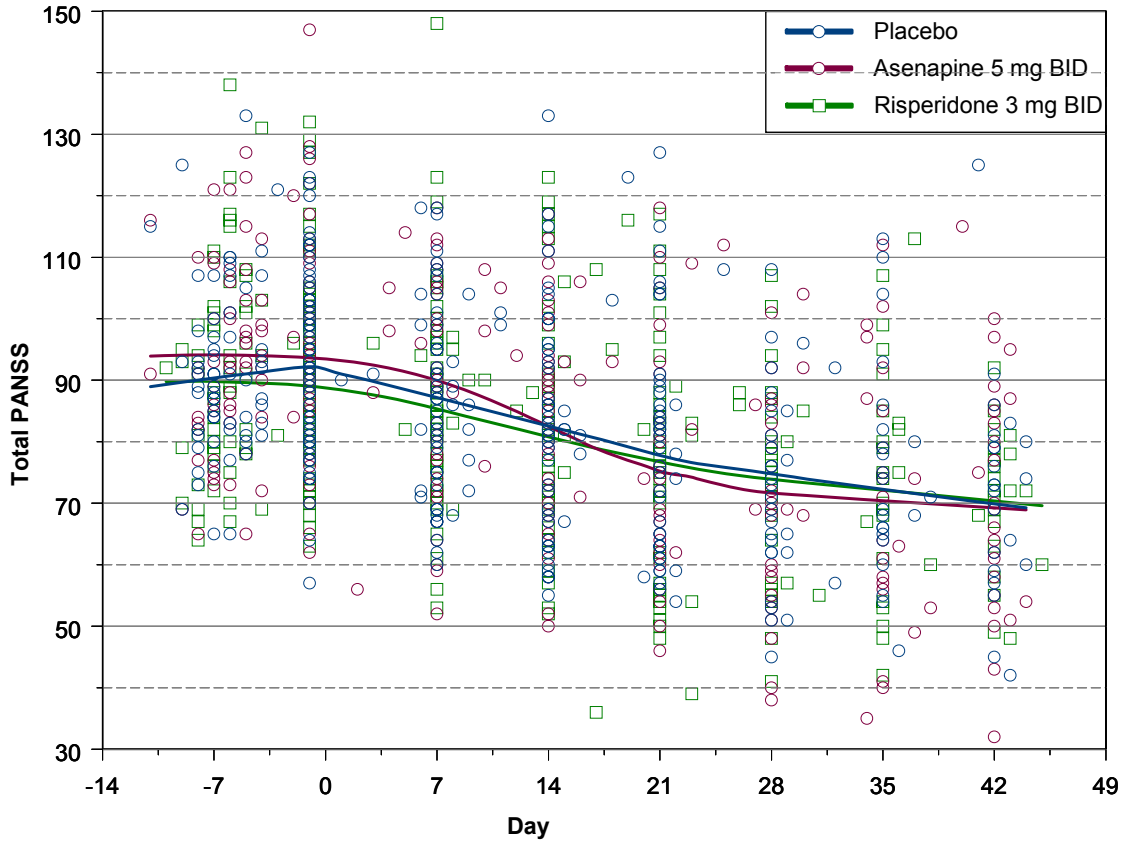
Source: Appendix A Table 41.1.S, Table 41.2.S, Table 41.3.S, and Table 41.4.S: referenced tables were (covariance structure = UN)
All values are mean (SE)
* indicates $p \leq 0.05$

5.6.2.1.1.1 Change in PANSS Score

5.6.2.1.1.1.1 Study 41004

Figure 161 plots Total PANSS score over time for the three treatment groups and is overlaid with LOESS curves. It's noteworthy that all treatments result in the same final value, thus the greater change from placebo with asenapine is due to a higher initial baseline score in the asenapine group.

Figure 161 Total PANSS Score vs. Time by Treatment – Study 41004



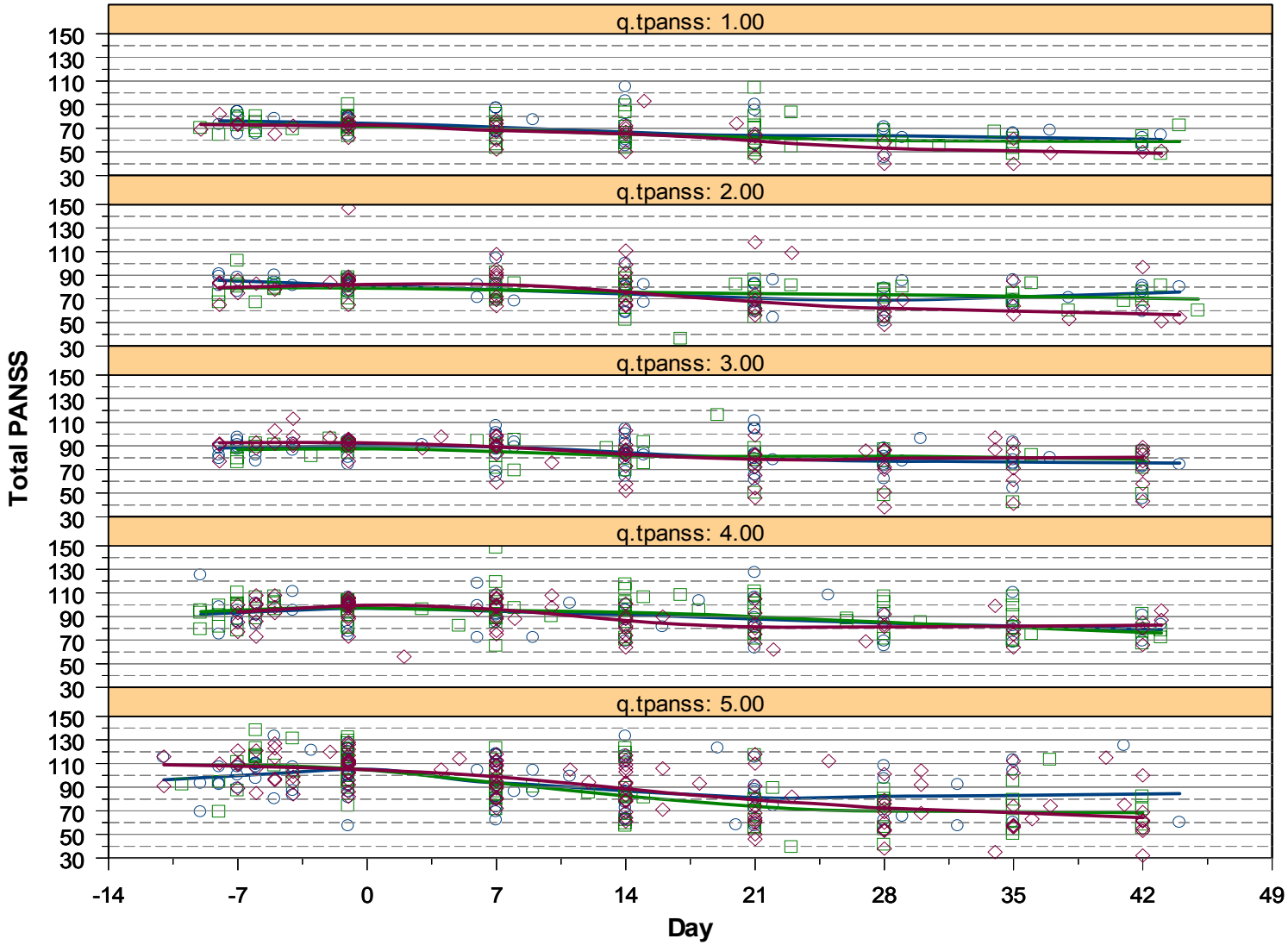
Next this reviewer examined the response while controlling for the initial severity of illness. To do this the highest PANSS score measured prior to treatment was determined for each subject. These scores were then divided into quintiles and the treatment responses for each quintile were compared. Table 172 shows the dividing points for each quintile for total PANSS score as well as for each of the subscores.

Table 172 Summary Statistics for Baseline Total PANSS Scores and Subscores – Study 41004

Metric	TPANSS	PPANSS	NPANSS	GPANSS
N	182	182	182	182
Mean ± SD **(%CV)** **Range** **[Median]** **Quintiles 20, 40, 60, 80**	98.8 ± 15.4 (15.6) 64 - 147 [98.5] 85, 95, 101, 111.4	26.5 ± 4.1 (15.3) 17 - 37 [26] 23, 25, 27.8, 30	25.1 ± 5.6 (22.5) 12 - 41 [25 20, 24, 26, 30	49.0 ± 8.6 (17.5) 26 - 80 [49] 42, 47, 51, 55

Figure 162 shows the overlaid LOESS curves for responses for each treatment by degree of initial severity assigned by quintile. No clear pattern can be discerned with regard to response by initial severity.

Figure 162 Total PANSS Score vs. Time by Quintile of Initial Severity by Treatment – Study 41004[a]



A Placebo - Blue; Asenapine – Red; Risperidone - Green

However when all three treatment groups are compared side by side it does appear that there may be a trend for greater response in the most severely ill patients, (see Figure 163 to Figure 165).

Figure 163 Total PANSS Score vs. Time (Days) for Placebo Treatment by Quintile of Severity - Study 41004

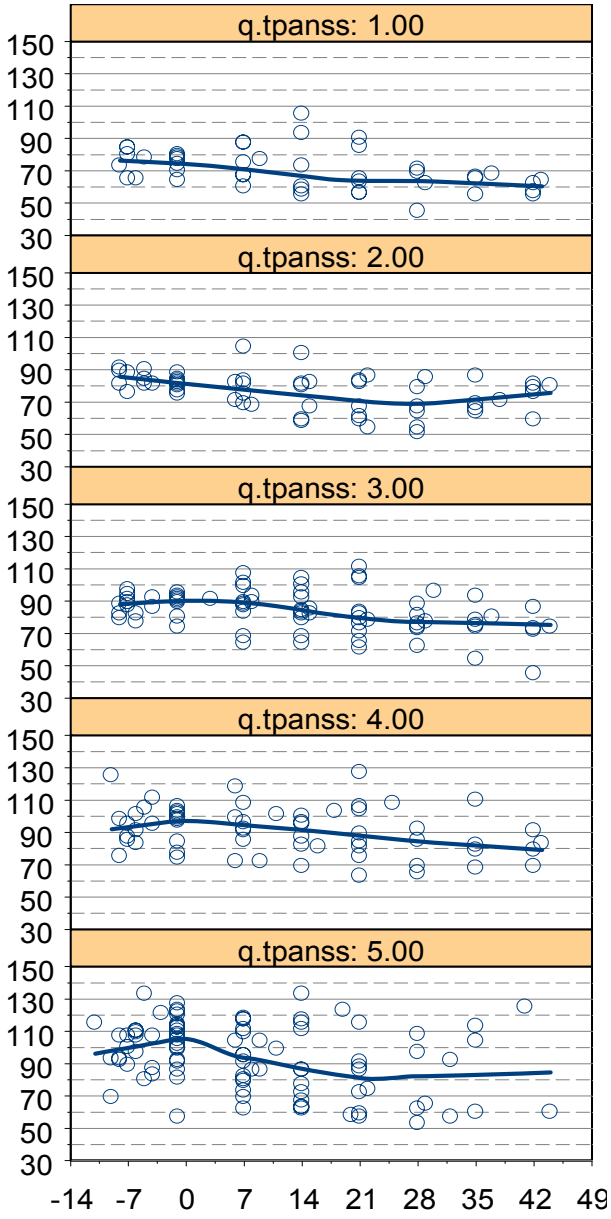


Figure 164 Total PANSS Score vs. Time (Days) for Asenapine 5 mg BID Treatment by Quintile of Severity - Study 41004

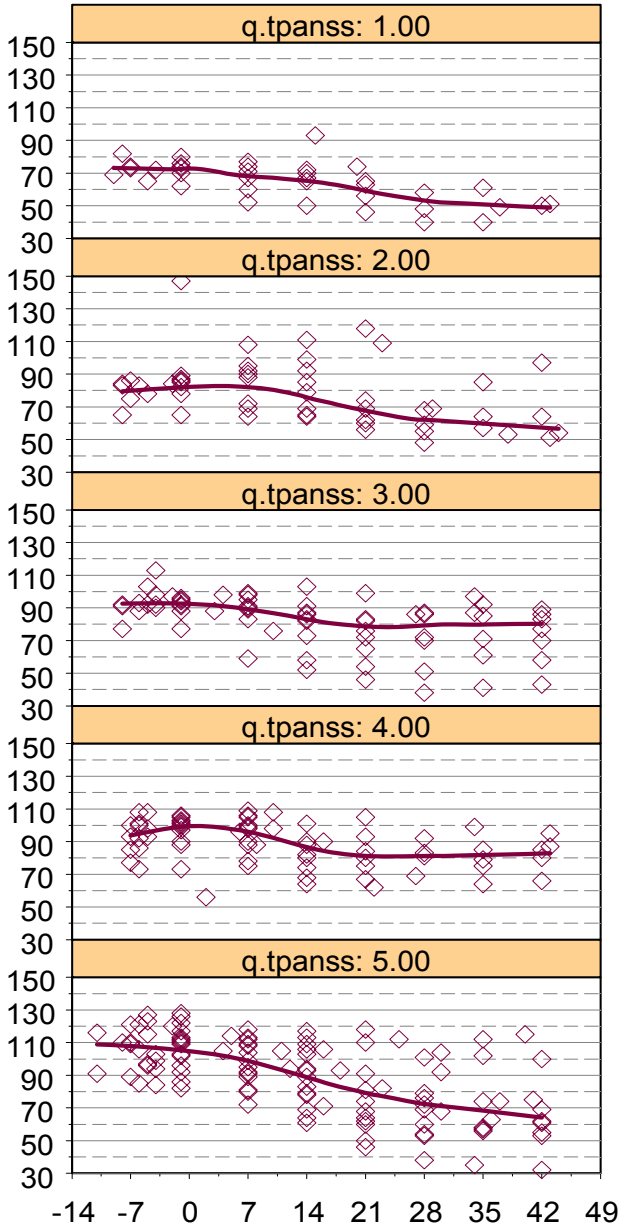
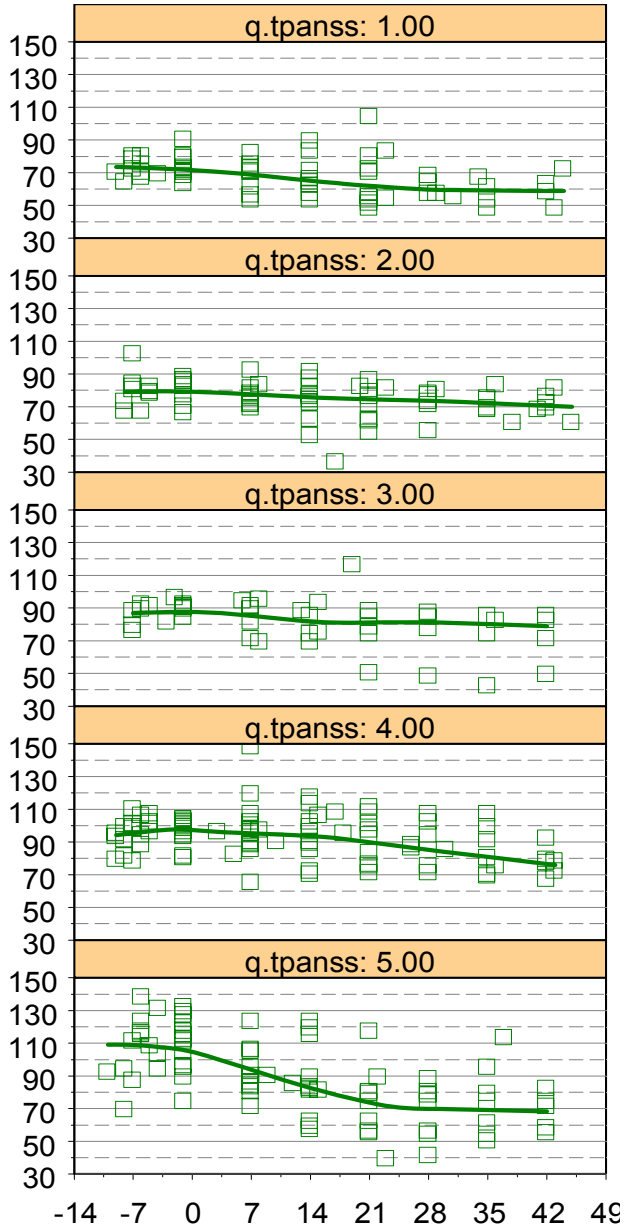


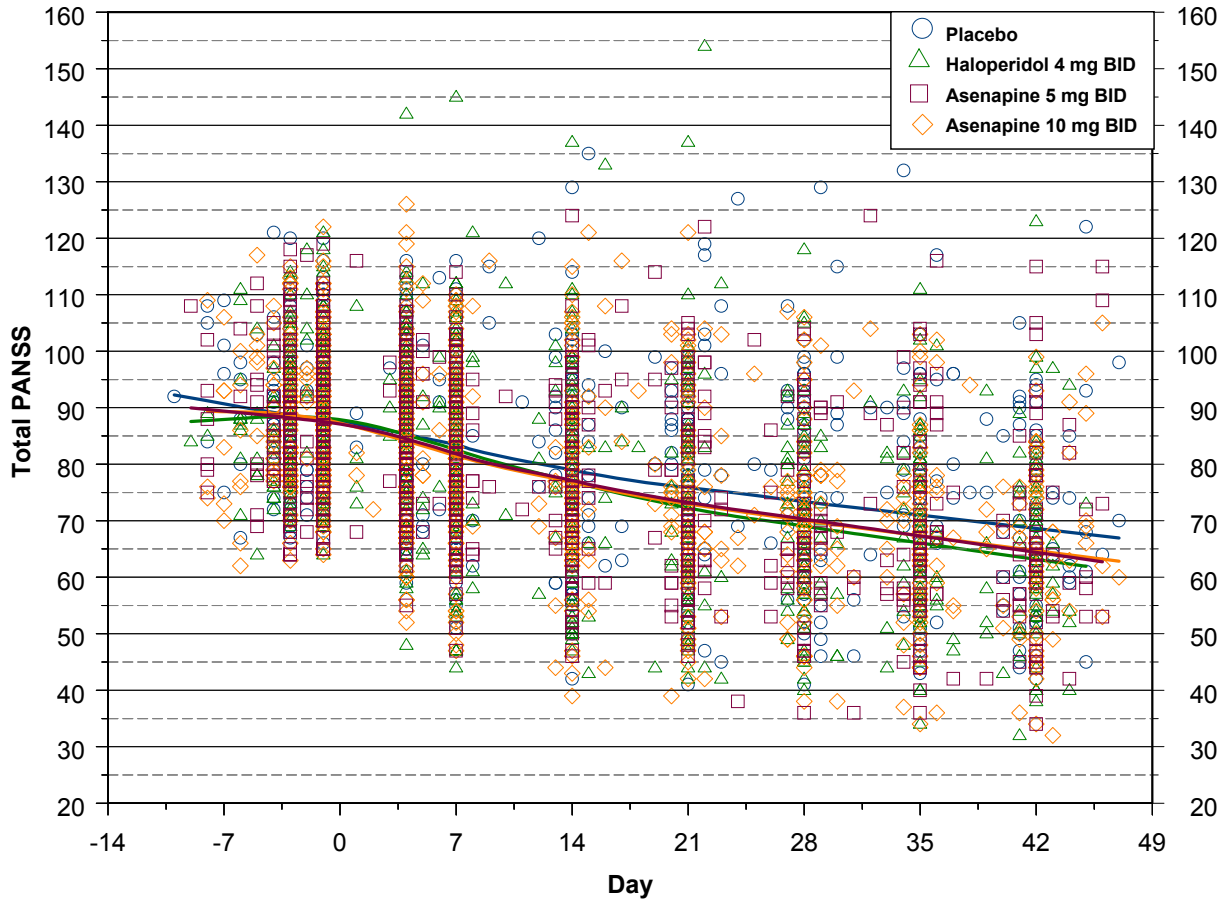
Figure 165 Total PANSS Score vs. Time (Days) for Risperidone 3 mg BID Treatment by Quintile of Severity - Study 41004



5.6.2.1.1.1.2 Study 41023

Figure 166 plots PANSS score over time for the four treatment groups in study 41023 and is overlaid with LOESS curves. In contrast to study 41004 the active treatments did result in final values different from placebo but the decrease in PANSS scores were only about 5 units greater than with placebo. Whereas the differences from placebo usually seen with active drugs in on the order of 12 – 15 units.

Figure 166 Total PANSS Score vs. Time by Treatment - Study 41023



In contrast to study 41004 the intial values were similar across treatments as shown by Table 173.

Table 173 Summary Statistics for Total PANSS Scores by Treatment – Study 41023

Treatment	Placebo	Asenapine 5mg BID	Asenapine 10mg BID	Haloperidol 4mg BID	All Treatments
N	123	111	106	115	456
Mean ± SD **(CV)** **Min - Max** **[Median]** **Quntiles 20, 40, 60, 80**	94.3 ± 10.7 (11.4) 74 - 121 [94] 83.8, 91.6, 97.4, 103	93.8 ± 10.7 (11.4) 72 - 122 [94] 84, 91, 96.2, 103.6	93.3 ± 12.4 (13.3) 63 - 121 [93] 82, 91, 95, 105.6	93.6 ± 12.4 (13.2) 65 - 118 [94] 82, 89.4, 98.6, 105	93.7 ± 11.5 (12.3) 63 - 122 [94] 83, 91, 97, 104

Figure 167 to Figure 170 shows total PANSS score vs. Time by quintile for each treatment. When examined there doesn't appear to be any clear pattern for efficacy by severity of illness. As with study 41004 quintles calculations were based on all treatments combined.

Figure 167 Total PANSS vs. Time by Quintile for Placebo – Study 41023

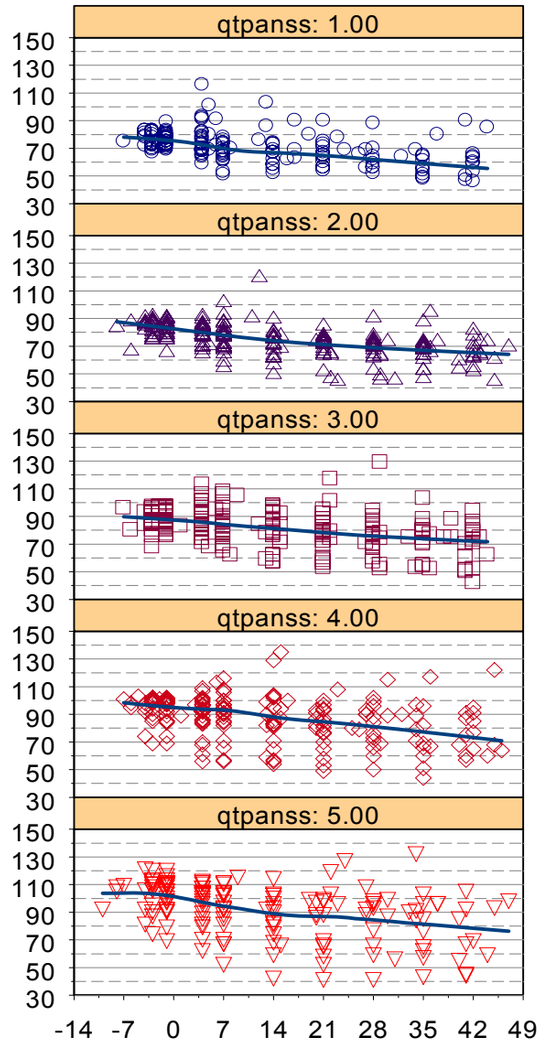


Figure 168 Total PANSS vs. Time by Quintile for Asenapine 5 mg BID – Study 41023

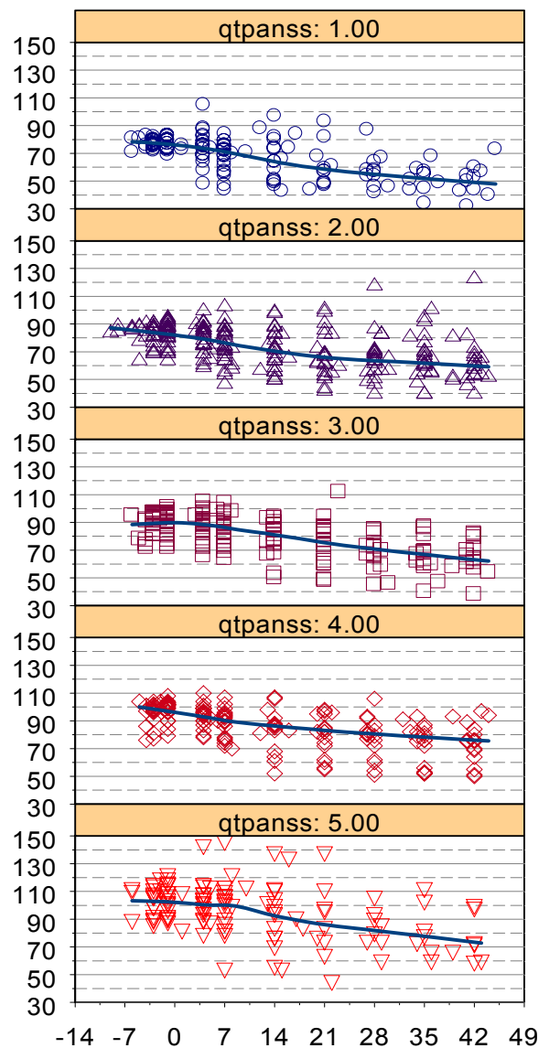


Figure 169 Total PANSS vs. Time by Quintile for Asenapine 10 mg BID – Study 41023

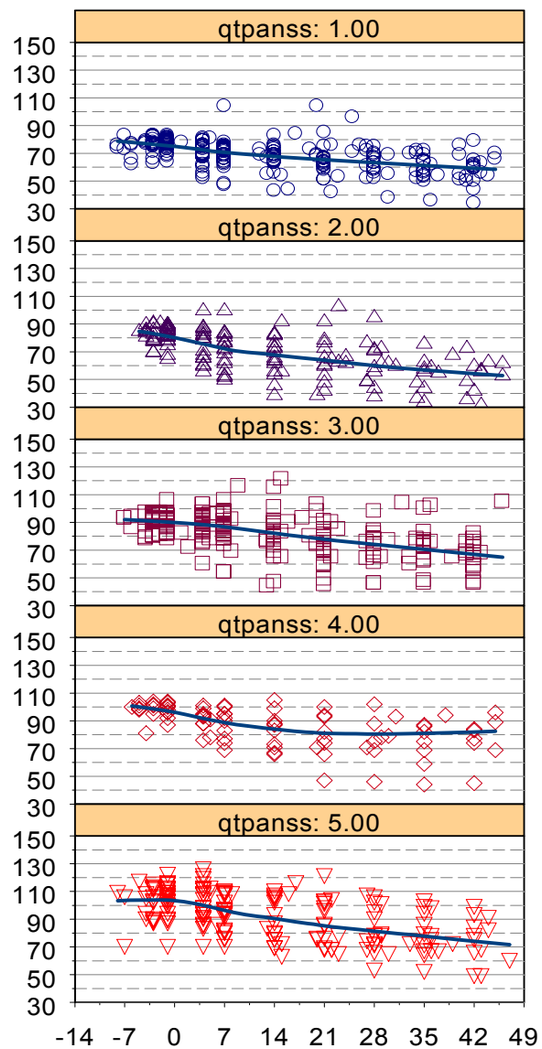


Figure 170 Total PANSS vs. Time by Quintile for Haloperidol 4 mg BID – Study 41023

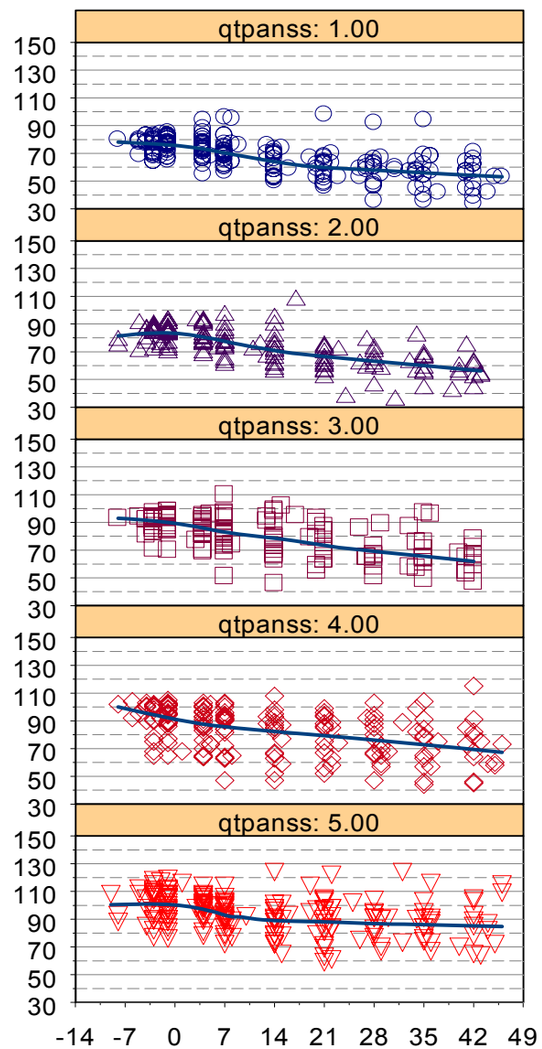


Figure 171 to Figure 174 shows similar plots but for positive PANSS score vs. Time by quintile for each treatment. Again there isn't any clear pattern for efficacy by severity of illness.

Figure 171 Positive PANSS vs. Time by Quintile for Placebo – Study 41023

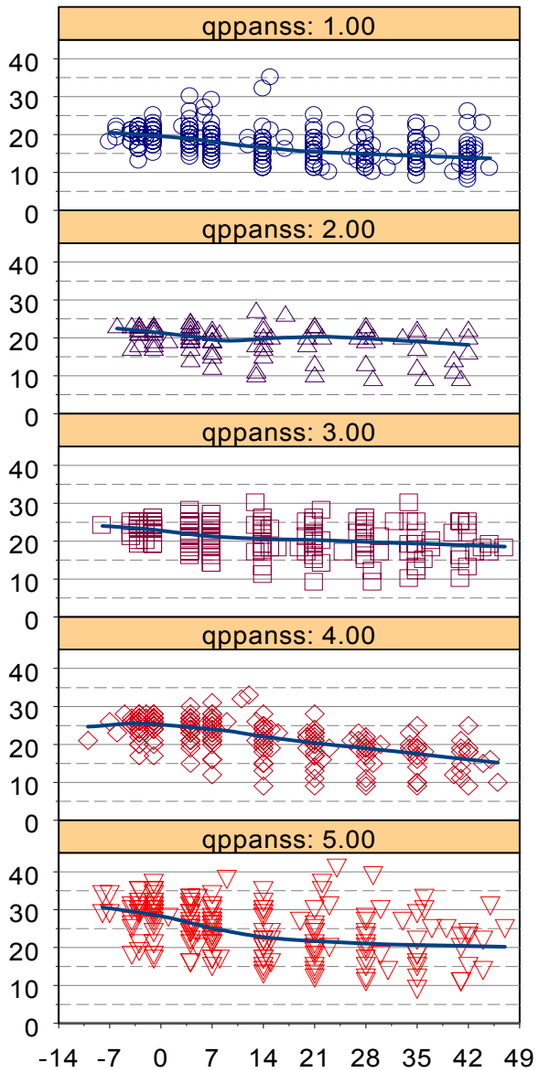


Figure 172 Positive PANSS vs. Time by Quintile for Asenapine 5 mg BID – Study 41023

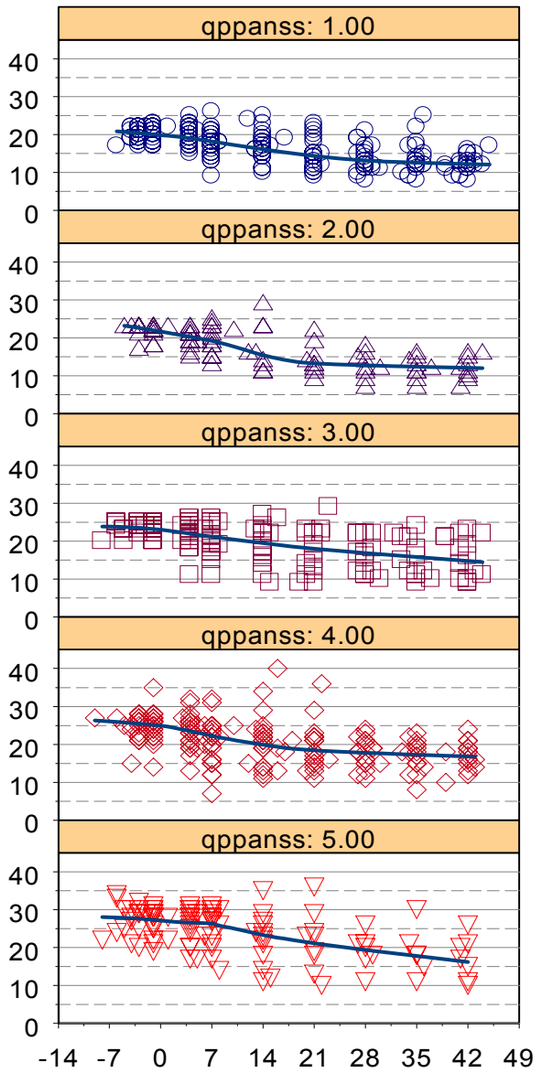


Figure 173 Positive PANSS vs. Time by Quintile for Asenapine 10 mg BID – Study 41023

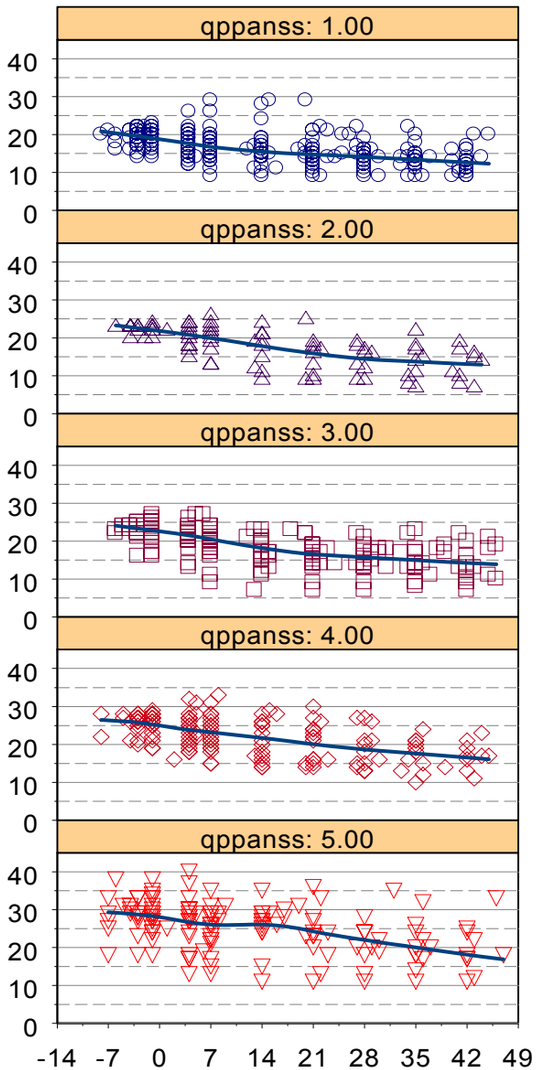
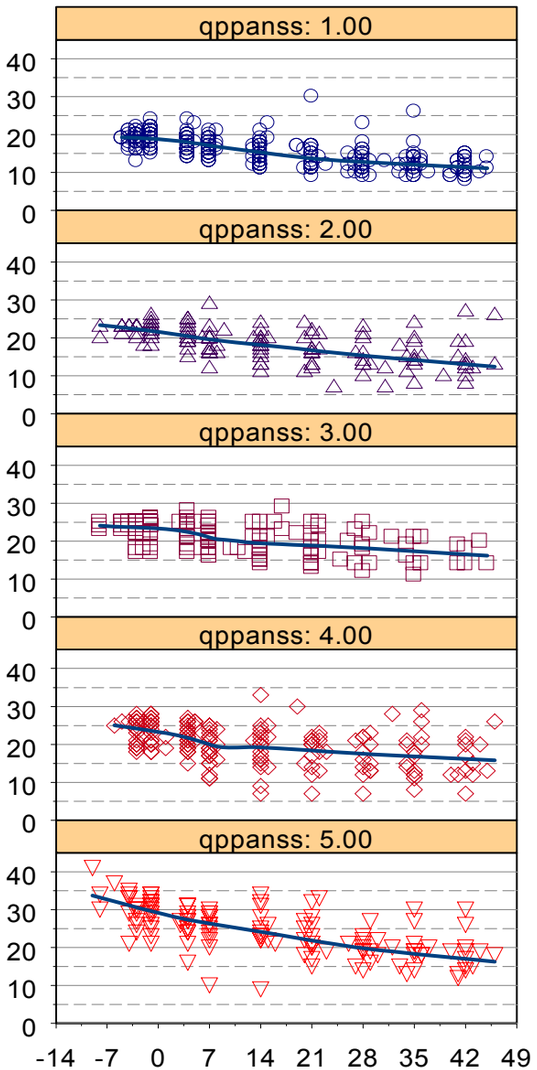


Figure 174 Positive PANSS vs. Time by Quintile for Haloperidone 4 mg BID – Study 41023



5.6.2.1.1.1.3 Sponsor's Combined ER Analysis of Phase IIb and III Acute Efficacy Studies

The sponsor performed an exposure response analysis of total PANSS score vs. asenapine exposure based on the following 3 Phase IIb and 3 Phase III 6-week efficacy studies for the efficacy in treating acute psychotic episodes associated with schizophreniae

The specifice studies included in the ER analysis follow:

Phase IIb studies
- 41002
- 41013
- 41004

Phase III studies
- 41021
- 41022
- 41023

Per the sponsor: *'The primary endpoint total PANSS was assessed at baseline and then weekly for 6 weeks with an extra assessment on Day 4 in the Phase 3 trials. Asenapine was administered sublingually and the doses ranged between 0.2 mg bid to 10 mg bid in the different treatment arms. Samples for the assessment of asenapine pharmacokinetics were obtained according to sparse sampling designs. The patients were hospitalized for 3 weeks in the Phase 2 trials and for at least 2 weeks in the Phase 3 trials.'*

'The dataset for analysis included all assessments on Total PANSS (except screening scores) and their time of observation, study number, study arm, treatment, dose, asenapine AUC, observed baseline PANSS, and the covariates weight, age, race, smoking status, ethanol intake, duration of present episode, patient studied in the United States or not and hospitalization status as well as information on dropout and reason for dropout. The placebo and asenapine treated patients were included in the exposure response analysis.' (See Table 174)

Table 174 Covariates Examined by the Sponsor in Exposure Response Modeling - Report INT00039918

Covariate	Abbreviation	Reason for Investigation
Age	AGE	Disease symptoms as well as placebo response could be different for different age classes, gender or race
Gender	SEX	
Race	RACE	
Smoking status	SMOK	Behavioral aspects may correlate with placebo response
Alcohol use	ETH	
Weight	WGT	
Duration of present episode	DDUR	More acute patients (shorter episode duration) could show a different placebo response
Inpatient/outpatient	HOSP	Hospitalized patients could show a different placebo response
US/non-US	US	US sites might have recruited different types of patients (not covered by above covariates)

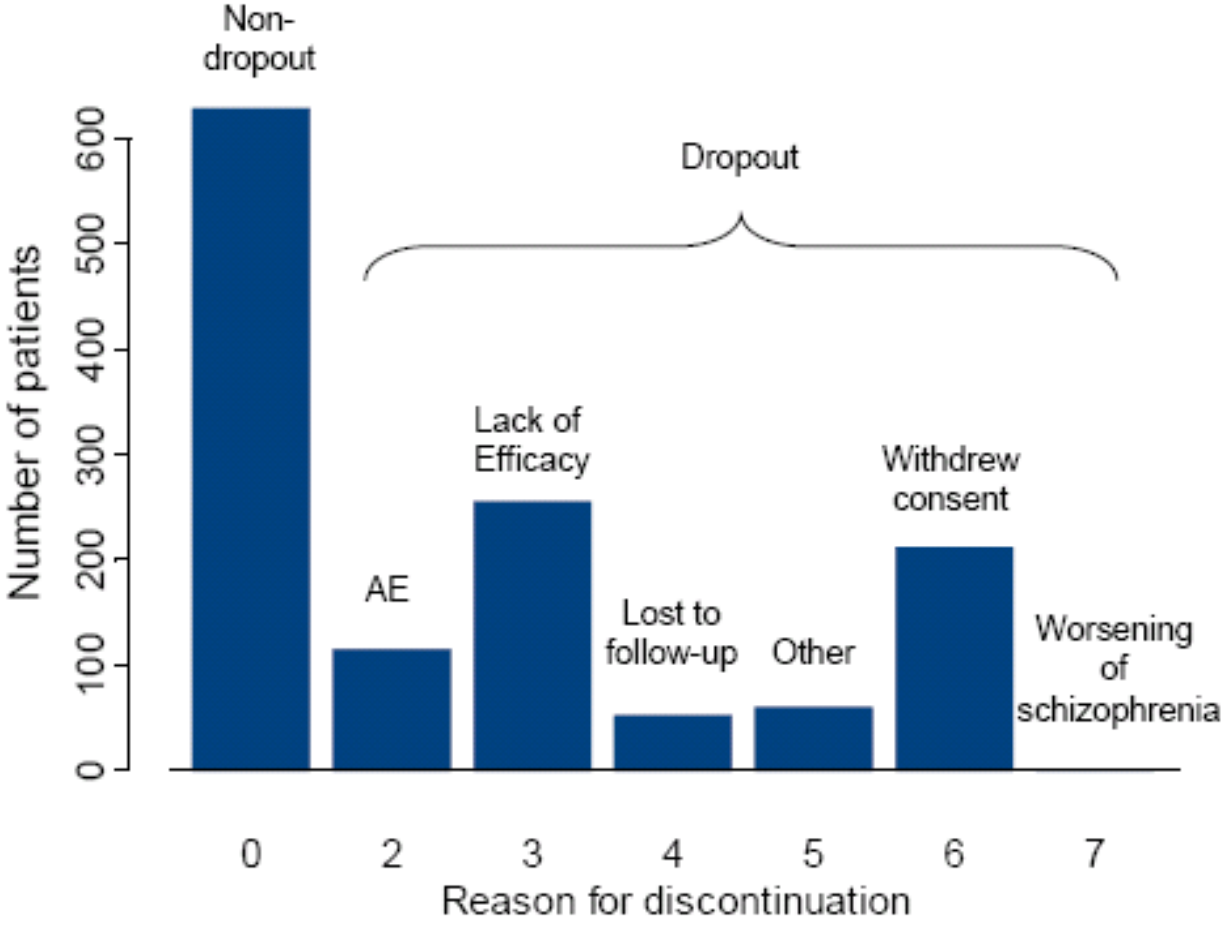
'A population pharmacokinetic-pharmacodynamic of Total PANSS time course was developed in NONMEM VI using AUC as a measure of asenapine exposure. In a first step a placebo model was

developed from the placebo data. In the next step the asenapine data were included and a drug effect model was added to describe the exposure response of asenapine. Covariate relationships were investigated for the covariates mentioned above. A logistic regression model to describe drop-out patterns was developed separately from the PANSS model. Simulations were performed from the combined model of Total PANSS and the model describing the time-course of dropout. The simulated LOCF responses were compared with observed trial results, and retrospective success rates for each of the asenapine treatment arms in comparison to placebo were calculated.'

Drop Out Model

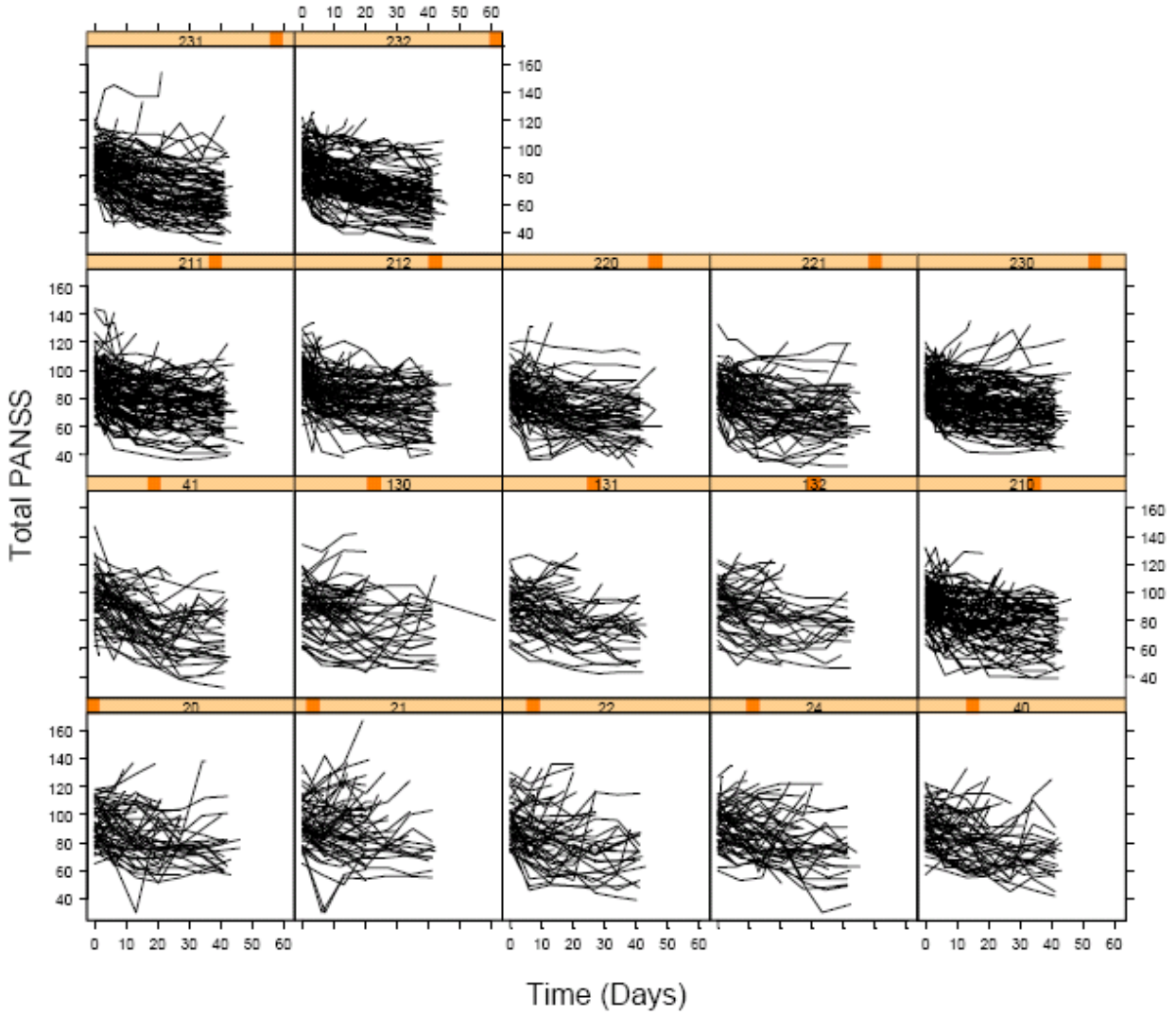
Figure 175 shows the categorization of reasons for drop-outs used by the sponsor. The large proportion of drop-outs categorized as lost to follow-up, other, and especially withdrew consent is troubling. In addition, that only one subject was assigned to worsening of schizophrenia is not believable as this appears to be inconsistent with spaghetti plots of response vs. time, (see Figure 176).

Figure 175 Reasons for Dropout and their Distribution - Report INT00039918



Other possibilities that need to be considered is whether subjects on drug may be more likely to remain in the study in spite of a lack of efficacy due to subconscious bias, or placebo subjects being more likely to remain on treatment if adverse effects are evident, as well as other possibilities. The only way to control for this may be to have a separate blinded individuals assess efficacy and tolerability and have no other communication with the subjects or each other so they can't influence drop out rate. Then have a third individual assessing the reason why a subject wants to drop out.

Figure 176 Spaghetti Plots of Individual Subject Total PANSS Scores vs. Treatment Duration by Study Treatment Arm[a]



a Numbers in shingles indicate treatment arms which are defined in Table 175.

Table 175 Sponsor's Treatment Arm Codes for Asenapine Exposure Response Analysis – Report INT00039918

Variable	Variable Label	Description including Categories and Units
STUDY Number	Study Number	ORG041002 = 2 ORG041004 = 14 ORG041013 = 13 ORG041021 = 21 ORG041022 = 22 ORG041023 = 23
STUDY ARM	**Study** Study Arm Number	**ORG041002** 20 : placebo 21 : 0.2 mg asenapine 22 : 0.4 mg asenapine 23 : 0.6 mg asenapine 24 : 0.8 mg asenapine 29 : risperidone 3 mg **ORG041004** 40 : placebo 41 : 5 mg asenapine 49 : risperidone 3 mg **ORG041013** 130 : placebo 131 : 1.6 mg asenapine 132 : 2.4 mg asenapine **ORG041021** 210 : placebo 211 : 5 mg asenapine 212 : 10 mg asenapine 219 : Olanzapine 15 mg **ORG041022** 220 : placebo 221 : 5-10 mg flex dose asenapine 229 : Olanzapine 10-20 mg **ORG041023** 230 : placebo 231 : 5 mg asenapine 232 : 10 mg asenapine 239 : haloperidol 4 mg
Treatment	Treatment Number	0=Placebo 1=Asenapine 2=Risperidone 3=Olanzapine

Figure 177 shows PANSS Score vs. Duration of Treatment divided into drop-out and non-drop groups for both asenapine and placebo. While the curves are similar for the subjects on placebo and asenapine who didn't drop out, which is noted elsewhere in this review by the super-imposition of the placebo and treatment groups, the dropout are different by treatment. The problem as noted in the discussion to Figure 175 is that the reason for dropping out especially by treatment and duration on treatment is poorly explained and therefore modeling dropouts while possible may not be especially accurate in the present ER analysis. This is demonstrated by the differing naïve drop-out models for placebo for the phase II and phase III trials as shown in Figure 178

Figure 177 PANSS Time Course by Treatment in Individuals who Dropped Out and Remained on Treatment – Report INT00039918

Figure 3. PANSS Time course in patients who dropped out and who did not drop out

Observed PANSS (o) and smooth through the observed data (—).

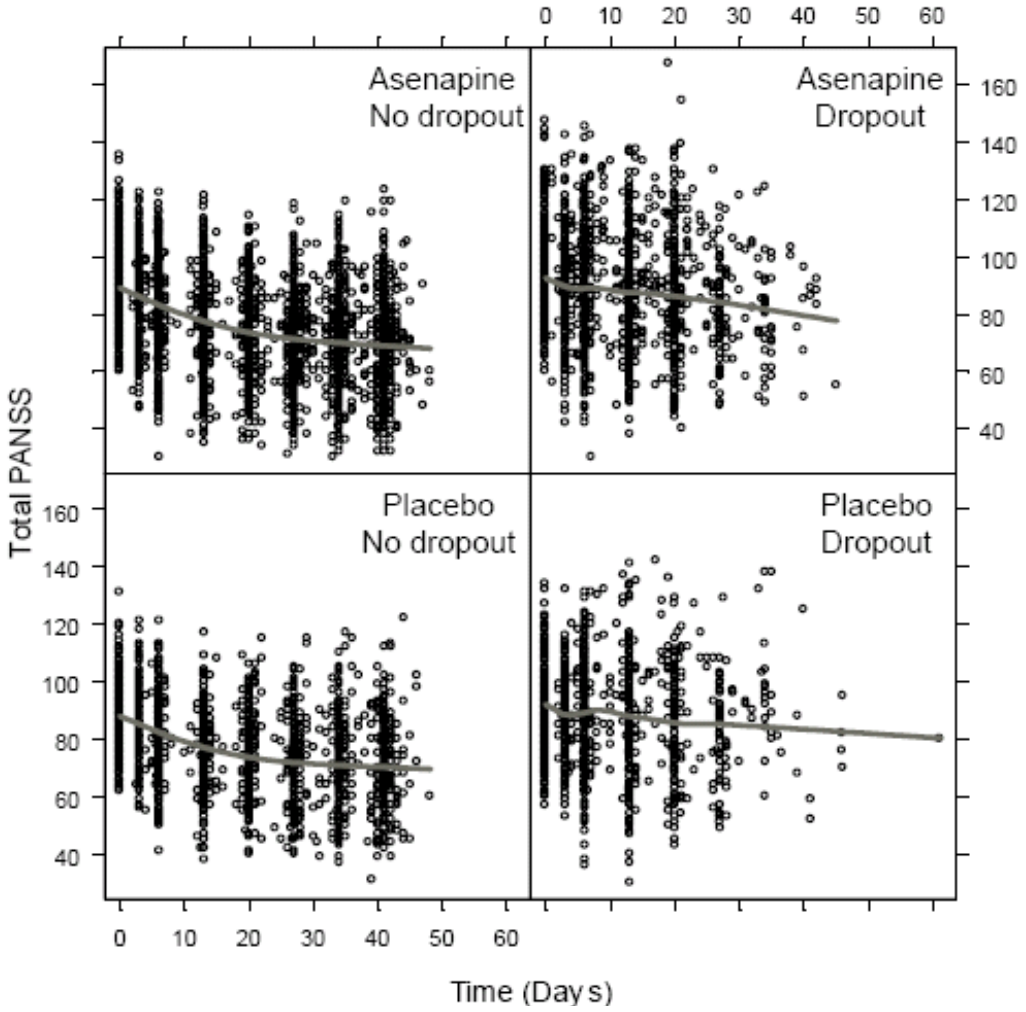
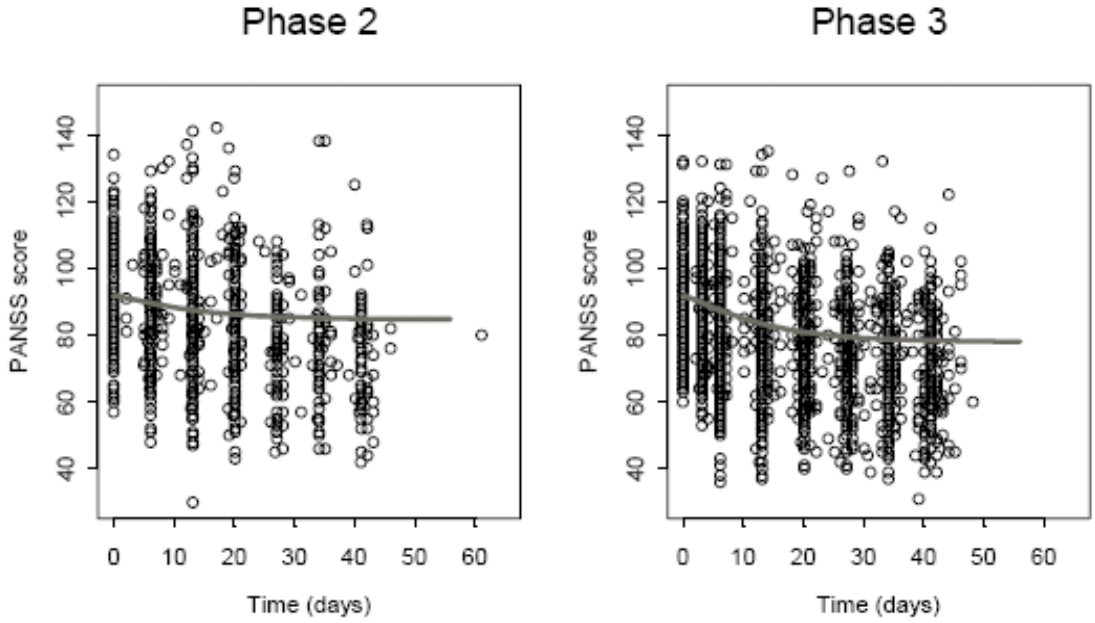


Figure 178 Typical PANSS Time Course as Predicted by the Final Placebo Model – Report INT00039918

Figure 4. Typical PANSS time course as predicted by the final placebo model.

Included are all observations (o) and model predictions for a typical individual without consideration of dropout (—).



Exposure Response Relationship for Asenapine

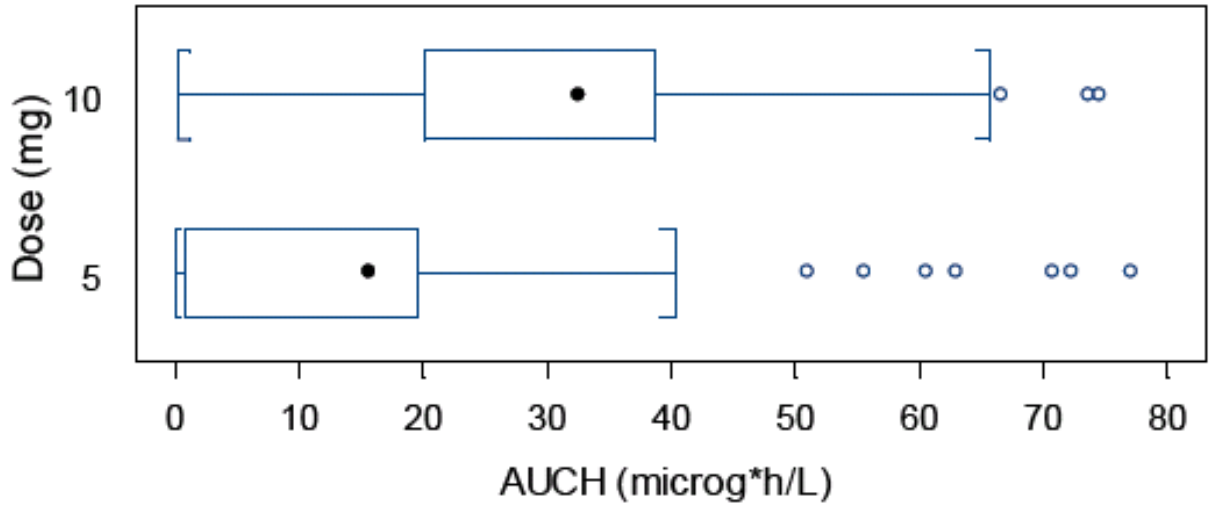
Exposure was assessed by AUCs assessed by sparse sampling and population pharmacokinetic modeling. The sponsor assessed various ways to model AUC, including the following:

- AUCH Individual AUC
- AUCI Individual AUCs differing for in- and outpatient periods due to differences in bioavailability
- IAUC Imputed AUCH after dropout
- AUCP Predicted Individual AUC

According to the sponsor AUCH was superior to dose as a measure of exposure (ΔOFV= -13.7) although there was not improvement in OFV <objective function value> when comparing the different exposure measurements of AUC, AUCI, AUCP, and AUCH. AUC was used in the initial modeling, however AUCH was later on in the modeling process chosen as it is less sensitive to differences due to deviations from the dosing protocol at the day of concentration determination but can account for the lower exposure in the outpatient period which was observed in some patients.

Figure 179 shows the sponsor's plots of the distribution of individual AUCs by dose for each asenapine dose used in the Phase IIb and III trials.

Figure 179 Asenapine AUC Distribution by Dose for 5 and 10 mg Doses in Phase IIb/III Efficacy Studies – Report INT00039918[a]



a Panel descr bes the observed individual AUC (AUCH) distribution in the phase IIb/III trials for 5 and 10 mg asenapine. AUCH values within the first and third quartiles are included in the boxes and dots indicate the medians. The whiskers represent 1.5 times the inter-quartile range or the range of the data, whichever is less. Circles are observations outside 1.5 times the inter-quartile range. In addition 3 AUCH values (range 104-1891 µg·h/L) were omitted from the plot.

Figure 180 shows the typical mean predicted decrease in PANSS score from baseline (solid lines) from Baseline and 90% PIs (dotted lines) vs, AUC grouped by study phase. The large discrepancy between the predictions for the two phases that includes the lack of overlap indicate that there are unknown cofactors influencing the relationship.

Figure 180 Predicted Mean Decrease from Baseline in PANSS at Day 42 and 90% vs. AUC by Study Phase IIb or III – Report INT00039918

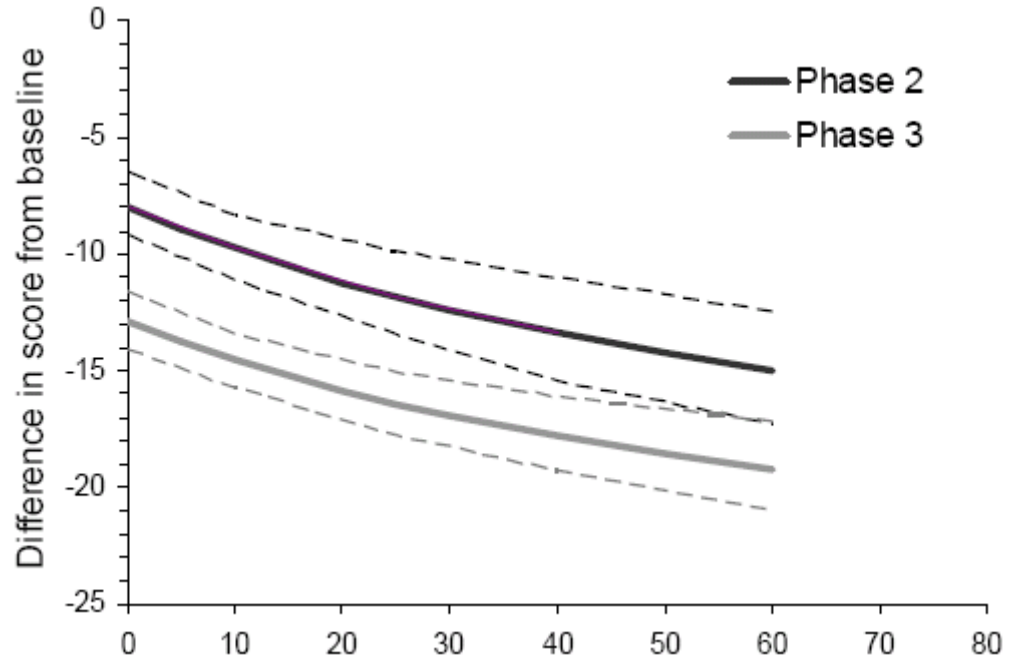
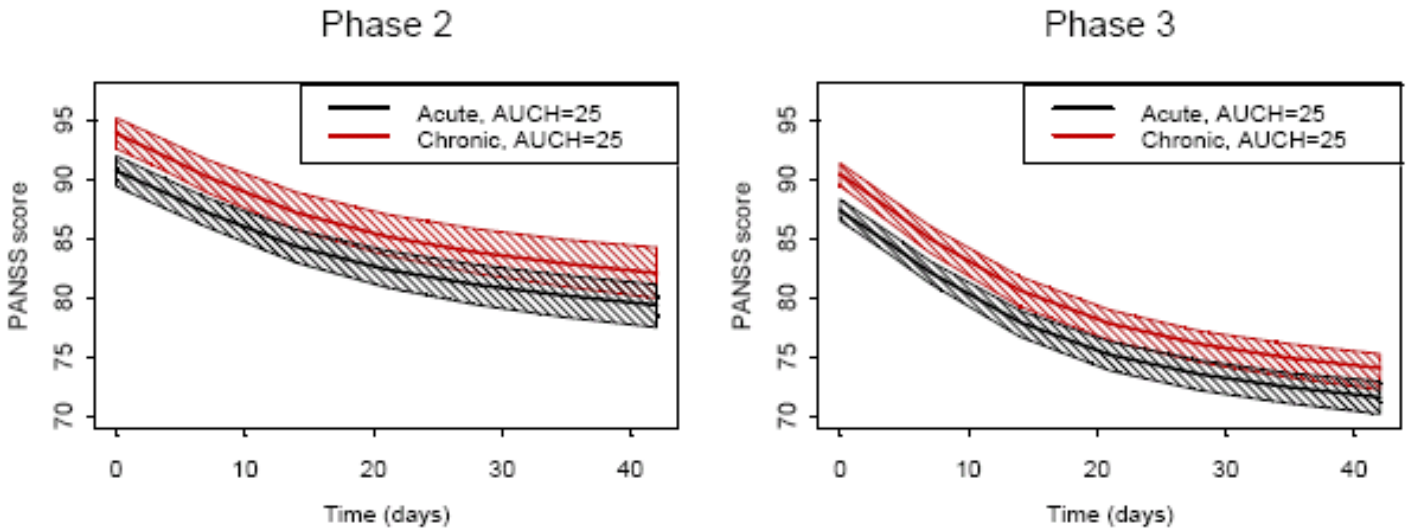


Figure 181 shows that when controlled for AUC this difference in response by study phase is partly due to the difference in baseline PANSS score as well as the duration of the current episode, however it's also clear that this cannot totally explain the difference as the 'chronic' subjects in the phase III studies had a greater response than the 'acute' subjects in the phase II studies in spite of similar baseline scores. This is opposite what is expected based on the sponsor's argument.

Figure 181 Fit of Individual AUCs versus Time with 90% CIs Asenapine Dose and Development Phase for Schizophrenic Patients with Current Acute Episodes of Less than 1 month Duration ('Acute') and Greater than 1 month Duration ('Chronic') – Report INT00039918



A N.B. Graphs only show the influence of duration of the psychotic episode patients for Phase 2 and Phase 3 for a mean AUC of 25 µg·h/L (5 mg) but not 40 25 µg·h/L (10 mg).

Figure 182 shows the sponsor's final predictions that appear to show a dose response relationship however, close examination of the plots indicate that the true values plateau and there is no increased response to a 10 mg dose over a 5 mg dose.

Figure 182 Observed and Simulated PANSS LOCF Time Course – Report INT00039918

Figure 9. Observed and from the final model simulated PANSS LOCF time course

Mean observed (---) and mean (90% PI) simulated (—) overall PANSS LOCF are visualized.

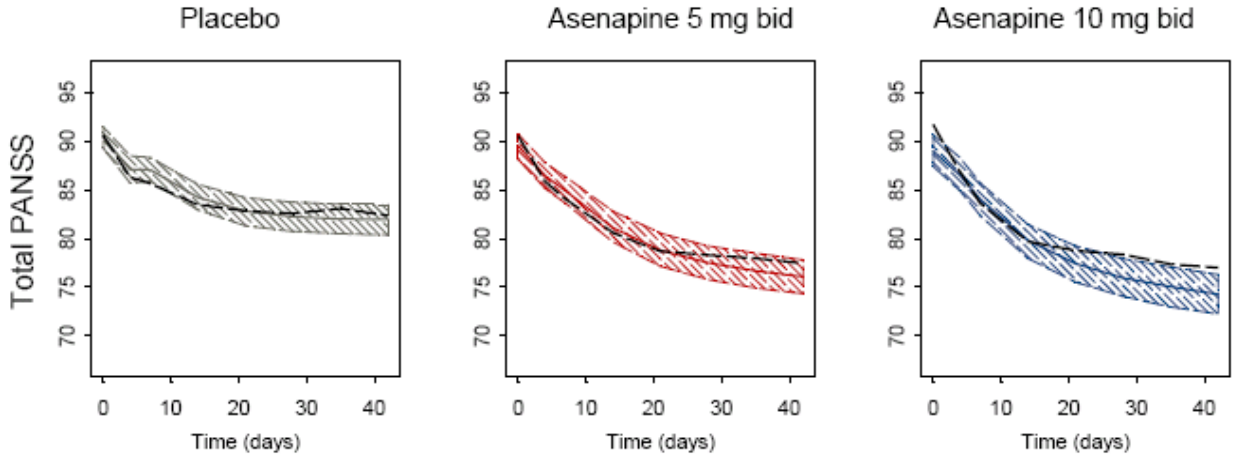
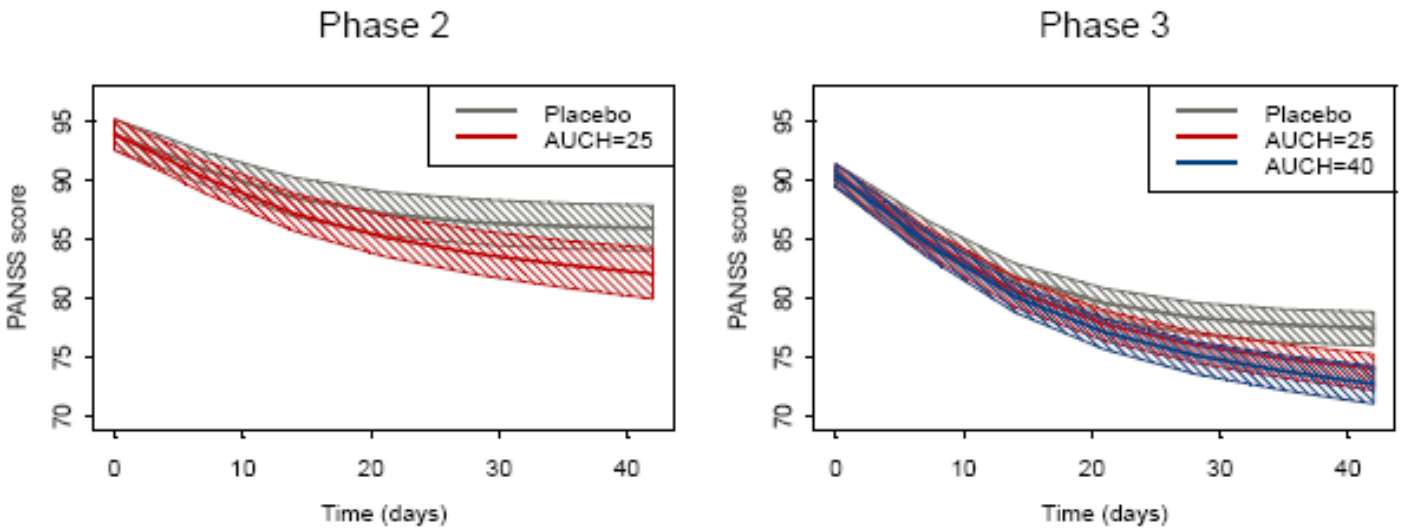


Figure 183 shows what the sponsor based this on. The sponsor assigned a typical AUC of 25 mcg/ml x hr^{-1} to a dose of 5 mg and 40 mcg/ml x hr^{-1} to a dose of 10 mg. Yet Figure 179 indicates that this is inappropriate as the true mean AUCs are respectively around 10 and 30 mcg/ml x hr^{-1}. This figure also indicates that even with a dose of 10 mg fewer than 25% of subjects with have an AUC of 40 mcg/ml x hr^{-1}.

Figure 183 Fit of Individual AUCs versus Time with 90% CIs by Asenapine Dose and Development Phase – Report INT00039918[a]



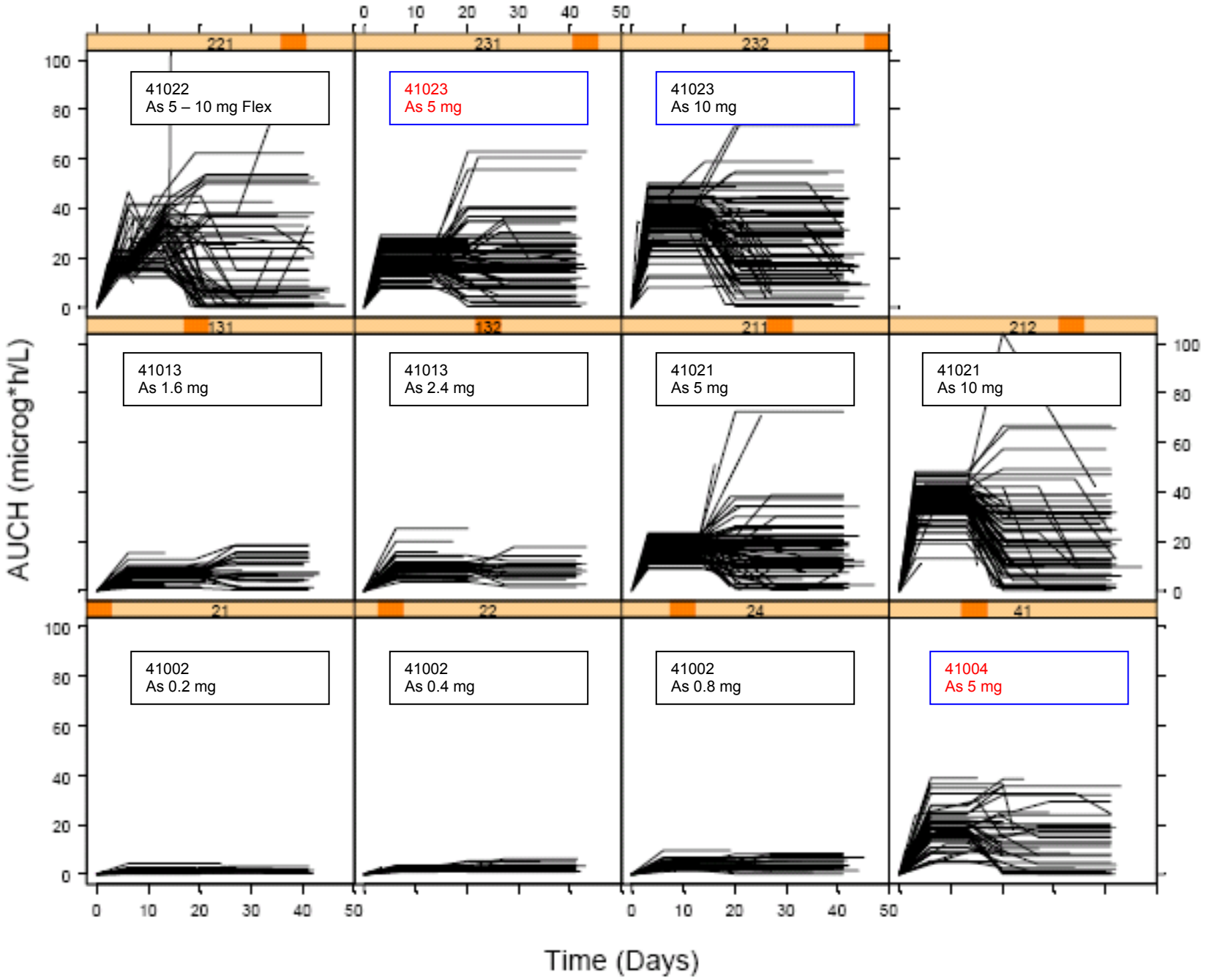
a Sponsor claims that graphs show the predicted mean and 90% CI for PANSS Score vs. time for placebo and for the typical individual AUC (AUCH) following 5 mg (AUCH=25 µg·h/L) and 10 mg (AUCH=40 µg·h/L).

In addition, the exposure response relationship shown in Figure 182 averages both the phase II and phase III studies when examining the effect if an AUCH of 25 mcg/ml x hr^{-1} on PANSS. Plus the correction for baseline severity is not clearly indicated. Even though the sponsor states: *'Thus the PANSS model predicts that a patient with a high baseline score will typically have a larger absolute decrease in PANSS from placebo than a patient with a low baseline score as the placebo response was slightly less than proportional to the baseline value. The placebo response was estimated to reach a plateau around 30 days after start of the study, while the maximum asenapine effect did not occur before the end of the study (Day 42). The model characterized the considerable difference in placebo effect between Phase 2 and Phase 3 well and all placebo arms were well predicted by the model (Figure X). The asenapine response was dependent on the underlying PANSS score so that patients with a high estimated baseline and a low estimated placebo response had typically a higher estimated absolute reduction in score than those with a low estimated baseline and high estimated placebo response. As the placebo response and asenapine effect response were predicted to have different time-courses subjects treated with asenapine can also contribute.'*

Lastly Figure 184 shows spaghetti plots of individual AUCs over time for each asenapine treatment arm in the phase IIb and phase III acute efficacy studies. This also shows that compliance is a major issue once subjects are discharged from the hospital. However the positive response in the phase II study vs. the phase III studies at 5 mg indicate that the baseline score and not the duration of treatment prior to discharge is a better predictor of response. In addition, the lower concentrations in addition to noncompliance may indicate change in diet and the elevated concentrations might indicate taking a additional doses immediately prior to a visit in contrast to being noncompliant the rest of the time.

In conclusion this analysis indicates that in spite of modeling in the 'real world' this drug may not be a useful addition to the antipsychotic armamentarium, although this could be shown to be untrue with additional studies.

Figure 184 Individual AUC (AUCH) versus Time by Asenapine Efficacy Study Treatment Arms[a,b]



a Numbers in shingles indicate treatment arms which are defined in Table 175.
b Blue boxes indicate studies with positive results for asenapine. Red text indicate treatment arms that were statistically significant different from placebo

5.6.2.1.1.2 Evaluation of Drop-Out Patterns

The sponsor evaluated modeling of drop-outs in two different sections of the NDA that were located under the following two pathways:

5. Clinical Study Reports
5.3.5 Reports of Efficacy and Safety Studies [Schizophrenia]
5.3.5.3 Reports of Analyses of Data from More than One Study
[INT00039918 – Exposure response of total PANSS based on Phase 2 and Phase 3 trials for Asenapine]
5.3.5.3.1 Legacy Study Report [INT00039918]
MODELING & SIMULATION ANALYSIS REPORT
Exposure response analysis of total PANSS based on Phase 2 and Phase 3 6-week trials for asenapine
May 2007

5. Clinical Study Reports
5.3.5 Reports of Efficacy and Safety Studies [Bipolar Disorder]
5.3.5.3 Reports of Analyses of Data fro More than One Study
[INT00039918 – Exposure response of total PANSS based on Phase 2 and Phase 3 trials for Asenapine]
5.3.5.3.1 Legacy Study Report [INT00043090]
Position Paper for Asenapine:
LOCF vs. MMRM in the Efficacy Analyses for Asenapine Trials
May, 2007

In section 2.5 of the NDA, in the clinical overview document under subsection 2.5.4., 'Overview of Efficacy' the sponsor reports the following *'During the February 22, 2007 Pre-NDA meeting, the sponsor was encouraged to further investigate the possibility of using a mixed model for repeated measures (MMRM) analysis as a primary method of analysis.'*

As reported in NDA 22-117 Amendment # 002 submitted Octocber 24th, 2007 in a response to an FDA request to provide the regulatory history the information in Table 176 was provided regarding this pre-NDA meeting.

Table 176 Regulatory History Regarding Pre-NDA Meeting Submitted in Amendment 002

Topic / Issue	Correspondence			Regulatory History
	Date	SN	Description	
Pre-NDA Meeting – February 22, 2007*	12/21/06	294	Letter to FDA	Type B (Pre-NDA) Meeting Request
	01/22/07	300	Letter to FDA	Type B (Pre-NDA) Meeting Information Package
	02/20/07		E-mail from FDA	Agency's preliminary responses to Pre-NDA Meeting Questions
	02/28/07	307	Letter to FDA	Sponsor's Minutes – Type B (Pre-NDA) Meeting
	03/06/07		Letter from FDA	Agency's Minutes – Type B (Pre-NDA) Meeting
	03/13/07	310	Letter to FDA	Organon provides comments on Agency's Minutes – Type B (Pre-NDA) Meeting
	03/21/07		E-mail from FDA	Agency states that Sponsor comments will be on permanent record as additions to the meeting minutes, correspondence related to the meeting minutes

* the serial numbers listed refer to those associated with IND No. 51,641. Certain information submitted to IND No. 51,641 may also have been applicable to IND No.70,329; this information was incorporated into IND No. 70,329 by cross-reference and has been denoted with an asterisk (*)

On March 26, 2008 upon attempting to check the FDA records regarding this meeting in DFS, no records or any type were returned upon a search of either IND 51.641 or IND 70,329.

As indicated in this review in §5.6.2.1.1 Acute Treatment of Psychosis the sponsor proposed using mixed models of repeated measures, (MMRM), and a critique of the sponsor's evaluation may be found there. Prior to reviewing this document this review had already performed an exploratory data analysis of drop-out patterns in the two pivotal acute schizophrenia trials, 41004 and 41023, and those analyses are presented here.

Figure 185 and Figure 186 show Kaplan-Meir survival curves of drop-outs over time by treatment for the two pivotal acute efficacy studies, 41004 and 41023. Ninty percent confidence intervals although not shown were approximately ± 0.1, and the curves are statistically indistinguishable.

Figure 185 shows a higher rate for dropouts in the Risperidone arm during the first week of treatment followed by greater dropouts in the placebo and asenapine arms until day 21 (1 week after discharge allowed) followed by greater dropouts in the placebo group compared to both active treatments.

Figure 186 shows similar dropouts in all groups in the first week followed by more dropouts in the haloperidol and asenapine 5 mg arms, which was eventually matched after 4 weeks by the dropout rate for placebo patients, with the dropout rate in the 10 mg arm being the lowest from week 1 onwards.

Subjects in this study had lower baseline PANSS scores and greater response than in study 41004. The increase in dropout rate for placebo in both studies after 3 and 4 weeks of therapy respectively during the outpatient phase might be due to unintentional bias from observers who might encourage subjects experiencing adverse effects to remain on drug. In addition the time to drop out may also have been influence both by initial severity and duration of inpatient treatment. However, more detailed analysis is needed than can be accomplished during the present review cycle.

Figure 185 Kaplan-Meir Plot of Dropout Rate over Time by Treatment Group - Study 41004

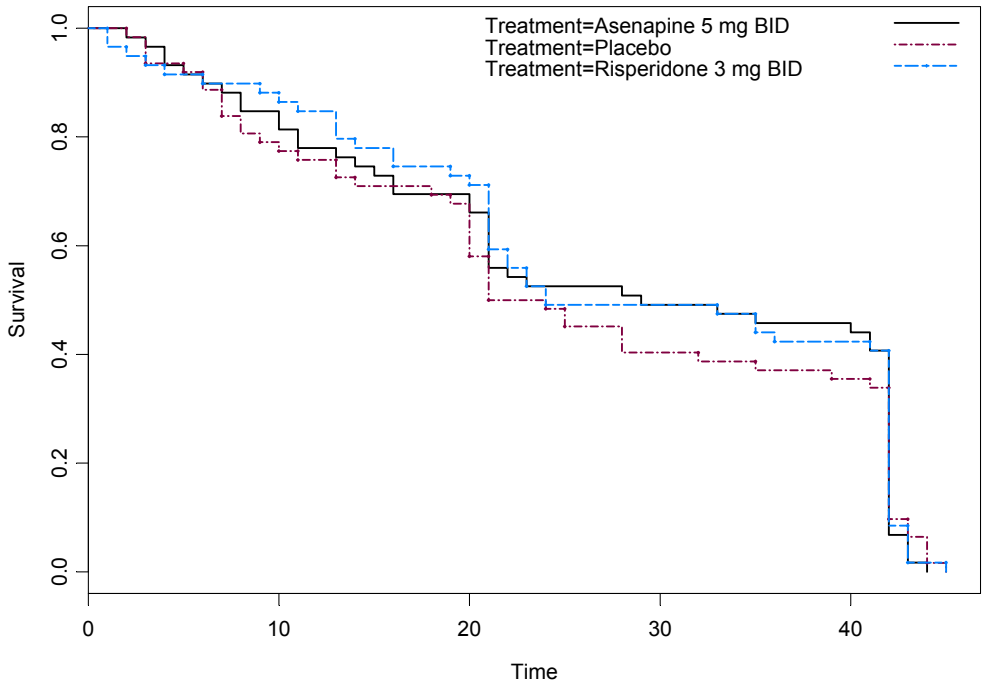


Figure 186 Kaplan-Meir Plot of Dropout Rate over Time by Treatment Group - Study 41023

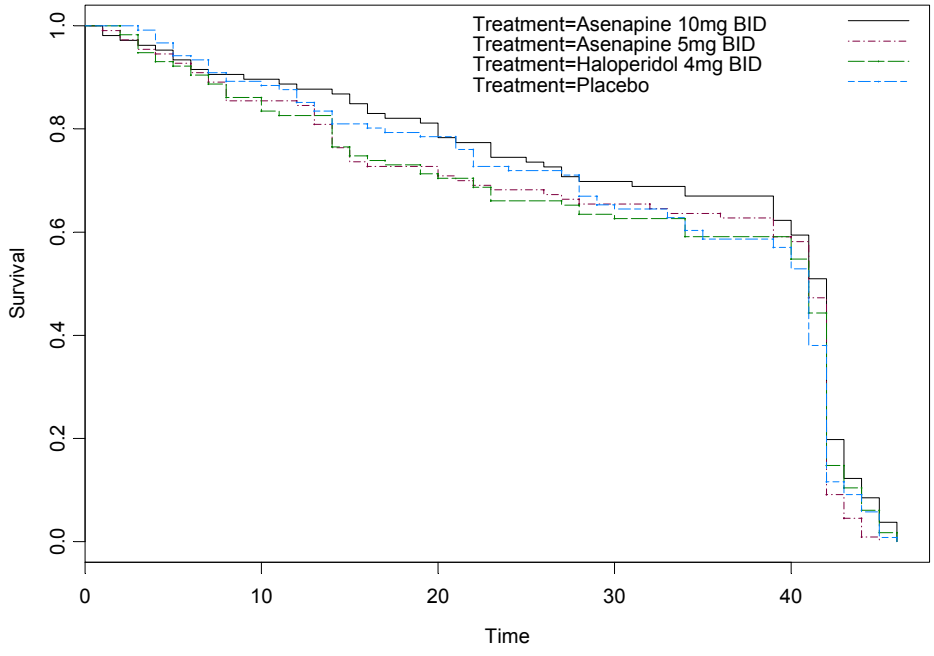


Figure 187 is an exploratory plot of dropout rates by intial disease severity in study 41004. It appears that for most subjects there is little difference in dropouts by treatment, whereas in the most severely ill patients after the first week of treatment drop outs increase for the placebo group and remain higher for the rest of the trial. There are two possible answers for this, a) there is poorer historicity and therefore greater dropouts in the placebo are for the most severely ill patients, b) the difference in drop outs is primarily due to an unconscious bias in the investigators on dropouts during the inpatient phase followed by little difference in the slope of the dropout rate thereafter.

Figure 187 - Dropout Rate (Precent) by Study Visit (week) by Initial Severity and Treatment - Study 41004

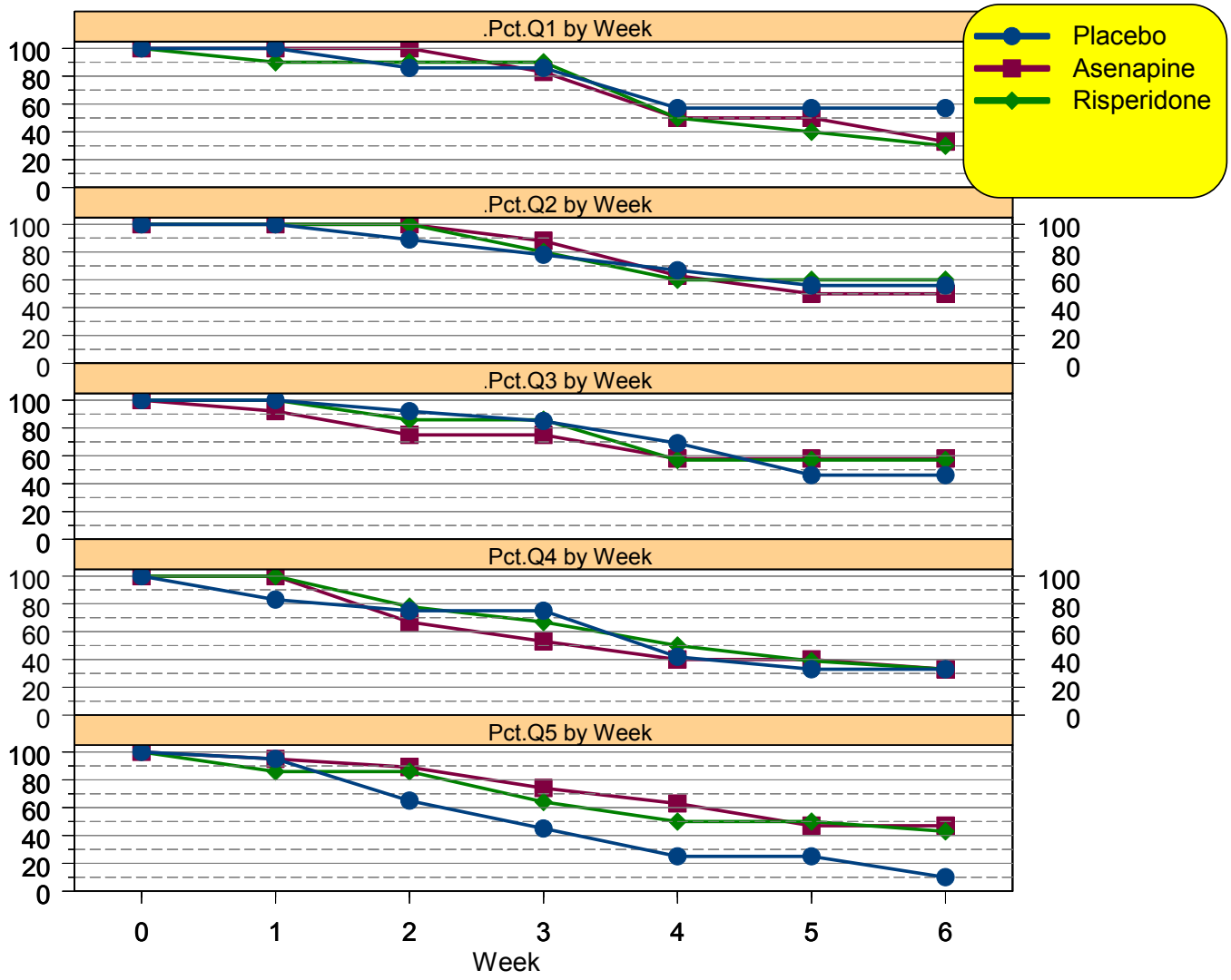


Table 177 and Table 178 show numerical calculations of drop out rates and odds ratios by treatment and initial disease severity for studies 41004 and 41023 respectively. Examination of Table 177 reveals an apparent pattern that in the phase II study 41004 with the more severely ill patients, the least severely ill were less likely to remain on drug compared to placebo but only toward the end of the study, whereas the most severely ill were much more likely to stay on drug.

Table 177 Numerical Calculations of Drop out Rates and Odds Ratio by Treatment and Initial Disease Severity – Study 41004

Treatment	Duration of Rx	Number of Subjects on Treatment						% Remaining on Treatment						Odds Ratio of Remaining on Active Drug Treatment Compared to Placebo					
		Q1	Q2	Q3	Q4	Q5	Total	Q1	Q2	Q3	Q4	Q5	Total	Q1	Q2	Q3	Q4	Q5	Total
Placebo	Baseline	7	9	13	12	20	61	100	100	100	100	100	100	–	–	–	–	–	–
	Screen	7	9	13	12	20	61	100	100	100	100	100	100	–	–	–	–	–	–
	Visit 1	7	9	13	10	19	58	100	100	100	83	95	95	–	–	–	–	–	–
	Visit 2	6	8	12	9	13	48	86	89	92	75	65	79	–	–	–	–	–	–
	Visit 3	6	7	11	9	9	42	86	78	85	75	45	69						
	Visit 4	4	6	9	5	5	29	57	67	69	42	25	48	–	–	–	–	–	–
	Visit 5	4	5	6	4	5	24	57	56	46	33	25	39	–	–	–	–	–	–
	Visit 6	4	5	6	4	2	21	57	56	46	33	10	34	–	–	–	–	–	–
Asenapine	Baseline	6	8	12	15	19	60	100	100	100	100	100	100	1.0	1.0	1.0	1.0	1.0	1.0
	Screen	6	8	12	15	19	60	100	100	100	100	100	100	1.0	1.0	1.0	1.0	1.0	1.0
	Visit 1	6	8	11	15	18	58	100	100	92	100	95	97	1.0	1.0	0.92	1.20	1.0	1.02
	Visit 2	6	8	9	10	17	50	100	100	75	67	89	83	1.17	1.13	0.81	0.89	1.38	1.06
	Visit 3	5	7	9	8	14	43	83	88	75	53	74	72	0.97	1.13	0.89	0.71	1.64	1.04
	Visit 4	3	5	7	6	12	33	50	63	58	40	63	55	0.88	0.94	0.84	0.96	2.53	1.16
	Visit 5	3	4	7	6	9	29	50	50	58	40	47	48	0.88	0.90	1.26	1.20	1.89	1.23
	Visit 6	2	4	7	5	9	27	33	50	58	33	47	45	0.58	0.90	1.26	1.00	4.74	1.31
Risperidone	Baseline	10	10	7	18	14	59	100	100	100	100	100	100	1.0	1.0	1.0	1.0	1.0	1.0
	Screen	10	10	7	18	14	59	100	100	100	100	100	100	1.0	1.0	1.0	1.0	1.0	1.0
	Visit 1	9	10	7	18	12	56	90	100	100	100	86	95	0.90	1.0	1.0	1.2	0.90	1.00
	Visit 2	9	10	6	14	12	51	90	100	86	78	86	86	1.05	1.13	0.93	1.04	1.32	1.10
	Visit 3	9	8	6	12	9	44	90	80	86	67	64	75	1.05	1.03	1.01	0.89	1.43	1.08
	Visit 4	5	6	4	9	7	31	50	60	57	50	50	53	0.88	0.90	0.83	1.20	2.00	1.11
	Visit 5	4	6	4	7	7	28	40	60	57	39	50	47	0.70	1.08	1.24	1.17	2.00	1.21
	Visit 6	3	6	4	6	6	25	30	60	57	33	43	42	0.53	1.08	1.24	1.00	4.29	1.23

In contrast, examination of Table 178 reveals an apparent pattern that in the phase III study 41023 with the less severely ill patients, the opposite pattern was seen with the highest asenapine dose with the least severely ill more likely to remain on drug compared to placebo.

Table 178 Numerical Calculations of Drop out Rates and Odds Ratio by Treatment and Initial Disease Severity – Study 41023

Treatment	Duration of Rx	Number of Subjects on Treatment						% Remaining on Treatment						Odds Ratio of Remaining on Active Drug Treatment Compared to Placebo					
		Q1	Q2	Q3	Q4	Q5	Total	Q1	Q2	Q3	Q4	Q5	Total	Q1	Q2	Q3	Q4	Q5	Total
Placebo	Baseline	24	25	25	25	21	120	100	100	100	100	100	100	—	—	—	—	—	—
	Visit 1	23	25	25	25	21	119	96	100	100	100	100	99	—	—	—	—	—	—
	Visit 2	18	23	23	23	18	105	75	92	92	92	86	88	—	—	—	—	—	—
	Visit 3	14	22	22	22	16	96	58	88	88	88	76	80						
	Visit 4	11	22	20	19	15	87	46	88	80	76	71	73	—	—	—	—	—	—
	Visit 5	11	20	19	14	14	78	46	80	76	56	67	65	—	—	—	—	—	—
	Visit 6	11	19	16	14	11	71	46	76	64	56	52	59	—	—	—	—	—	—
Asenapine 5 mg BID	Baseline	21	28	24	19	18	110	100	100	100	100	100	100	1.00	1.00	1.00	1.00	1.00	1.00
	Visit 1	21	26	21	19	18	105	100	93	88	100	100	95	1.04	0.93	0.88	1.00	1.00	0.96
	Visit 2	17	26	19	17	15	94	81	93	79	89	83	85	1.08	1.01	0.86	0.97	0.97	0.98
	Visit 3	11	26	16	17	10	80	52	93	67	89	56	73	0.90	1.06	0.76	1.02	0.73	0.91
	Visit 4	10	24	14	17	9	74	48	86	58	89	50	67	1.04	0.97	0.73	1.18	0.70	0.93
	Visit 5	10	23	14	17	8	72	48	82	58	89	44	65	1.04	1.03	0.77	1.60	0.67	1.01
	Visit 6	10	22	14	16	7	69	48	79	58	84	39	63	1.04	1.03	0.91	1.50	0.74	1.06
Asenapine 10 mg BID	Baseline	27	16	28	11	23	105	100	100	100	100	100	100	1.00	1.00	1.00	1.00	1.00	1.00
	Visit 1	27	16	27	10	22	102	100	100	96	91	96	97	1.04	1.00	0.96	0.91	0.96	0.98
	Visit 2	25	16	25	10	19	95	93	100	89	91	83	90	1.23	1.09	0.97	0.99	0.96	1.03
	Visit 3	23	15	22	9	18	87	85	94	79	82	78	83	1.46	1.07	0.89	0.93	1.03	1.04
	Visit 4	22	14	18	8	17	79	81	88	64	73	74	75	1.78	0.99	0.80	0.96	1.03	1.04
	Visit 5	21	11	18	8	15	73	78	69	64	73	65	70	1.70	0.86	0.85	1.30	0.98	1.07
	Visit 6	21	11	18	8	13	71	78	69	64	73	57	68	1.70	0.90	1.00	1.30	1.08	1.14
Haloperidol 4 mg BID	Baseline	29	21	17	22	26	115	100	100	100	100	100	100	1.00	1.00	1.00	1.00	1.00	1.00
	Visit 1	28	17	17	21	26	109	97	81	100	95	100	95	1.01	0.81	1.00	0.95	1.00	0.96
	Visit 2	24	15	16	19	22	96	83	71	94	86	85	83	1.10	0.78	1.02	0.94	0.99	0.95
	Visit 3	20	14	13	17	20	84	69	67	76	77	77	73	1.18	0.76	0.87	0.88	1.01	0.91
	Visit 4	19	13	11	17	16	76	66	62	65	77	62	66	1.43	0.70	0.81	1.02	0.86	0.91
	Visit 5	18	12	11	17	14	72	62	57	65	77	54	63	1.35	0.71	0.85	1.38	0.81	0.96
	Visit 6	17	11	11	15	14	68	59	52	65	68	54	59	1.28	0.69	1.01	1.22	1.03	1.00

5.6.2.2 Bipolar Disorder

5.6.2.2.1 Acute Efficacy

5.6.2.2.1.1 Sponsor's Exposure Response Modeling of Effect of Asenapine on Young Mania Rating Scale (YMRS)

The sponsor developed an exposure response model relating asenapine exposure to YRMS score for bipolar disorder, by combining the data from both acute treatment studies A7501004 and A7501005. This model was development and results were reported in report INT00039919.

The sponsor used the population two compartment PK model with an absorption lag phase and nonlinear bioavailability previously developed using phase 1/2 pharmacokinetic data, (see §5.5.8.1 for PK model development and critique).

A number of empiric (non mechanism based) pharmacodynamic models were fit to the data. Due to the low number of subjects receiving a dose of 5 mg, a dose reponse model was not examined. However the pharmacokinetic data was incorporated into an exposure response model with all other data.

Table 179 shows the study designs of the two acute mania studies used for the exposure reponse modeling.

Table 179 Acute Mania Study Designs Used for Exposure Response Modeling – Report INT00039919

Study	Phase	Design	Inclusion Criteria	Dose/Regimen[a]	Asenapine (PK) Assessment Schedule	YMRS (PD) Assessment Schedule
A7501004	3	Randomized, DB, PBO and Active Controlled Parallel Design in subjects with Acute Manic Attack	YMRS ≥20 at Baseline	Placebo Aasenapine 10 mg SL BID × 1 day then 5 or 10 mg SL BID for 3 weeks	**Days 1, 14, and 21:** Predose **Day 7:** Predose and 1-3, 4-6, and 8-12 hours postdose	Screening and Days 1,2,4,7,14, and 21 / Study Endpoint
A7501005	3	Randomized, DB, PBO and Active Controlled Parallel Design in subjects with Acute Manic Attack	YMRS ≥20 at Baseline	Placebo Asenapine 10 mg SL BID × 1 day, then 5 or10 mg SL BID for 3 weeks	**Days 1, 14, and 21:** Predose **Day 7:** Predose and 1-3, 4-6, and 8-12 hours postdose	Screening and Days 1,2,4,7,14, and 21 / Study Endpoint

a excluding active control olanzapine

Table 180 shows the summary of subject demographics in the two acute mania studies. It's especially noteworthy that over 1/3 of subjects are nonsmokers and thus may have higher exposures than seen with similar doses in the schizophrenia studies.

Table 180 Demographic Summary by Acute Mania Study Patient – Report INT00039919

Patient Attribute	Study		Total (%)
	A7501004	A7501005	
	N (%)	N (%)	
Race			
Caucasian	155 (56.0)	177 (60.4)	332 (58.3)
Black	52 (18.8)	49 (16.7)	101 (17.7)
Hispanic	8 (2.9)	6 (2.1)	14 (2.5)
Asian	62 (22.4)	54 (18.4)	116 (20.4)
Other	0 (0)	7 (2.4)	7 (1.2)
Sex			
Female	138 (49.8)	130 (44.4)	268 (47.0)
Male	139 (50.2)	163 (55.6)	302 (53.0)
Smoking Status			
None	117 (42.2)	99 (33.8)	216 (37.9)
<1 pack/day	97 (35.0)	132 (45.1)	229 (40.2)
1-2 packs/day	60 (21.7)	59 (20.1)	119 (20.9)
>2 packs/day	3 (1.1)	3 (1.0)	6 (1.1)
Hormonal Statusa			
Pre-menopausal	93 (33.7)	96 (32.8)	189 (33.2)
Post-menopausal	44 (15.9)	34 (11.6)	78 (13.7)
Male	139 (50.4)	163 (55.6)	302 (53.1)
Ethanol Consumption (Past 1 Month)			
None	0 (0)	0 (0)	0 (0)
<1 drink/week	234 (84.5)	246 (84.0)	480 (84.2)
1-6 drinks/week	37 (13.4)	36 (12.3)	73 (12.8)
7-12 drinks/week	5 (1.8)	7 (2.4)	12 (2.1)
13-18 drinks/week	1 (0.4)	3 (1.0)	4 (0.7)
19-24 drinks/week	0 (0)	0 (0)	0 (0)
25-35 drinks/week	0 (0)	0 (0)	0 (0)
36+ drinks/week	0 (0)	1 (0.3)	1 (0.2)

N = number
a1 missing value

The final structural model as defined by the sponsor is shown below:

$$Y = \exp\left[\left(base + \eta_{base}\right) + \left(slp + \eta_{base}\right)t^{\gamma} - \left(dslp + \eta_{dslp}\right) \bullet C_e(t)\right] + \varepsilon$$

Figure 188 and Figure 189 show model fits overlaid on observed data for asenapine and placebo respectively.

It's clear even with the modeling there's minimal difference between drug and placebo indicating a statistical difference but possibly not a clinical difference.

Figure 188 Observed YMRS Measurements and the Average IPRED and Population Mean Response for Asenapine (Mean for the Final Model (OM1-DM1+keo)§ – Report INT00039919

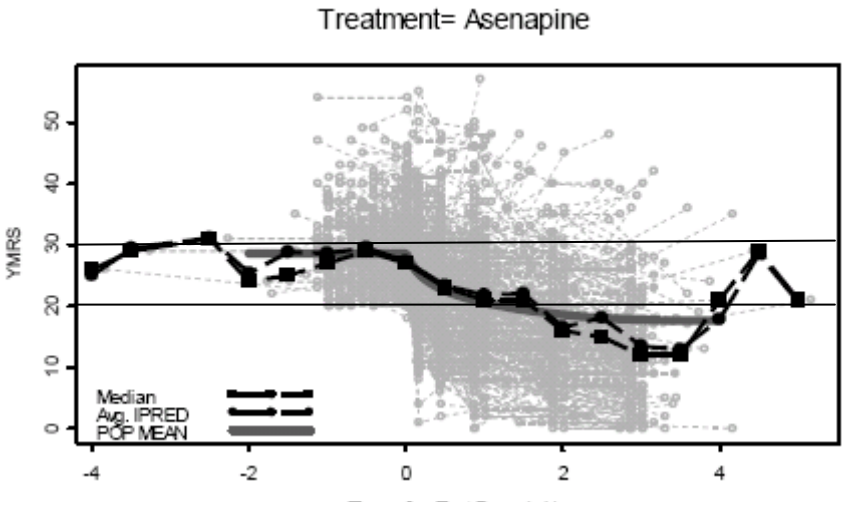


Figure 189 Observed YMRS Measurements and the Average IPRED and Population Mean Response for Placebo – Report INT00039919

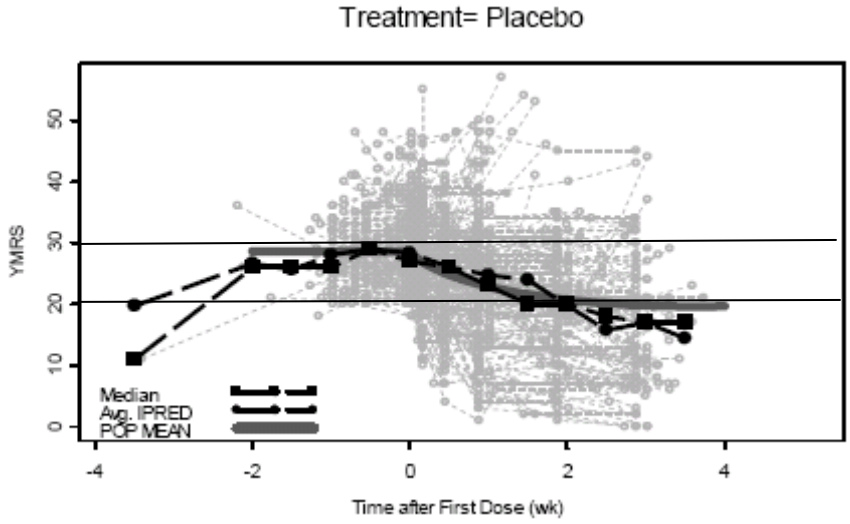


Table 181 of the Sponsor's analysis confirms that the differences although statistically significant may have minimal clinical significance.

Table 181 Medians of the Typical Individual Model Predictions of the YMRS Response, Median Differences in the Typical Individual YMRS Response (ΔYMRS), and 90% Confidence Intervals

	Week	Placebo		5 mg BID		10 mg BID	
		Median	90%CI	Median	90%CI	Median	90%CI
YMRS[a]	0	28.5	(28.1, 28.9)	28.5	(28.1, 28.9)	28.5	(28.1, 28.9)
	0.5	24.4	(23.8, 26.1)	22.9	(22.5, 24.4)	22.0	(21.5, 23.5)
	1	21.8	(21.2, 24.3)	20.3	(19.8, 22.3)	19.5	(18.9, 21.3)
	1.5	19.8	(19.0, 22.8)	18.4	(17.8, 20.9)	17.6	(17.0, 19.8)
	2	18.1	(17.2, 21.4)	16.8	(16.1, 19.6)	16.1	(15.4, 18.7)
	2.5	16.6	(15.7, 20.2)	15.4	(14.7, 18.4)	14.8	(14.0, 17.6)
	3	15.3	(14.4, 19.0)	14.2	(13.4, 17.4)	13.6	(12.8, 16.6)
	Week	10 mg BID−5 mg BID		5 mg BID−Placebo		10 mg BID−Placebo	
		Medianb	90%CI	Medianb	90%CI	Medianb	90%CI
ΔYMRS[b,c]	0	0 [0]	--	0 [0]	--	0 [0]	--
	0.5	-0.8 [-3.7]	(-1.1,-0.4)	-1.5 [-6.3]	(-2.1, -0.7)	-2.4 [-9.7]	(-3.2, -1.2)
	1	-0.8 [-4.1]	(-1.2,-0.4)	-1.5 [-7.0]	(-2.3, -0.7)	-2.4 [-10.8]	(-3.5, -1.1)
	1.5	-0.8 [-4.2]	(-1.2,-0.4)	-1.4 [-7.0]	(-2.2, -0.7)	-2.2 [-10.9]	(-3.4, -1.0)
	2	-0.7 [-4.2]	(-1.1,-0.3)	-1.3 [-7.0]	(-2.1, -0.6)	-2.0 [-10.9]	(-3.2, -1.0)
	2.5	-0.6 [-4.2]	(-1.1,-0.3)	-1.2 [-7.0]	(-2.0, -0.6)	-1.8 [-10.9]	(-3.1, -0.9)
	3	-0.6 [-4.2]	(-1.0,-0.3)	-1.1 [-7.0]	(-1.9, -0.5)	-1.7 [-10.9]	(-2.9, -0.8)

a Medians of the typical individual predictions with parameter uncertainty on the YMRS scale
b Median of the differences between the typical individual predictions for treatments.
c The numbers in brackets, [ ], represent median percent changes (i.e., median of 100×ΔYMRS/YMRS).

5.6.2.2.1.2 Reviewer's Exploratory Assesments of Exposure Response of Asenapine on Young Mania Rating Scale (YMRS)

This reviewer performed an exploratory assessment of response by baseline disease severity. Rather than define baseline severity as the sponsor did, i.e. YMRS on immediately before the first dose of drug or placebo, this reviewer used the highest YMRS score at anytime prior to beginning treatment, i.e. screening, 'baseline', or other evaluations. Baseline values from all subjects regardless of treatment were then divided into quintiles based on the combined values for subjects from both studies A7501004 and A7501005. The data from the two efficacy studies were then combined to compensate for the smaller numbers of subjects per quintile as the studies were powered without the regard to any plan for division into quintiles, and the cutoffs were then used for all treatments.

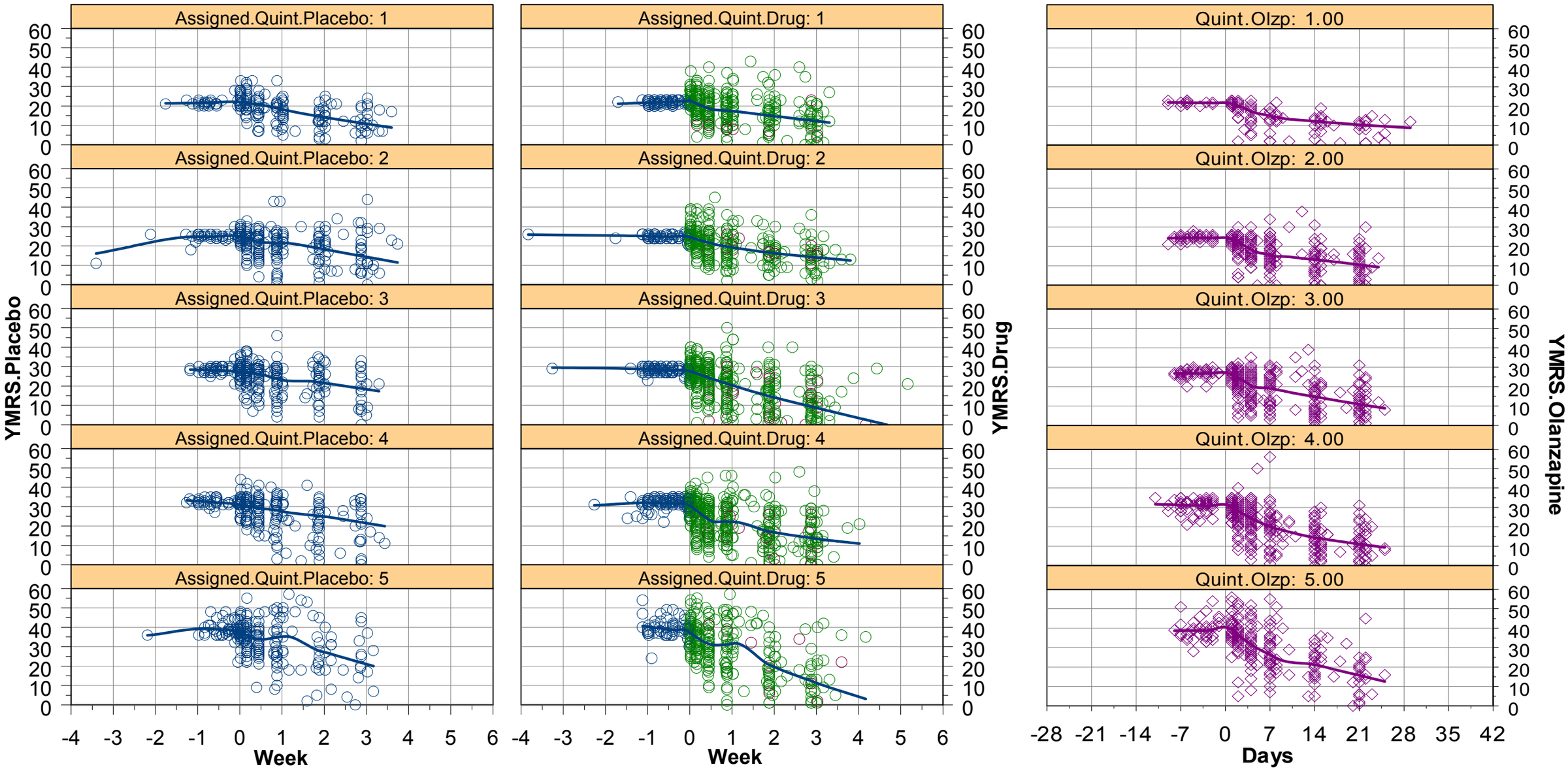
YMRS was then plotted over time using the actual day the evaluations were performed rather than the nominal day (visit) employed by the sponsor. It was noted that each of these steps resulting in the patterns becoming more readily visible, (data not shown), and emphasizes the importantance of using the best data available rather than rounding the data in some way.

Figure 190 shows the YMRS over time by quintile for each of the three treatment arms overlaid with LOESS curves. In addition, for asenapine pretreatment YMRS scores are shown by blue circles, the 10 mg dose by green circles and decreases to the 5 mg dose by purple circles. The sparcity of doses administered and their distribution indicate that they should not influence the interpretation. For olanzapine almost all subjects received 15 – 20 mg so the dose was not differentiated as that level of granularity was not included in the data files, and to pursue this would have been onerous.

Examination of the YMRS score over time by quintile in Figure 190 reveals that for placebo the final score at 3 weeks is correlated with the initial baseline score indicating that initial disease severity is a good predictor of placebo response. When the plots for asenapine and for the active control olanapine are examined regardless of the initial baseline score the mean final score at the end of 3 weeks of treatment is approximately 10 – 13 which is consistent with hypomania. Comparison of the responses with active treatments to placebo by quintile of severity reveals that the responses to the first two quintiles are virtually identical between active treatment and placebo and only differentiate with the 3 more severe quintiles. In addition, there appears to be a greater difference from placebo as severity increases.

Although this suggests that the drug might be approved in more severe cases, since these results are only achieved by combining the data from two studies we do not have the robustness of repeated study results and we may even have an underpowered study. Consequently this may be insufficient for approval and a second study may be needed.

Figure 190 Change in Young Mania Rating Score over Time by Baseline Severity for Asenapine 10 mg SL BID and the Active Control Olanzapine 5 - 20 mg QD Compared to Placebo from Studies 1004 and 1005


Assigned.Quint.Placebo: 1
Assigned.Quint.Placebo: 2
Assigned.Quint.Placebo: 3
Assigned.Quint.Placebo: 4
Assigned.Quint.Placebo: 5
Assigned.Quint.Drug: 1
Assigned.Quint.Drug: 2
Assigned.Quint.Drug: 3
Assigned.Quint.Drug: 4
Assigned.Quint.Drug: 5
Quint.Olzp: 1.00
Quint.Olzp: 2.00
Quint.Olzp: 3.00
Quint.Olzp: 4.00
Quint.Olzp: 5.00
YMRS.Placebo
YMRS.Drug
YMRS.Olanzapine
Week
Week
Days

This raises two important points. First until about 2000 practice treatment guidelines for the use of antipsychotics in mania were limited to subjects essentially who were hypermanic, and by inclusion of all subjects with full blown mania in drug trials we may have driven the mean results by these morely severely ill subjects. Second, it indicates that promotion of off-label use and current 'expert opinion' practice treatment guidelines for the off-label use of antipsychotics in hypomania and especially in bipolar spectrum disorder in children such as promoted by NIMH in a May 5th, 2007 press release are likely inappropriate. Since, the YMRS scores in children with BSD are on the order of 4 for a few hours at a time whereas in this study efficacy only appears to be with scores equal to or greater than 27, (see) and the drugs barely bring the YMRS scores to 5 after 3 months, (see Figure 223). The patterns seen in this study was also confirmed by analysis of data from studies with other antipsychotics from other NDAs and there are even hints in some of the statistics reviews for other NDAs. (As data or information from one NDA or IND is not generally included in the review of another submission these analyses are not shown here.)

Table 182 shows the YMRS scores associated with each quintile and the overall distribution. This table indicates that asenapine should only be employed with in a patient who has a YMRS at any time prior to treatment of 27 or greater. However, further analyses with more subjects and other drugs are needed to refine the cutoff.

Table 182 Quintile Calculations Associated with Acute Mania Studies A7501004 and A7501005

Quintile	Ideal YMRS Percentiles Included in quintile	Ideal Number of Subjects in Quintile	Ideal Subject Number Cutoff (Inclusive)	Actual Subject Number Cutoff (Inclusive)	Actual Number of Subjects in Quintile	Cumulative % of Subjects in Quintile	YMRS Scores Associated with Quintile
1	0% - 20%	97	97	93	93	19.2	≤23
2	>20% - 40%	97	194	206	113	42.5	24 - 26
3	>40% - 60%	97	291	302	96	62.5	27 - 30
4	>60 % - 80%	97	388	405	103	83.5	31 - 35
5	>80% - 100%	97	—	—	80	83.5	≥36
Total	—	485	—	—	—	—	Range 11 - 56

A preliminary examination of subscale data by combined symptoms indicative of psychotic features was performed but was insufficient to even result in clear differentiation by psychotic features or not. Thus without much larger studies with sufficient power we cannot presently determine whether asenapine or other drugs work on the psychotic features of mania, and whether this is driving the efficacy in more severely ill subjects or not, or if the efficacy is independent of psychotic features but only a function of severity alone.[13] If the latter is true and the drug does not work well in schizophrenia but does work in mania due to a differential response by indication. Then there may be a different mechanistic reason for differential responses by indication and even by the antipsychotic employed unrelated to D2 receptor blockade.

Discussion of the differential response by severity with the statistician revealed that the statistician had found differing degrees of efficacy by race, with Asians driving the statistical significance of the study. As this reviewer had previously found an increased pharmacodynamic sensitivity to olanzapine in healthy Chinese to psychometric testing that was not explainable by pharmacokinetic differences this reviewer decided to examine whether the distribution of subjects by race was similar across quintiles.

[13] Even with schizophrenia examination of the PPANSS subscale in schizophrenia which did not improve the evaluation over total PANSS score even though total PANSS score is thought to be primarily driven by PPANSS. This indicates that there may be additional minor non-specfic or secondary effects on NPANSS or GPANSS simply due to improvement in PPANSS.

This exploratory analysis by study is shown in Table 183 and Table 184. There were clearly a greater percentage of subjects in quintiles 4 and 5 in study A7501004 and Study A7501005 but the ratio was not higher in quintile 3, where there was also a difference in efficacy. In addition the percentage of Asians was equal or greater in the placebo arms indicating that disease severity and not race is the important predictive factor.

Table 183 Racial and Ethnic Characteristics in Acute Mania by Treatment and Disease Severity - Study A7501004

Treatment	Group	Number of Subjects							% of Subjects					
	Quintile	Total	Asian	Black	Caucasian	Ethiopian	Hispanic	Puerto Rican	Asian	Black	Caucasian	Ethiopian	Hispanic	Puerto Rican
Placebo	1	32	4	1	25	0	2	0	12.5	3.1	78.1	0.0	6.3	0.0
	2	16	3	3	8	0	2	0	18.8	18.8	50.0	0.0	12.5	0.0
	3	19	3	5	11	0	0	0	15.8	26.3	57.9	0.0	0.0	0.0
	4	13	5	1	6	0	1	0	38.5	7.7	46.2	0.0	7.7	0.0
	5	16	7	5	4	0	0	0	43.8	31.3	25.0	0.0	0.0	0.0
	Total	96	22	15	54	0	5	0	22.9	15.6	56.3	0.0	5.2	0.0
Asenapine	1	46	7	5	34	0	0	0	15.2	10.9	73.9	0.0	0.0	0.0
	2	32	5	5	21	0	1	0	15.6	15.6	65.6	0.0	3.1	0.0
	3	44	7	11	25	0	1	0	15.9	25.0	56.8	0.0	2.3	0.0
	4	28	8	8	11	0	1	0	28.6	28.6	39.3	0.0	3.6	0.0
	5	34	13	9	12	0	0	0	38.2	26.5	35.3	0.0	0.0	0.0
	Total	184	40	38	103	0	3	0	21.7	20.7	56.0	0.0	1.6	0.0
Olanzapine	1	44	7	8	26	0	3	0	15.9	18.2	59.1	0.0	6.8	0.0
	2	33	2	1	27	0	3	0	6.1	3.0	81.8	0.0	9.1	0.0
	3	50	9	12	28	0	0	1	18.0	24.0	56.0	0.0	0.0	2.0
	4	38	13	8	16	0	1	0	34.2	21.1	42.1	0.0	2.6	0.0
	5	37	13	9	13	1	1	0	35.1	24.3	35.1	2.7	2.7	0.0
	Total	202	44	38	110	1	8	1	21.8	18.8	54.5	0.5	4.0	0.5

Table 184 Racial and Ethnic Characteristics in Acute Mania Efficacy Study A7501005 by Treatment and Disease Severity

Treatment	Group	Number of Subjects								% of Subjects						
	Quintile	Total	Asian & Oriental	Asian Indian	Black	Caucasian	Hispanic	Latino	Native American & American Indian	Asian & Oriental	Asian Indian	Black	Caucasian	Hispanic	Latino	Native American & American Indian
Placebo	1	20	0	0	3	14	3	0	0	0.0	0.0	15.0	70.0	15.0	0.0	0.0
	2	18	0	0	6	10	0	1	1	0.0	0.0	33.3	55.6	0.0	5.6	5.6
	3	20	1	0	4	15	0	0	0	5.0	0.0	20.0	75.0	0.0	0.0	0.0
	4	20	5	0	4	11	0	0	0	25.0	0.0	20.0	55.0	0.0	0.0	0.0
	5	26	13	1	2	10	0	0	0	50.0	3.8	7.7	38.5	0.0	0.0	0.0
	Total	104	19	1	19	60	3	1	1	18.3	1.0	18.3	57.7	2.9	1.0	1.0
Asenapine	1	47	4	0	9	32	2	0	0	8.5	0.0	19.1	68.1	4.3	0.0	0.0
	2	35	4	0	6	25	0	0	0	11.4	0.0	17.1	71.4	0.0	0.0	0.0
	3	43	5	0	7	28	1	1	1	11.6	0.0	16.3	65.1	2.3	2.3	2.3
	4	40	7	0	5	28	0	0	0	17.5	0.0	12.5	70.0	0.0	0.0	0.0
	5	27	14	1	4	8	0	0	0	51.9	3.7	14.8	29.6	0.0	0.0	0.0
	Total	192	34	1	31	121	3	1	1	17.7	0.5	16.1	63.0	1.6	0.5	0.5
Olanzapine	1	51	6	0	8	33	3	1	0	11.8	0.0	15.7	64.7	5.9	2.0	0.0
	2	39	6	1	8	21	2	0	1	15.4	2.6	20.5	53.8	5.1	0.0	2.6
	3	40	5	0	7	27	1	0	0	12.5	0.0	17.5	67.5	2.5	0.0	0.0
	4	25	7	0	4	14	0	0	0	28.0	0.0	16.0	56.0	0.0	0.0	0.0
	5	33	10	1	4	17	1	0	0	30.3	3.0	12.1	51.5	3.0	0.0	0.0
	Total	188	34	2	31	112	7	1	1	18.1	1.1	16.5	59.6	3.7	0.5	0.5

An additional concern is whether a 5 mg dose may be sufficient in this population, not only because it was not studied, but also as it appeared effective in the schizophrenia studies and as the bipolar subjects are not as likely to be smokers and therefore are expected to have higher exposures than the subjects with schizophrenia and thereby have a different risk benefit ratio.

5.6.2.2.1.3 Evaluation of Drop out Patterns

Drop out patterns were not assessed by this reviewer. The sponsor indicated that they applied their assessment of drop out patterns from the schizophrenia studies to bipolar disorder, however this reviewer believes this may not be a valid approach as the the level of historicity and insight between the two diseases are different as was the dose and the use of tobacco that may result in higher exposures in bipolar patients.

5.6.2.2.2 Maintenance Effect

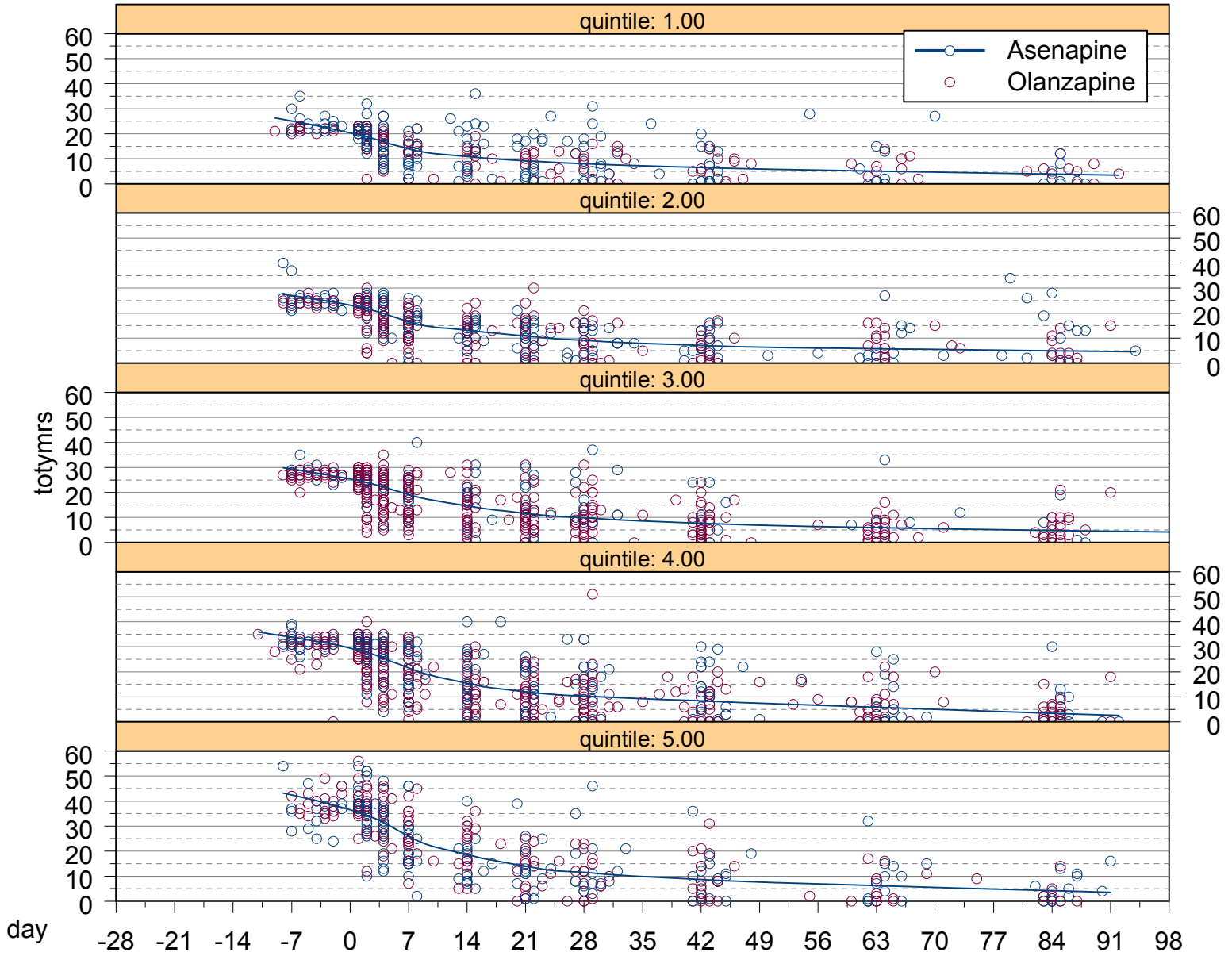
Study A7501007 was a double-blind, 40-week continuation study evaluating the safety of asenapine and olanzapine in the treatment of subjects with acute mania. The primary objective of this study is to characterize the longterm safety of asenapine and olanzapine in the treatment of acute mania in subjects with manic or mixed episode associated with Bipolar-1 Disorder for up to 52 weeks. Patients on placebo were not included as a comparator group.

Figure 191 shows plots of YMRS over time for all subjects on asenapine and olanzapine from screening until just over 90 days of dosing. Between 3 and 4 weeks of treatment Mean YMRS falls to 10 regardless of intial severity in contrast to placebo treated subjects who have similar patterns in the lowest two quinitles but not in the more severely ill subjects.

Regardless of severity (i.e. quintile) the mean YMRS in Figure 191 continues to decrease slowly so that shows by 2.5 – 3 months of treatment the mean score is below 5 which is on the order of severity with 'bipolar spectrum disorder' which these drugs are being recommended for by NIMH. However, it's clear that even by 3 months most subjects have dropped out with only 85 of 213 subjects (40%) still enrolled. This raises the question whether long term maintanence treatment is truly appropriate or if it's simply a function of who had a response at 3 or 4 weeks regardless of any continuing effect. This is especially concerning as there is no placebo control and other approved treatments have shown minimal advantages over placebo, and as this is only a single study and not two separate studies.

A better design would be a controlled withdrawal trial that was preferably placebo controlled. Consequently, there is insufficient information for a maintenance effect claim.

Figure 191 YMRS over Time for Subjects on Asenapine or Olanzapine from Studies A7501004 or A7501005 – 'Maintenance Effect' Study A7501007



5.6.2.3 Extrapyramidal Symptoms

In Amendment 010, the 4 month Safety Update, submitted Dec 27, 2007 the sponsor included study report INT00065682, Exploratory exposure response analyses of extrapyramidal symptoms (EPS) based on Phase 2 and Phase 3 trials for asenapine.

According to the sponsor, *'The dataset for analysis included all assessments on SARS (except screening scores) and their time of observation, study number, study arm, treatment, dose, asenapine AUC, information on dropout and reason for dropout as well as recorded adverse events. Only EPS-related adverse events were used in the analysis. The placebo and asenapine treated patients were included in the time-to EPSrelated adverse event analysis.*

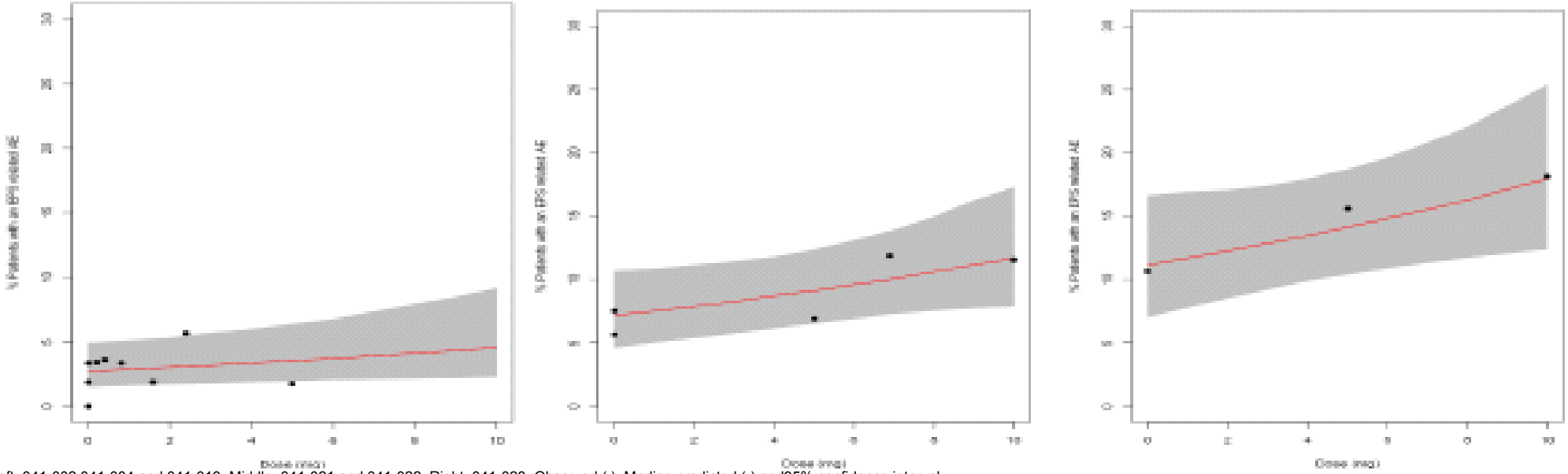
Possible dose- or exposure-response for asenapine using SARS scores and the incidence of EPS related adverse events were explored graphically. Model development was undertaken if a relationship was indicated. A time-to-event model was developed to describe the time to first EPS related AE. Bootstrapping was applied to evaluate the robustness of the final model. The final model was used to simulate proportions of patients with an EPS-related AE versus dose, which were compared with the observed proportions of patients with an EPS-related AE in the different trials.'

There was insufficient time for the reviewer to perform a detailed critique of the study report and data submitted however even examination of the sponsor's graphical analysis indicates a dose response relationship with symptoms of EPS over a period of six weeks, (see Figure 192 to Figure 196). Although the SARS scores decrease over 6 weeks (see Figure 193 to Figure 196), over a longer period of time we might see a dose response with tardive dyskinesia. Although haloperidol had higher SARs scores, observations consistent with this have been seen with other atypicals and may also be due to the saturable bioavailability with asenapine. Thus comparative risks of EPS cannot be determined for these analyses with respect to tardive or with respect to other atypical antipsychotics.

It should be noted that SARS scores only reflect pseudoparkinsonism. Thus effects on other types of EPS were not addressed. Due to high incidence of restless legs syndrome akathisia is also expected to be a problem.

Figure 192 appears to show an incidence of EPS of around 10% at a dose of 5 mg BID, which is in the range of what this reviewer expects based on his limited experience with reviewing antipsychotics.

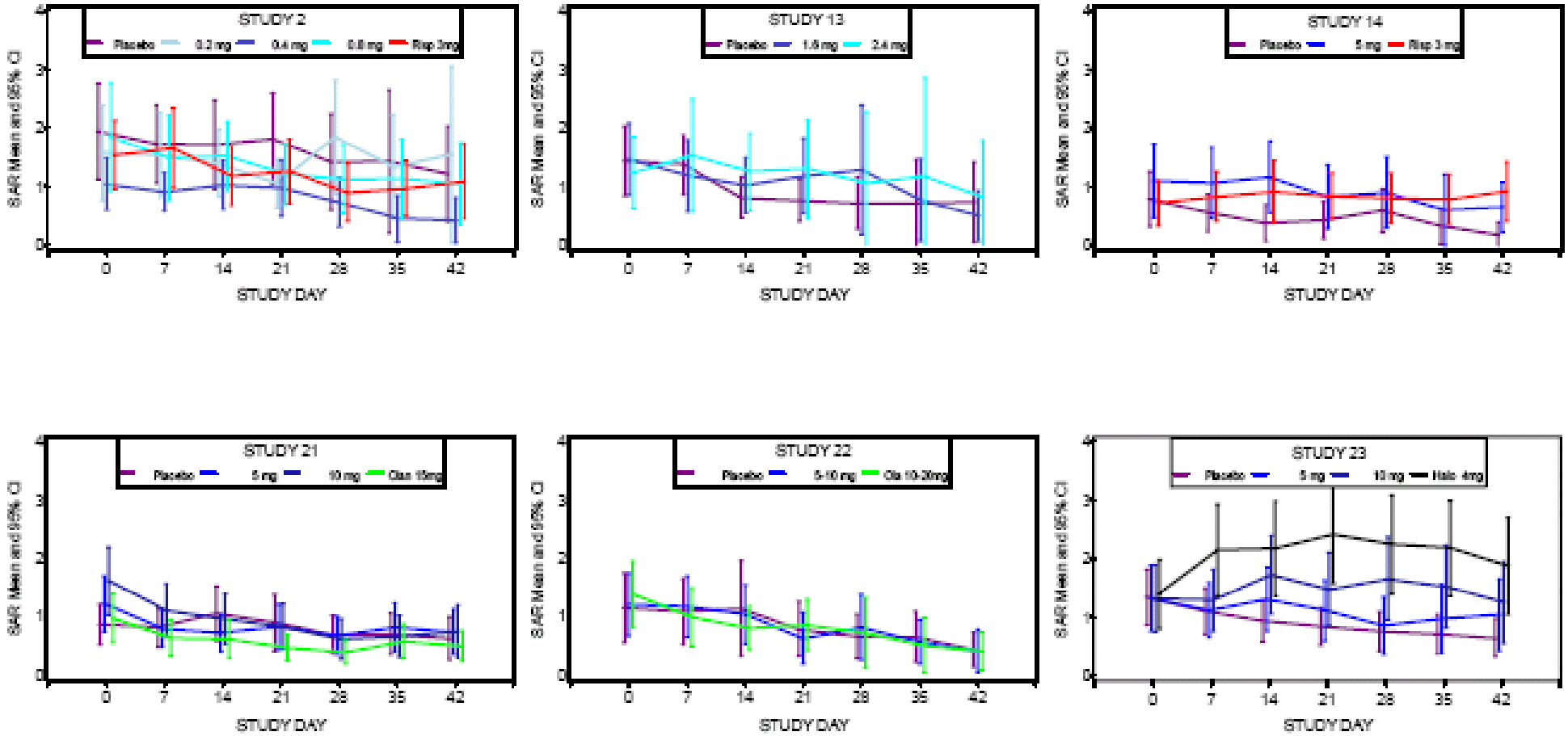
Figure 192 Proportion of Subjects with an EPS-Related Adverse Event in the Different Acute Schizophrenia Trials vs. Dose in Milligrams – Report INT00065682



Left: 041-002,041-004 and 041-013. Middle: 041-021 and 041-022. Right: 041-023. Observed (.), Median predicted (-) and95% confidence interval.

Figure 193 shows a decrease in the SARS score over time, possibly due to drop outs, with mixed results otherwise.

Figure 193 Mean SARS (95% confidence interval) versus Time per Treatment Arm by Trial – Report INT00065682



Note: Numbers in legends refer to studies as follows: 2: 041002; 13: 041013; 14: 041004; 21: 041021; 22: 041022 and 23: 041023. Source: Appendix A, Figures 1-3 to 1-8.

Figure 194 and Figure 195 show two other analyses of EPS rate vs. asenapine dose and AUC also indicating a dose response relationship.

Figure 194 Histogram of EPS Rate vs. Asenapine Dose – Report INT00065682

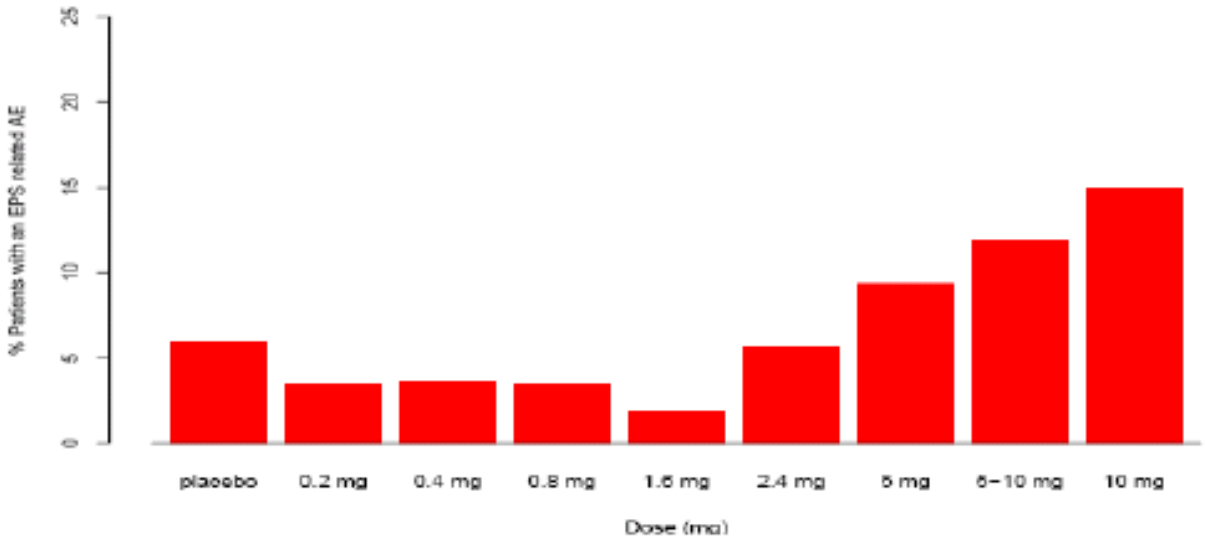


Figure 195 Histogram of EPS Rate vs. Asenapine AUC – Report INT00065682

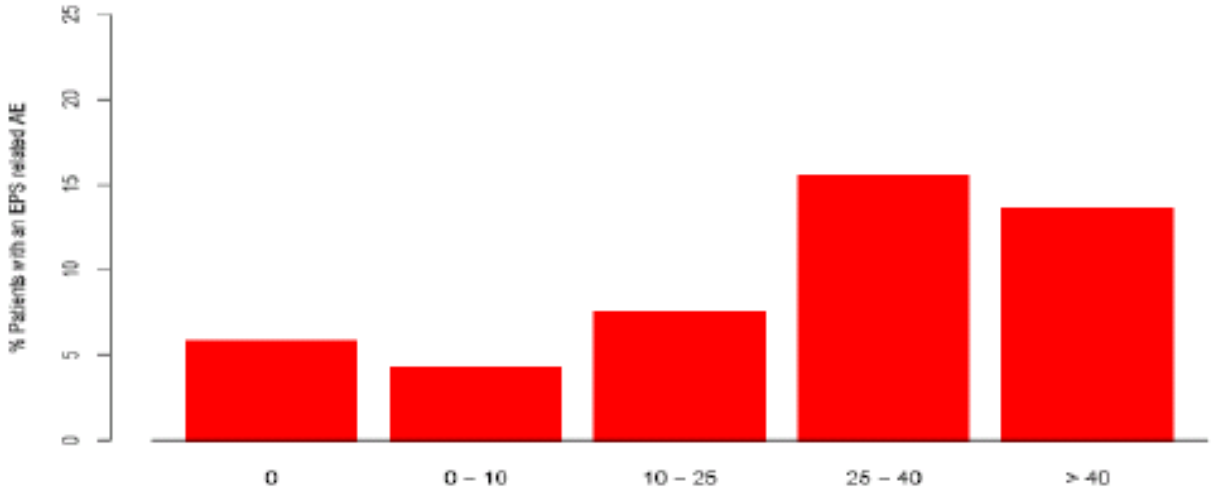
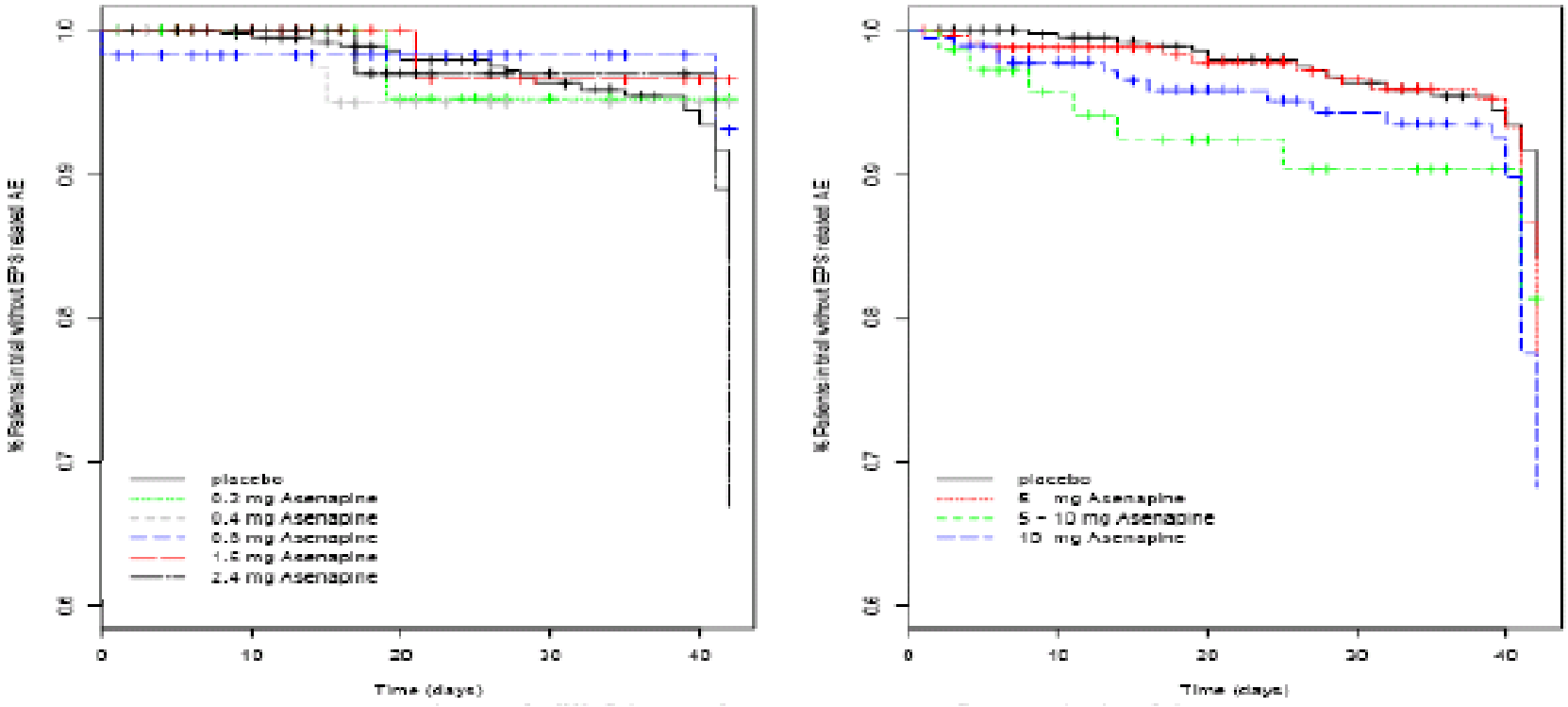


Figure 196 also indicates an increased incidence of EPS over time with asenapine doses of 5 - 10 mg as compared to placebo.

Figure 196 Proportion of Patients without an EPS-Related Adverse Event versus Time by Asenapine Dose. – Report INT00065682



Source: Appendix A Figure 2-3.

5.6.2.4 Suicidality

During one of the early meetings with the clinical meeting, (probably the scoping meeting) the issue of suicidality was raised by the clinical reviewer. It was stated that the number of cases of suicidality was high compared to placebo, but that it was lower than placebo when corrected for duration than exposure. Since no placebo was employed in the maintenance trials this reviewer performed a preliminary evaluation of exposure response for suicidality and found that when suicidality was appropriately compared for treatments of similar duration that there were similar rates between the drug treatments and placebo. In addition, suicidality was highest in the 1 – 2 weeks after discharge for acute treatment of schizophrenia, with a delay for the drug groups (presumably due to allowing any effect to wear off due to noncompliance). This is noteworthy for two additional reasons. The timing is similar to what is generally considered the period of highest risk and occurred in spite of subjects being evaluated prior to discharge as to risk of suicide. Consequently, the ability to assess risk of suicide is questionable and studies should be performed to determine if a longer duration of inpatient or another supervised living situation will decrease the risk of suicidality.

The following tables are slight modifications of tables taken from the Integrated summary of safety in section 2 of the NDA or from Appendix 1 of the Summary of Clinical Safety from NDA section 5.3.5.3.25.8

Table 185 and Table 186 show general information on adverse events. Table 185 indicates that there is a higher prevalence of severe AEs with the atypical antipsychotics compared to haloperidol.

Table 185 Overview of Adverse Events from All Phase 2/3 Studies Combined, (Cohort E)

Adverse Event	Placebo	Asenapine			Risperidone 3 mg BID	Haloperidol 4 mg BID	Olanzapine 5 – 20 mg QD
		<5 mg BID	5 - 10 mg[a] BID	All			
n (%)	(N=706)	(N=298)	(N=1953)	(N=2251)	(N=120)	(N=115)	(N=899)
Any Adverse Event	483 (68.4)	246 (82.6)	1523 (78.0)	1769 (78.6)	105 (87.5)	87 (75.7)	682 (75.9)
Related AEs	290 (39.7)	134 (45.0)	1099 (56.3)	1233 (54.8)	64 (53.3)	65 (56.5)	494 (54.9)
Severe AEs	52 (7.4)	59 (19.8)	260 (13.3)	319 (14.2)	21 (17.5)	7 (6.1)	105 (11.7)
Serious Adverse Events	61 (8.6)	50 (16.8)	275 (14.1)	325 (14.4)	21 (17.5)	8 (7.0)	87 (9.7)
Deaths	1 (0.1)	2 (0.7)	9 (0.5)	11 (0.5)	0	0	3 (0.3)
Discontinuations from any AE/SAE[b]	69 (9.8)	57 (19.1)	285 (14.6)	342 (15.2)	28 (23.3)	12 (10.4)	103 (11.5)
D/C'd 2^0 SAEs	36 (5.1)	16 (5.4)	125 (6.4)	141 (6.3)	12 (10.0)	5 (4.3)	40 (4.4)

a fixed and flexible doses
b data obtained from action taken on adverse event case report form
Risp=risperidone, Halo=haloperidol, Olan=Olanzapine
Source: 2.7.4 Appendix Table 2.0.E

Whereas Table 186 shows the prevalence of certain common AEs for asenapine as compared with the atypical antipsychotics risperidone and olanzapine, as well as with the classic antipsychotic haloperidol. Asenapine has a higher incidence of worsening schizophrenia whereas other AEs are closer to olanzapine. With the exception of weight gain which is intermediate. In contrast Risperidone has a high incidence of insomnia, agitation, anxiety and headache. Haloperidol in contrast has similar or lower incidences of common side effects.

Table 186 Adverse events by Preferred Term with an Incidence Greater Than or Equal to 2.0% for all Phase 2/3 Studies Combined, (Cohort E)

Adverse Event (Preferred Term)	Placebo	Asenapine			Risperidone 3 mg BID	Haloperidol 4 mg BID	Olanzapine 5 – 20 mg QD
		<5 mg BID	5 - 10 mg[a] BID	All			
n (%)	(N=706)	(N=298)	(N=1953)	(N=2251)	(N=120)	(N=115)	(N=899)
Any Adverse Event	483 (68.4)	246 (82.6)	1523 (78.0)	1769 (78.6)	105 (87.5)	87 (75.7)	682 (75.9)
Insomnia	80 (11.3)	52 (17.4)	293 (15.0)	345 (15.3)	28 (23.3)	16 (13.9)	98 (10.9)
Headache	114 (16.1)	79 (26.5)	207 (10.6)	286 (12.7)	28 (23.3)	5 (4.3)	105 (11.7)
Schizophrenia	30 (4.2)	39 (13.1)	177 (9.1)	216 (9.6)	7 (5.8)	8 (7.0)	47 (5.2)
Agitation	66 (9.3)	46 (15.4)	118 (6.0)	164 (7.3)	16 (13.3)	9 (7.8)	42 (4.7)
Anxiety	53 (7.5)	36 (12.1)	186 (9.5)	222 (9.9)	19 (15.8)	7 (6.1)	41 (4.6)
Somnolence	16 (2.3)	16 (5.4)	181 (9.3)	197 (8.8)	5 (4.2)	2 (1.7)	84 (9.3)
Sedation	31 (4.4)	6 (2.0)	179 (9.2)	185 (8.2)	8 (6.7)	4 (3.5)	129 (14.3)
Weight increased	3 (0.4)	1 (0.3)	167 (8.6)	168 (7.5)	6 (5.0)	1 (0.9)	150 (16.7)

Table 187 to Table 190 shows the information on suicidality.

Table 187 is the summary data the sponsor uses to claim that despite a higher prevalence of suicidality with active treatment as compare to placebo that the incidence when normalized to 100 patient years is lower with asenapine than with placebo and is comparable to Olanzapine.

Table 187 Psychiatric Adverse events Related to Suicidality for <u>all</u> Phase 2 and 3 Studies Combined, (Cohort E)

Adverse Event SOC/ Preferred Term			Placebo	Asenapine			Risp BID	Halo BID	Olan QD
				<5 mg BID	5-10 mg[a] BID	All			
Number of Subjects			(N=706)	(N=298)	(N=1953)	(N=2251)	(N=120)	(N=115)	(N=899)
N (%)	Psychiatric SAEs		2 (0.3)	3 (1.0)	33 (1.7)	36 (1.6)	2 (1.7)	–	17 (1.9)
	Discontinuations due to Psychiatric AEs		4 (0.6)	2 (0.7)	15 (0.8)	17 (0.8)	2 (1.7)	–	7 (0.8)
	Suicidal and self-injurious behaviours		7 (1.0)	9 (3.0)	37 (1.9)	46 (2.0)	3 (2.5)	–	18 (2.0)
	Self injurious ideation		–	–	1 (0.1)	1 (0.04)	–	–	–
	Intentional self injury		1 (0.1)	1 (0.3)	2 (0.1)	3 (0.1)	–	–	2 (0.2)
	Suicidal ideation		5 (0.7)	8 (2.7)	22 (1.1)	30 (1.3)	2 (1.7)	–	6 (0.7)
	Suicidal behaviour		1 (0.1)	1 (0.3)	–	1 (0.04)	–	–	1 (0.1)
	Suicide attempt		1 (0.1)	–	9 (0.4)	9 (0.4)	1 (0.8)	–	7 (0.8)
	Completed suicide		–	–	6 (0.3)	6 (0.3)	–	–	2 (0.2)
	Total		15 (2.1)	19 (6.4)	77 (3.9)	96 (4.3)	6 (5.0)	0.0	36 (4.0)
Patient exposure years			52	34	611	645	21	10	285
Number of Cases and Incidence Per 100 Patient years	Suicidal and Self-Injurious Behaviors	Cases	7	9	37	46	3	–	17
		Incidence[b]	13.49	26.24	6.06	7.13	14.29	–	5.97
	Self Injurious Ideation	Cases	–	–	1	1	–	–	–
		Incidence[b]	–	–	0.16	0.16	–	–	–
	Intentional Self Injury	Cases	1	1	2	3	–	–	2
		Incidence[b]	1.9	2.9	0.3	0.5	–	–	0.7
	Suicidal Ideation	Cases	5	8	22	30	2	–	6
		Incidence[b]	9.63	23.32	3.60	4.65	9.52	–	2.11
	Suicidal behaviour	Cases	1	1	–	1	–	–	1
		Incidence[b]	1.9	2.9	–	0.3	–	–	0.4
	Suicidal Attempt	Cases	1	–	9	9	1	–	7
		Incidence[b]	1.93	–	1.47	1.40	4.76	–	2.46
	Completed Suicide	Cases	–	–	6	6	–	–	2
		Incidence[b]	–	–	0.98	0.93	–	–	0.70
	Total	Cases	15	19	77	96	6	–	35
		Incidence[b]	28.8	55.9	12.6	14.9	28.6	0.0	12.3

a fixed and flexible doses
b incidence /100 exposure years
Risp=risperidone, Halo=haloperidol, Olan=olanzapine
Source: 2.7.4 Appendix Tables 2.2.E, 2.18.E, 2.26.2.E, and 2.30.E

Consequently this reviewer compared only the data from studies that had similar durations of exposure to active drug and placebo.

Table 188 shows this data by week of treatment for the combined data for the phase II/III 6 week studies for the treatment of acutely ill schizophrenics, and Table 189 shows similar data for acutely ill patients with bipolar I disease.

Table 188 shows that the incidence of suicidal and self-injurious behaviours, as reported by the sponsor, were similar regardless of treatment an incidence of around 1%, (range 0.8% - 1.2%). As stated previously peak occurence is around week 4 or 5 just after discharge. Not all other categories were reported by the sponsor so each category was included in Table 188 by the reviewer.

Table 188 Prevalence of AEs Indicative of Suicidality over Time by Treatment in Acute Schizophrenia Trials, (Cohort A)

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Total Weeks 1 - 6
Placebo	N=503	N=439	N=372	N=301	N=263	N=233	N=503
Suicidal and self−injurious behaviours NEC	1 (0.2)	–	1 (0.3)	2 (0.7)	–	1 (0.4)	5 (1.0)
Self−injurious ideation	–	–	–	–	–	–	–
Intentional self−injury	–	–	–	–	–	–	–
Suicidal ideation	1 (0.2)	–	1 (0.3)	2 (0.7)	–	–	4 (0.8)
Suicide attempt	–	–	–	–	–	2 (0.9)	2 (0.4)
Completed Suicide	–	–	–	–	–	–	–
Total	**2 (0.4)**		**2 (0.5)**	**4 (1.3)**		**3 (1.3)**	**11 (2.2)**
Asenapine 5 mg BID (fixed)	N=274	N=247	N=215	N=186	N=167	N=159	N=274
Suicidal and self−injurious behaviours NEC	–	–	–	–	2 (1.2)	–	2 (1.2)
Self−injurious ideation	–	–	–	–	–	–	–
Intentional self−injury	–	–	–	–	–	–	–
Suicidal Ideation	–	–	–	–	1 (0.6)	–	1 (0.36)
Suicide attempt	–	–	–	–	1 (0.6)	1 (0.6)	2 (1.2)
Completed Suicide	–	–	–	–	–	–	–
Total					**4 (2.4)**	**1 (0.6)**	**3 (1.1)**
Asenapine 10 mg BID (fixed)	N=274	N=208	N=183	N=147	N=132	N=126	N=274
Suicidal and self−injurious behaviours NEC	–	–	–	–	1 (0.8)	–	1 (0.8)
Self−injurious ideation	–	–	–	–	1 (0.8)	–	1 (0.8)
Intentional self−injury	–	–	–	–	–	–	–
Suicidal ideation	–	–	–	–	–	–	–
Suicide attempt	–	–	–	–	–	–	–
Completed Suicide	–	–	–	–	–	–	–
Total					**2 (1.5)**		**2 (0.73)**
Asenapine 5 -10 mg BID (fixed & Flexible)	N=870	N=758	N=663	N=529	N=455	N=424	N=870
Suicidal and self−injurious behaviours NEC	1 (0.1)	–	1 (0.2)	2 (0.4)	3 (0.7)	1 (0.2)	8/870 (0.92%)
Self−injurious ideation	–	–	–	–	1 (0.2)	–	1 (0.1)
Intentional self−injury	–	–	1 (0.2)	–	–	–	1 (0.1)
Suicidal ideation	1 (0.1)	–	–	2 (0.4)	1 (0.2)	1 (0.2)	5 (0.6)
Suicide attempt	–	–	–	–	1 (0.2)	1 (0.2)	2 (0.2)
Completed Suicide	–	–	–	–	–	–	–
Total	**2 (0.2)**		**2 (0.3)**	**4 (0.8)**	**6 (1.32)**	**3 (0.7)**	**17 (2.0%)**
Olanzapine 10−20 mg QD	N=194	N=161	N=146	N=124	N=110	N=102	N=194
Suicidal and self−injurious behaviours NEC	–	–	–	1 (0.8)	–	–	1 (0.8)
Self−injurious ideation	–	–	–	–	1 (0.8)	–	1 (0.8)
Intentional self−injury	–	–	–	–	–	–	–
Suicidal ideation	–	–	–	1 (0.8)	–	–	1 (0.8)
Suicide attempt	–	–	–	–	–	–	–
Completed Suicide	–	–	–	–	–	–	–
Total				**2 (1.6)**	**1 (0.9)**		**3 (1.5)**

Adverse events coded using MedDRA (version 9.0). N is the number of subjects at risk from the beginning of that week.

Table 189 shows similar data for bipolar I disorder but due to the small sample size no firm conclusions can be drawn although suicides only occurred in the drug treatment groups.

Table 189 Prevalence of AEs Indicative of Suicidality over Time by Treatment in Acute Bipolar I Trials, (Cohort C)

	Week 1	Week 2	Week 3	Total Weeks 1 - 3
Placebo	N=203	N=166	N=131	203
Suicidal and self−injurious behaviours NEC	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Self−injurious ideation				
Intentional self−injury				
Suicidal ideation				
Suicide attempt				
Completed Suicide				
Total				0 (0.0)
All Asenapine 5−10 mg BID (fixed and flexiible)	N=379	N=317	N=260	379
Suicidal and self−injurious behaviours NEC				
Self−injurious ideation				
Intentional self−injury	0 (0.0)	1 (0.3)	1 (0.4)	2 (0.53%)
Suicidal Ideation	0 (0.0)	0 (0.0)	1 (0.4)	
Suicide attempt				
Completed Suicide	0 (0.0)	1 (0.3)	0 (0.0)	
Total		2	2	4 (1.06%)
Olanzapine 5−20 mg QD	N=394	N=358	N=323	394
Suicidal and self−injurious behaviours NEC	0 (0.0)	2 (0.6)	0 (0.0)	2 (0.51%)
Self−injurious ideation				
Intentional self−injury				
Suicidal ideation				
Suicide attempt	0 (0.0)	1 (0.3)	0 (0.0)	
Completed Suicide	0 (0.0)	1 (0.3)	0 (0.0)	
Total		4		4 (1.02%)

Table 190 is mainly useful as by combining data is appears to indicate that the incidence of self-injurious behaviour may be lower with Olanzapine.

Table 190 Sponsor's Table of Suicidal and Self−injurious Behaviors by Treatment for both Acute Schizophrenia and Acute Bipolar Studies Combined, (Cohorts A and C)

Placebo	5/503 (1.0%)
Asenapine	10/1249 (0.8%)
Olanzapine	3/588 (0.51%)

5.6.3 Other Safety Issues

Significant insights into exposure response and PK/PD relating to safety were gleaned from several phase I trials. Originally the reviewer was told not to review these studies (i.e. early phase I studies, studies of development formulations, and the QT study) and the reviewer had to agree in writing, however the reviewer included the provision that if any information pointed to the need to examine these studies in more detail then this reviewer would do so.

Review of the PET studies indicated dose and time dependent hepatotoxicity had been seen with high oral doses. However review of the original data was not pursued by this reviewer, rather the medical officer was informed. Then on April 10, 2008 while checking the history of the formulation for the executive summary of the review (i.e. §2.2.3 Pertinent Clinical Pharmacology and Biopharmaceutic Questions) this reviewer sereptitiously came across descriptions of serious cardiotoxicity in the early phase I studies. Since a potential myocardial infarction was identified in the paroxetine drug-drug interaction study (25525) that was dismissed as musculoskeletal in origin, this reviewer examined these cases more closely prior to communication with the medical officer. It was then noted that some of these serious cardiac toxicities were noted in the QT study but that they hadn't been highlighted and had been explained largely as vasovagal in origin. While looking into the cardiotoxicity issue additional pertinent information on hepatotoxicity came to light.

Upon further examination of the various study designs it was noted that virtually all studies used low doses of short duration and tended to avoid subjects who might be at increased risk of hepatotoxicity. In addition in those studies where the risk might be apparent, i.e. the QT study and the adolescent study laboratory and other data were not reported so that a safety assessment could not be performed. In addition, the medical team leader requested a review of the adolescent study on Friday April 11, 2008 immediately prior to the DFS due date (April 14, 2008) when a quick review was likely to overlook this important safety information, (see §6.6 April 11, 2008 Consult Request from Medical Team Leader).

With regards to cardiotoxicity there appears to be a high incidence of AV block with junctional rhythms. Thus the vaso-vagal explanation for the large number of subjects fainting is suspect. Generally this is not a great concern clinically however, in the elderly and in the presence of certain other drugs this could be quite important. This asw well as the risk of agranulocytosis may explain why the sponsor did not include data in elderly subjects in this submission.

A synopsis of a PK study in the elderly was accidentally found in the 120 day safety report several levels down under a folder for an efficacy study. This study synopsis was only identifiable by a study report code without a title and was only looked at because the study code did not match the study code for higher level folder. As with the adolescent study only mean PK data was provided without any safety information or laboratory values.

Abbreviated information on these serious AEs follow:

5.6.3.1 Hepatotoxicity

5.6.3.1.1 Single Rising Dose Oral Study 85029

The clinical study report for study 85029 was dated November 1989. However based on the study title, (A Phase I, double-blind, placebo controlled, single rising oral dose study with Org 5222 in healthy male volunteers to assess tolerance and safety), it appears to be the first in human study. In the background information for this study, dose and time dependent hepatotoxicity in dogs were noted as shown in Figure 197.

Figure 197 Background Information on Preclinical Safety for First in Man Study - Study 85029

A 13 week oral toxicological study in dogs has been completed. Doses used were 1.25, 7.5 and 20 mg/kg/day. Interim analysis was performed after one month because in previous studies the lowest dose (20 mg/kg/day) still caused hepatotoxicity. The interim analysis did not show any abnormality of some biochemical (in particular plasma liver enzyme concentrations) and haematological parameters in the 1.25 and 7.5 mg/kg/day groups. In the 20 mg/kg/day group a slight increase in plasma liver enzyme concentrations was elicited, although the values observed were still within normal limits. The final analysis of this study indicated signs of hepatotoxicity in some (but not all) dogs treated with 7.5 and 20 mg/kg/day. No indications of hepatotoxicity were apparent in the 1.25 mg/kg/day dose group of dogs. Neither reproductive toxicological nor mutagenicity studies revealed any effects which preclude evaluation in man.

No significant adverse events were reported for this trial.

5.6.3.1.2 PO MRD PK S/T Study 85136

Although this clinical study report, (Feb 3, 1988), predates the previous study report. The title, (A Phase I, double-blind, placebo controlled, sub-chronic study with increasing doses of Org 5222 up to 30 mg daily in healthy male volunteers) and other indicators suggest that study 85136 was the second study in man.

The sponsor's conclusions that are shown in the following figures clearly indicate a dose and time dependent direct hepatocellular hepatotoxicity (see Figure 198 to Figure **200**), and that occurs sooner with higher doses and later with lower doses, (i.e. as soon as Day 2 with 20 mg PO BID and no sooner than day 10 with 10 mg PO BID and below), (see Figure 201). Although transaminases declined with drug discontinuation in two of the nine subjects LFT increases were greater than 3 fold, (see Figure 202 and Figure 203).

Figure 198 Sponsor's Safety Conclusions Regarding Hepatotoxicity – Study 85136

V. **Conclusion**

1. ORG 5222 caused mild to moderate liver enzyme increases probably due to direct hepatocellular toxicity.

Figure 199 Sponsor's Safety Conclusions Regarding Hepatotoxicity (Continued A) – Study 85136

In summary, 9 out of 20 subjects given active medication developed changes in plasma liver enzymes during the study. Three of six subjects who received the highest dosage of ORG 5222 experienced elevation of AST and/or ALT to greater than twice the upper limit of normal. One of 8 placebo subjects had an elevated alkaline phosphatase throughout the study and had a single mildly elevated ALT level recorded.

Figure 200 Sponsor's Safety Conclusions Regarding Hepatotoxicity (Continued B) – Study 85136

The pattern of enzyme changes - elevation of transaminases with normal alkaline phosphatase and no accompanying rise in total bilirubin - suggests direct hepatocellular toxicity rather than cholestasis as the underlying mechanism. Enzyme induction alone is unlikely to have caused such changes in the plasma liver enzymes.

Figure 201 Sponsor's Table of Subject Characteristics for Cases of Hepatotoxicity – Study 85136

Group No.	Subject No & Initials	Dose	Abnormal Tests	Day of Onset of rise	Time of Peak of rise	Day of 1st subsequent normal value	Severity
II	14.JT	3 mg bd	ALT	10	10	14	++
III	18.A3	10 mg bd	ALT	10	11	21	++
			AST	10	11	13	+
IIIA	101.?B	20 mg bd	T.bili	2 & 10	2 & 10	5 & 14	+ & +
	102.TT	Placebo	Alk Phos	Raised at screening and throughout			+
			ALT	14	14	21	+
	104.MB	20 mg bd	ALT	10	15	-	++
			AST	0	2 & 14	5 & 21	+
IV	28.DG	30 mg bd	ALT	9	9	-	+++
			AST	9	9	-	+++
	29.AM	30 mg bd	ALT	0	12	15	+++
			AST	10	12	14	+
			GGT	0	6	15	+
	30.NB	30 mg bd	ALT	6	11	-	+++
			AST	6	9	27	+++

\+ = 0-49%
++ = 50-99%
+++ = 100%+

Figure 202 Plot of Significantly Elevated Liver Function Tests (> 3X ULN) vs. Time - Case 1 – Study 85136

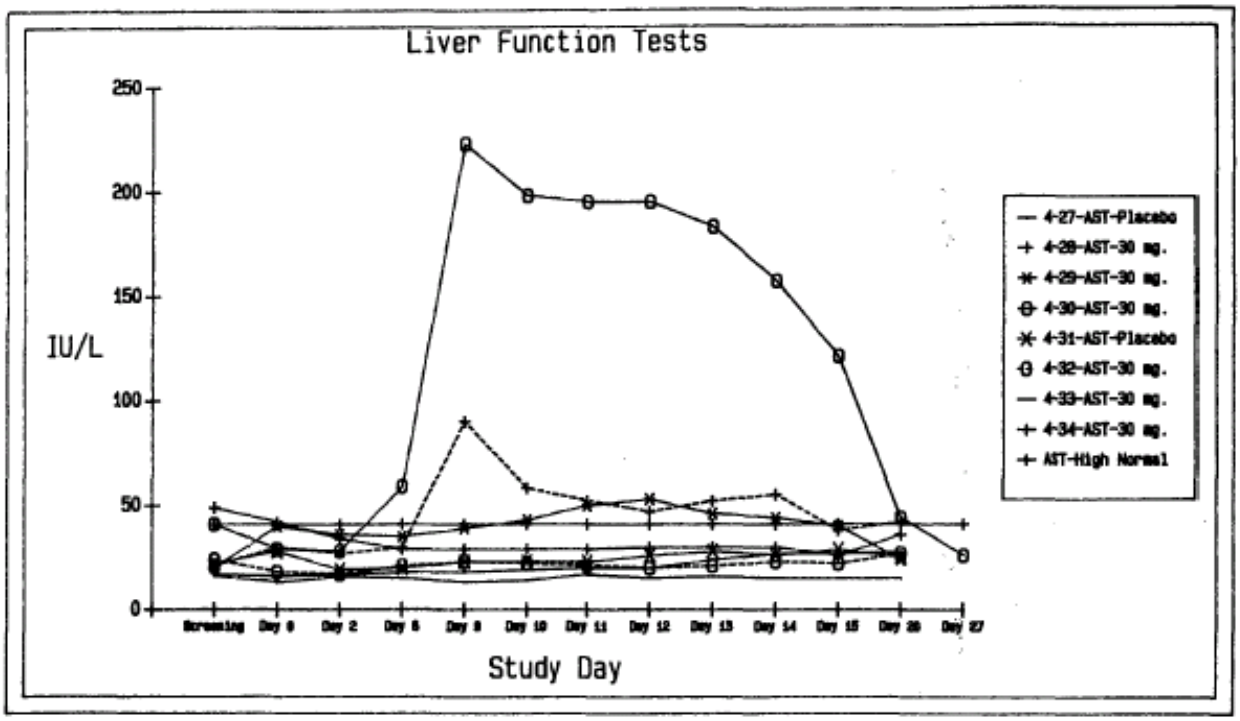
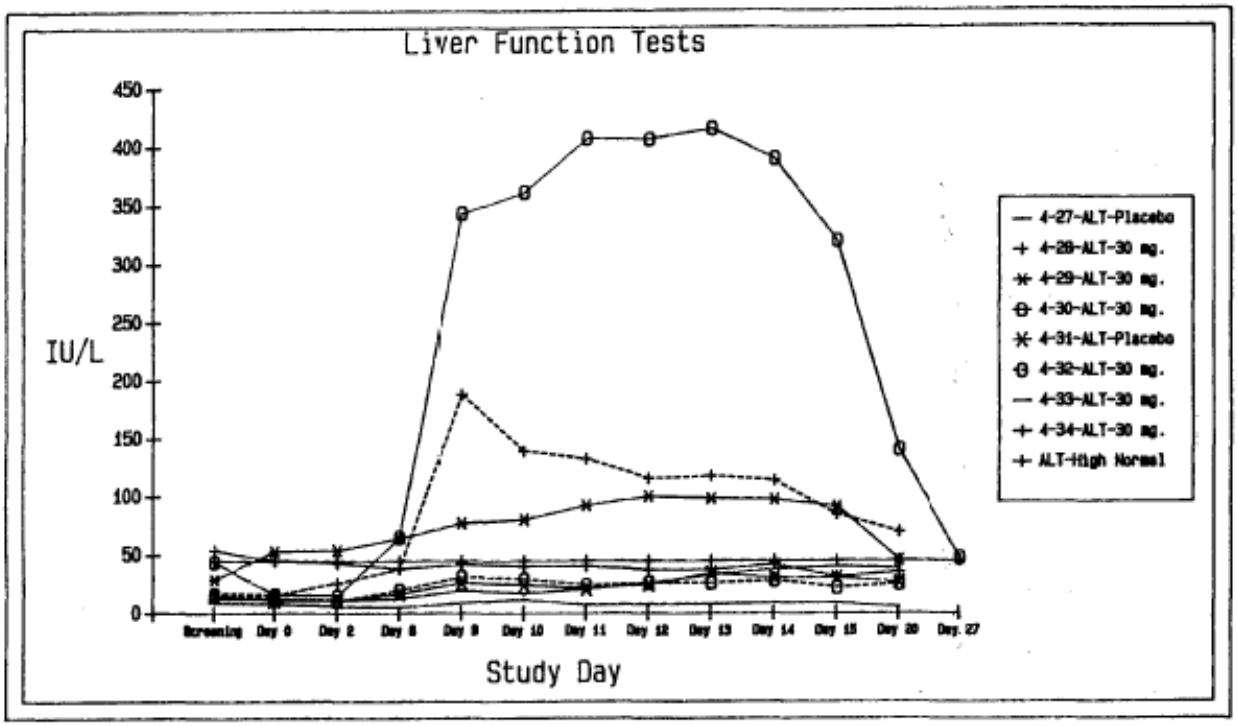


Figure 203 Plot of Significantly Elevated Liver Function Tests (> 3X ULN) vs. Time - Case 2 – Study 85136



5.6.3.1.3 Pivotal BE Study – (b) (4) vs. (b) (4) - Study 41026

Study 41026 was a pivotal bioequivalence study of a sublingual tablet manufactured by (b) (4) to the (b) (4) clinical trial formulation. The reason given for this proposed change in formulation was that asenapine maleate is bitter and this may improve the organoleptic characteristics. This is reasonable as a slower dissolving tablet would minimize the bitterness. However, the (b) (4) tablet was bio-inequivalent, presumably due to the slower disintegration and dissolution resulting in more drug being swallowed.

Subject 19 had elevated ALAT levels from Day 2 after treatment with the (b) (4) tablet, which resolved 14 days later. Since the pharmacokinetic characteristics are so close to the tablets with (b) (4) and since the margin of safety is so small this raises the concern whether the safety profile with (b) (4) tablets may be different than seen with the clinical trial formulation.

5.6.3.1.4 Paroxetine Drug Interaction Study - Study 25525

In study 25525 subject 15 in sequence A dropped out due to elevated ALAT (main reason) and elevated ASAT at Day 15. The ALAT concentration increased to a maximal value of 474 U/L at Day 16 (Upper Normal Limit (ULN): 50 U/L). ALAT increased the day after paroxetine administration and 4 days after administration with dextromethorphan raising the concern that there may be increased risk of toxicity when administered with other drugs, whether this is due to interactions via CYP2D6 and shunting or pharmacodynamic interactions cannot be discerned from this study.

Several other subjects had lessor degrees of increases in ALAT and ASAT, (see Figure 204 and Figure 205).

Figure 204 Text from Paroxetine DDI Study 25525

Seven clinically relevant abnormalities were observed in Sequence A.

Subject 02 had elevated ALAT (73 U/L) and ASAT (108 U/L) starting at Day 17, one day after administration of the last trial medication in Sequence A. Both elevations were judged probable related to the trial medication and of mild intensity. Ten days later ALAT and ASAT concentrations were decreased within normal ranges to 21 and 46 U/L, respectively (ULNs for ALAT and ASAT are 50 U/L and 40 U/L, respectively).

Subject 05 had elevated ALAT (99 U/L) starting at Day 17, one day after administration of the last trial medication in Sequence A (judged possibly related to the trial medication and of mild intensity). Six days later the ALAT was 86 U/L declining to 60 U/L after 14 days (judged to be abnormal but not clinically relevant).

Subject 12 had an elevated cholesterol level (8.4 mmol/L) starting at Day 17, one day after administration of the last trial medication in Sequence A (judged unlikely related to the trial medication and of mild intensity). Six days later the cholesterol level was decreased to 6.9 mmol/L (judged to be abnormal but not clinically relevant).

Subject 15 had an elevated ALAT concentration (58 U/L) starting at Day 7, after 3 days of administration of 1, 3 and 5 mg asenapine b.i.d., respectively (judged probably related to the trial medication and of moderate intensity). The ALAT concentration increased to a maximal value of 474 U/L at Day 16. Subsequently, the ALAT concentration declined to 78 U/L in 14 days (judged to be abnormal but not clinically relevant). Administration of trial medication was ended after dosing of 5 mg

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Figure 205 Text from Paroxetine DDI Study 25525 (continued)

asenapine in the morning of Day 15. Subject 15 had an elevated ASAT concentration (63 U/L) starting at Day 13, after 6 days of administration of asenapine b.i.d. (judged probably related to the trial medication and of mild intensity). Two days later the ASAT was 179 U/L declining to 44 U/L in 8 days (judged to be abnormal but not clinically relevant).

Subject 114 had elevated ALAT (119 U/L) starting at Day 7, after 3 days of administration of 1, 3 and 5 mg asenapine b.i.d., respectively, (judged probably related to the trial medication and of moderate intensity). From Day 26 the ALAT declined to 59 U/L 7 days later (judged to be abnormal but not clinically relevant).

No clinically relevant abnormalities were observed in Sequence B.

5.6.3.1.5 Thorough QT Study - Study A7501001

When examining the population pharmacokinetic report this reviewer observed that there a number of subjects with elevated bilirubins. The majority of these elevated bilirubins were in the thorough QT study. The medical reviewer was notified and lab values were requested from the sponsor, (see section 6.4 Identification of Elevated Bilirubins and Medical Reviewer Notification and the Pop PK Thorough QT study A7501001 in section 5.6.1.3 because it was reported over 4 different study reports.

There is some confusion regarding the units reported for some of these studies and whether conversion was done appropriately. However, what's disconcerting is that the sponsor only reported laboratory values from before and after treatment and not during treatment.

5.6.3.1.6 Relative BE Study New Formulation - Study 41009

This was a comparison of different polymorphic forms. One subject (0002) had ALT elevations of 5 fold ULN and a second subject (008) had ALT elevations of 3 fold ULN.

5.6.3.2 Cardiotoxicity

A number of cases of serious cardiotoxicity have been found in young healthy volunteers. These include myocardial infarction, AV block with junctional rhythms, and Afib. In addition a there have been a number of reported cases of tachycardia as well as bradycardia and syncope.

Some of these are reported in the QT study report but were not highlighted by the QT team.

It appears that there may be a concentration dependent effect on AV conduction that occurs at higher doses than QT prolongation, thus explaining the QT effect at the lower dose but not at the higher dose. Whether this is due to differing effects at different concentrations and/or due to a metabolite formed via first pass from swallowed drug is presently unknown. If there is AV block we might expect to see a shortened QT at higher exposures.

There is also some indication that the cardiac toxicity may be worse in individuals taking other drugs that might effect cardiac conduction or CYP2D6, e.g. paroxetine, etc.. Thus the risk with concomitant drugs such as lithium, paroxetine, carbamazepine, dextromethorphan, OTC sympathomimetics etc. needs to be investigated and assessed

In study 25509 the sponsor indicates that the asenapine is unsafe at drug exposures obtained with clinical dosages and due to cardiotoxicity and direct hepatotoxicity.

The fact that little information is included in this NDA regarding expected combination use with other drugs or use in women or the elderly and the increased risk the elderly have with this type of arrhythmia indicates further safety assessment is needed if development of the compound is pursued.

Additional information on events indicative of cardiotoxicity follow:

A summary of the selected cardiac AEs that were found in the limited time available (2 days) are shown in Table 192.

5.6.3.2.1 IV Study - Study 25506 - Nov 1992

Study 25506 was a pharmacokinetic study of intravenous administration of asenapine at four different doses, with each dose to be administered to two healthy male volunteers which was then to be followed by a pilot bioavailability study of 30 mg orally in the two volunteers who received the highest tolerated intravenous dose.

The study was stopped after the first two subjects due to asystole requiring external cardiac massage and atropine. Although attributed by the sponsor to a vasovagal effect, an external cardiologist deemed it a serious AE of asenapine affecting the conducting system of the heart, (see Figure 206 to Figure 211).

What is particularly worrisome is that this occurred at a dose of 0.7 mg shortly after a 30 minute infusion in a young healthy individual with no evidence of any cardiac disease. With an average absolute bioavailability of 33% (and up to 50%) this translates into a sublingual dose of 1.4 mg - 2.1 mg and is unlikely due to metabolites. Thus arrhythmias are a concern with clinical doses.

Figure 206 Text from IV Study 25506

This study was stopped after one of the two subjects collapsed in asystole. Prompt resuscitation resulted in the patient being asymptomatic 24 minutes after the initial collapse. Anxiety about the other subject's adverse event may have contributed to subject's 1/2(0.7mg) dizziness.

Figure 207 Text from IV Study 25506 (Continued)

Cardiac investigations - including a 24 hour Holter ECG, echocardiogram, exercise ECG and carotid sinus massage - revealed no cardiac pathology that may have predisposed to the event.

Org 5222 has alpha-blocking activity. It is possible that the drug aggravated hypotension (during sitting) and this precipitated an inappropriate vagal response in a vagotonic (athletic) subject. However, this does not adequately explain the persistence of the sinus arrest and the lack of response to lying supine.

Figure 208 Text from IV Study 25506 (Continued)

This study was stopped because subject 1/1(0.7mg) collapsed 45 minutes after the start of the 30-minute infusion, while having his sitting blood pressure measured. Before he collapsed he stated that he felt dizzy and unwell, then immediately fell back onto the bed. The ECG monitor showed asystole. The subject was shaken and made a transient verbal

Figure 209 Text from IV Study 25506 (Continued)

response. He had no pulse and was very pale. The foot of the bed was elevated. Cardiac massage commenced and after approximately five thrusts to the sternum, he made a transient verbal response: he asked what was happening. The cardiac massage, which lasted about 5 seconds, appeared to stimulate a nodal bradycardia before reverting to asystole. The subject again lost consciousness. The cardiac massage was repeated for another 5 seconds, with improvement in consciousness. The subject was continuously unconscious for not more than 30 seconds. However, severe bradycardia with intermittent nodal complexes and AV dissociation persisted until two doses of atropine (0.6mg i.v.) had been administered at 01 00 49 and 01 00 54. Haemaccel (one unit i.v.) was administered at 01 00 59. Oxygen was removed at 01 01 10. Sinus tachycardia resulted within seconds, the subject became normotensive and fully regained consciousness. Twenty-four minutes after the initial collapse, the subject was asymptomatic. Plasma electrolytes (Na, K, Ca and Mg) in the additional blood samples taken (see section 6.2) were normal. Subsequent cardiac investigations and cardiological opinion (see letter of 23 december 1991 in appendix 14) revealed no predisposing or post-event cardiac pathology. The cardiological investigations - a physical examination, 24-hour tape-recorded ECG, two-dimensional echocardiogram, treadmill exercise ECG, and carotid sinus massage - could not identify any cardiac abnormality.

Subject 1/2(0.7mg) had been dosed and began to feel dizzy before subject 1/1(0.7mg) collapsed. This adverse event was initially considered mild, but when he felt dizzy on standing - 30 minutes after dosing - it was considered to be of moderate severity. By that time subject 1/1(0.7mg) had collapsed.

Figure 210 Cardiologist's Report from IV Study 25506

Dr. Graham Jackson

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Secretary and Appointments
Tel: 071-407 5887
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27 Tooley Street, London, SE1 2PR
Tel: 071-403 4884 ext: 2311

GJ/HS

23rd December 1991

Dr. Tim Mant,
Guy's Drug Research Unit,
6 Newcomen Street,
London, SE1 1YR

Dear Tim,

Re: (b) (4) 001 ORG 5222 I.V. 57-DY

Thank you for asking me to assess this 27 year old chap who had an unfortunate event as a result of participating in a normal volunteer study. I've looked at the sequence of ECGs and there's no doubt that he became asystolic and as you pointed out you had to perform cardiac massage to sustain an output. It is interesting looking at the sequence of events because in the first instance there's obviously sinus arrest but then as he recovers there's evidence of AV conduction abnormalities also with a gradual return back to normal sinus rhythm.

With regard to him, he's always been fit, well and very active and though he currently works as a casino manager, in the past he's had a healthy lifestyle being an ex-marathon runner and still keeping reasonably fit. He's single, a non smoker, only drinks alcohol at the weekends. He's never been ill apart from a road traffic accident five years ago when he had some cervical spine damage.

EXAMINATION

He looks fit and well. JVP not raised, sinus rhythm, blood pressure 110/80. There were no murmurs, there were two heart sounds, there was no suggestion of heart failure and the lungs were normal and clear.

INVESTIGATIONS

24 Hour Tape Recorded ECG: Normal sinus rhythm with respiratory variation.

2D Echocardiogram: Normal.

Treadmill Exercise ECG: He managed an above average 15 minutes going to his maximal heart rate of 194 beats per minute. There were no arrhythmias and no ischaemic changes.

Carotid Sinus Massage: Massage of both the right and left carotids did not induce any significant bradycardia.

OPINION

First of all I cannot identify any cardiac problem in (b) (4) and I've reassured him that there's no evidence of any cardiovascular disease.

Figure 211 Cardiologist's Report from IV Study 25506 (Continued)

Secondly, this almost certainly has to be classed as a drug induced effect with a serious adverse effect on the conducting system of the heart.

If you require any further report or details from me please let me know.

Kind regards,

Yours sincerely,

Graham Jackson
CONSULTANT CARDIOLOGIST

5.6.3.2.2 Multiple Rising Oral Dose Study - Study 25501 – June 1993

Study 25501 was a multiple rising dose study to examine the pharmacokinetics in 12 young, healthy, male volunteers using Org 5222 both after a single oral dose (30 mg) and at steady state (5 days, 15 mg twice daily orally).

One subject had asystole for 8.7 seconds with a junctional escape rhythm. Even though this was a single oral dose of 30 mg and the asenapine exposures was low compared to what is typically seen with sublingual dosing, the N-desmethylasenapine exposures were similar to those seen in multiple dose studies with sublingual dosing, (see Table 191). It's noteworthy that the sponsor did not include the data range for the most important study in any of the summary tables for the pharmacokinetics. In addition, the study durations were short, (5 and 6 days), and with a half-life in some cases of a couple of days and likely time dependent kinetics for desmethyl-asenapine the true exposures at steady-state are likely underestimated.

Figure 212 Text from PO MRD Study 25501

A previous study showed that multiple dosing with Org 5222 15mg twice daily for six or more days increased serum alanine aminotransferase and aspartate aminotransferase in three out of six healthy, male subjects.

Figure 213 Text from PO MRD Study 25501 (Continued)

In a previous study at GDRU, intravenous Org 5222 was associated with a cardiac arrest.

After oral administration the bioavailability of Org 5222 is minimal in most subjects.

Figure 214 Conclusions from PO MRD Study 25501

SUMMARY - CONCLUSIONS

After the single, oral dose of Org 5222 to the six subjects of the first group, the study was terminated due to a serious adverse event in one subject.
Two hours, 25 minutes post dosing the subject suffered an 8.7 second asystolic episode followed by junctional escape rhythm until sinus rhythm was restored. A subsequent 24-hour ECG was normal and no abnormalities were detected on echo cardiography. There were no other serious events. In general, subject's supine blood pressure and pulse rate showed only the random fluctuations expected. Apart from the subject who suffered the asystolic episode, there were no clinically significant changes in the 12-lead-ECG recordings following Org 5222 in the 5 other subjects. There were no clinically significant abnormalities on either physical examination, Multistix® urinalysis, clinical chemistry or haematology.

Figure 215 PK from PO MRD Study 25501

Pharmacokinetics

Blood samples were taken at pre-dose, and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 14, 24, 36 and 48 hours after drug administration. Mean values (n=6) for the pharmacokinetic parameters are summarized in the table below.

Summary of the pharmacokinetic data

Parameter	Org 5222				Org 30526			
	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.
C_{max} (pg.ml^{-1})	390	186	144	682	3813	617	3330	4930
t_{max} (h)	1.50	0.89	0.50	3.00	2.86	1.13	1.50	4.00
$AUC_{0-\infty}$ (pg.ml^{-1}.h)	3701	1146	1937	4988	44119	10804	29824	58452
$t_{1/2}$ (h)	7.87	1.96	6.27	11.13	10.54	1.50	8.54	12.11

SD = Standard Deviation; Min. = Minimal value; Max. = Maximal value

Conclusions

The Org 30526 plasma levels were considerably higher than those of Org 5222. The elimination half-life of Org 30526 was slightly, but significantly longer than the half-life of Org 5222. A single oral dose of 30 mg Org 5222 in healthy male subjects was not well tolerated as it produced a serious adverse event in one of the six subjects treated.

Table 191 Comparison of Selected Pharmacokinetic Metrics for Study 22501 and Multiple Dose PK Studies.

Metric	Cmax (ng/mL)			AUCτ[b] (ng/ml x hr^{-1})		
Study	**Study 22501**	**25542**	**41012**	**Study 22501**	**25542**	**41012**
Dosage Regimen	**30 mg PO x 1**	**10 mg SL BID x 6 days**	**10 mg SL BID x 5 days**	**30 mg PO x 1**	**10 mg SL BID x 6 days**	**10 mg SL BID x 5 days**
Asenapine	0.39 ± 0.18 0.14 – 0.68	5.57±2.36 0.94 – 8.81	8.84 2.17 - 15.5	3.7±1.2 1.9 - 5.0	28.2±16.0 6.0 – 53.5	37.3 16.5 - 58.1
Desmethyl-Asenapine	3.8 ± 0.62 3.33 - 4.93	3.14±1.2 0.48 – **5.16**	1.33 1.23 - 1.42	44.1±10.8 29.8 – 58.4	31.8±14.3 4.7 – **53.8**	12.7 11.0 - 14.4

a Text in red was not reported in clinical study report or in any summary tables, had to be extracted from raw data
b For single dose study AUC = AUCinf

5.6.3.2.3 Initial SL Single Rising Dose Study - Study 25509

The following is the background safety information from the initial sublingual dose study with a dose range of 10 - 100 mcg, (see Figure 216 and Figure 217).

What noteworthy about this summary is that it is precludes chronic oral dosing of greater than 4 mg / day due to safety reasons, which is equivalent to 8 – 12 mg /day administered sublingually. In addition it indicates that subjects with high Cmax's have serious AEs, and that interindividual variability results in greater risk in some individuals. Although it's reported that high Cmax's are potentially related to serious AEs individual Cmax's from these studies are not reported and it's unclear if this is related to asenapine or desmethyl-asenapine concentrations.

This was another study that this reviewer was told not to review as it did not include the proposed clinical dose range.

Figure 216 Text from SL SRD Study 25509

1.2 Summary of relevant safety data

Org SL94 appears to be safe in endocrinological, biochemical and haematological terms, however single high doses of Org SL94 may induce cardiovascular adverse experiences in animals and humans.

Single dose i.v. administration of Org SL94 to rats at dose levels up to 21 mg/kg caused no mortalities but was associated with neurological symptoms. The i.v. toxicity studies in rats and dogs with daily administration for 2 weeks at dose levels up to 3 mg/kg caused no overt signs of toxicity. Results from cardiotoxicity studies suggested that Org SL94 may cause postural hypotension at high doses.

In the initial Phase I studies in healthy male volunteers, single oral doses up to 30 mg Org SL94 did not cause any safety problems. In a two week multiple dose study oral doses up to 15 mg twice daily were administered. Time and dose dependent increases in ALT and AST serum levels were observed.

In two subsequent studies with healthy male volunteers, two serious adverse experiences (SAEs) were observed. The first SAE (cardiac arrhythmia - asystole) occurred 15 min after the i.v. infusion of 0.7 mg Org SL94 (given over 30 min), when the subject was asked to sit up. He required brief external cardiac massage and atropine and made a full

Figure 217 Text from SL SRD Study 25509 (Continued)

recovery. He was never unconscious for more than 30 seconds. The second SAE occurred 2 h 35 min after a single oral dose of 30 mg Org SL94 without an obvious precipitating factor. This subject collapsed whilst already sitting and recovered spontaneously. His ECG at the time of the collapse showed a prolonged sinus pause. The pharmacokinetic results revealed large inter-individual variation in oral Org SL94 plasma levels and relatively high C_{max} values were observed in the individuals exhibiting serious adverse events. However, in view of the limited data it is not possible to draw definite conclusions as to the quantitative relationship between C_{max} and the SAE. The oral bioavailability of Org SL94 was calculated to be approximately 1%.

Three Phase II studies have been conducted with orally administered Org SL94 in the treatment of schizophrenic patients. The results indicate that the highest dose applied (4 mg/day) may be considered the minimal effective dose. No safety problems were encountered.

From a safety point of view, chronic administration of doses higher than 4 mg/day is precluded for two reasons: 1) the risk of hepatotoxicity 2) due to the fact that low oral bioavailability predisposes to highly variable plasma levels, patients may be put at increased risk for cardiovascular adverse experiences.

5.6.3.2.4 Pivotal BE Study (b) (4)) - Study A7501015

The sponsor states that there were 12 serious AEs however other than indicating the number of AEs they are not identified in any way. In addition two subjects withdrew due to "hypotension" 2 withdrew consent and 2 for other reasons however they were not identified so even the hypotension cannot be verified.

In the background information the co-sponsor (Pfizer) identified the above cardiac arrhythmias as Neurally Mediated Reflex Bradycardia, (see Figure 218). It is inconceivable to this reviewer how the sponsor can make this statement.

Figure 218 Pfizer's Discussion of Previously Observed Cardiotoxicity – Study A7501015

In early trials, a total of 4 young healthy male volunteers experienced an untoward adverse experience identified as Neurally Mediated Reflex Bradycardia (NMRB) with sinuspause; ie, 1 subject after receiving 0.15 mg asenapine by the sublingual route, 1 after receiving placebo via the sublingual route, 1 after receiving 30 mg via the oral route, and one 45 minutes after receiving 0.7 mg/30 min asenapine intravenous. All occurred after the first dose and after postural challenge. This reflex is seen in 5%-10% of the general population and is benign and self-limiting. It occurs typically secondary to postural changes, younger age, and high vagal tone (low resting heart rate).

5.6.3.2.5 Pivotal BE Study (TBM vs. CTF) - Study A7501016

Study A7501016 was a pivotal bioequivalence study of a To-Be-Marketed formulation using (b) (4) asenapine to the Clinical-Trial-Formulation that used (b) (4) asenapine. The D95 for the (b) (4) (b) (4)

The following is from the clinical study report:

"During telemetry monitoring, 10 subjects experienced bradycardia; eight subjects experienced tachycardia; seven subjects experienced sinus pause, 3 subjects experienced junctional rhythm; and 1 Subject experienced bradycardia with junctional rhythm (Appendix B9.3)."

This was a single dose study with a 5 mg dose that included both healthy men and women. Due to the lack of time further evaluation was not feasible but needs to be done, including evaluation of exposure response.

5.6.3.2.6 Pivotal BE Study – (b) (4) vs. (b) (4) - Study 41026

For study 41026 with single 5 mg doses and low bioavailability in young healthy volunteers the sponsor reported a variety of AEs that may be indicative of cardiotoxicity. The sponsor's descriptions follow: It's unclear if these are the same or different subjects and if they refer to the same AEs or not. A minimum of 4 subjects were effected, 3 with the formulation with the lower bioavailability. Additional review would be needed to clarify this.

'Vital signs: several adverse events regarding vital signs were reported. Three subjects had a vasovagal reflex after treatment with the (b) (4) tablet and one subject after treatment with the (b) (b) (4) tablet.

One subject showed hypotension after treatment with the (b) (4) tablet. Two subjects showed orthostatic hypotension after treatment with the (b) (4) tablet.

One subject (Subject 20) had a neurally mediated reflex bradycardia (without loss of consciousness) in supine position after treatment with the (b) (4) tablet.

Another subject (Subject 23) had a neurally mediated reflex bradycardia (without loss of consciousness) after standing up after treatment with the (b) (4) tablet.'

However, the description of subject 20 is not consistent with othrostatic hypotension.

5.6.3.2.7 Paroxetine Interaction Study - Study 25525

Study 25525 was a multiple dose interaction study of asenapine 5 mg SL BID with paroxetine 20 mg x and dextromethorphan 30 mg. See section 5.5.7.5.2 CYP2D6 Interactions - Study 25525 for a description of the study design.

The following AEs were described:

Besides Afib requiring cardioversion, a myocardial infarction (possibly two), and hepatotoxicity were the most serious AEs observed.

8.7.1.3 Discontinuation Due to Adverse Events

Eight subjects discontinued the trial. Six subjects discontinued due to adverse events.

Sequence B

The main observation is the drop out of subject 29 (101029) a black male due to an SAE (atrial fibrillation), which was considered related to the treatment with asenapine in combination with (steady state concentrations of) paroxetine at Day 13.

Subject 29. At Day 13 (07 November 2005) during Sequence A (Day 8 asenapine day after DM) atrial fibrillation was reported. The subject was dosed at 08:38 hr with 20 mg paroxetine and at 09:08 hr with 5 mg asenapine. Atrial fibrillation started 1 hr and 22 minutes after administration of 5 mg asenapine and was ended after chemical cardioversion with sotalol at 09:27 the next day. The investigator judged the SAE of mild intensity and probable related to either asenapine or paroxetine or the combination of both trial medications. After the trial, the subject visited the cardiologist of the CWZ for several assessments.

The cardiologist concluded that the subject had no structural heart disease (see for more details Appendix A, narratives). In this period (lasting until March 2006) the subject was diagnosed with presumably diabetic ketoacidosis due to new-onset of diabetes mellitus at 02 March 2006. The outcome of the SAE was recovered with sequelae (diabetes). The investigator judged this SAE of severe intensity and unlikely related to asenapine, unlikely related to paroxetine and not related to dextromethorphan administered at Day 11.

*Subject 37 (treatment **sequence B**) showed a vasovagal syncope when he went to the toilet a few minutes prior to placebo dosing. The investigator judged the subject not eligible for participation without knowing he had been given placebo. Therefore, this subject was actually discontinued due to a pre-dose adverse event.* (reviewer's note – this subject had received paroxetine for 1 week and this was two days after dextromethorphan so it was only pre-dose with respect to asenapine).

Sequence A

During **Sequence A**, 4 subjects discontinued the trial due to the occurrence of AEs.

Subject 09 dropped out due to ECG changes (negative T in II, III and AVF, main reason), non-cardiac chest pain, pain between scapulae and shortness of breath at Day 7. (Day 2 of asenapine)

Subject 14 dropped out due to hypertension (154/88 mmHg with a PR of 93 bpm, main reason), mental restlessness, insomnia, intermittent night sweating, emotional lability, fatigue, nightmares, myalgia shoulders and neck and headache at Day 9. (Day 4 of Asenapine)

Subject 08 dropped out at Day 15 due to persistent moderate headache (main reason), drowsiness and intermittent nightmares. (Day 10 of asenapine 1 day after paroxetine day 4 after DM)

Subject 15 dropped out due to elevated ALAT (main reason) and elevated ASAT at Day 15. The ALAT concentration increased to a maximal value of 474 U/L at Day 16 (Upper Normal Limit (ULN): 50 U/L) (day after paroxe Day 4 DM)

Subjects 08 and 15 discontinued dosing with asenapine but completed all other assessments and were not replaced.

Although samples were taken for genotyping, genotyping was not performed.

In addition to these AEs other AEs seen included restless legs syndrome in 54% in the paroxetine arm and in the asenapine Arm diarrhea 71% and agitation 18%

For paroxetine the labeling lists the following AEs (tremor 8%) 2% bradycardia QT prolongation (warning labeling suggests it's due to a DDI with thioridazine. AEs states no clinically significant ECG changes seen but listing of individual AEs by body system lists as rare).

High pre-dose asenapine concentrations are explained as due to carryover due to dextromethorphan but review indicates it may be due to suicide inhibition due to asenapine 2 weeks earlier.

5.6.3.2.8 Imipramine DDI Study - 25526

No serious AEs were listed, however there several cases of prolonged QT as well as elevated triglycerides similar to what was seen in other studies.

In this subject there was a subject who was found unconscious 1.3 days after dosing with imipramine 75 and 10 days after dosing with asenapine. Although it was not ascribed to asenapine the timing is similar to that seen in subject 37 in study 25525 and a drug interaction with one or more other drugs a week or two after a single dose of asenapine cannot be ruled out.

Structurally similar drugs manufactured by the sponsor that cause significant sedation like asenapine are specifically labeled to avoid alcohol and benzodiazepines due to excessive sedation. The manner of the labeling suggests that this was more than class effect labeling.

Figure 219 Text from Imipramine DDI Study 25526

Reason for subject narrative:
Adverse event (syncope e.c.i.).

Demographic data:
Healthy, non-smoking subject

Date of birth	: 13-01-1953
Race	: Caucasian
Sex	: Male
Height	: 186 cm
Weight	: 75,6 kg

Exposure to trial medication:

Drug name and regimen	: Period 1 (Treatment C): A single sublingual dose of placebo asenapine (Org 5222) on 03-OCT-2005. A single sublingual dose of 5 mg asenapine and a single oral dose of 75 mg of imipramine on 04-OCT-2005. Period 2 (Treatment B): A single oral dose of 75 mg imipramine on 11-OCT-2005.
Treatment start	: 03-OCT-2005
Treatment stop	: 11-OCT-2005

Description event:
On Wednesday 12-OCT-2005 (day 2 of the second dosing period, treatment schedule: C, B, A), the subject discontinued the trial due to smoking. Smoking was prohibited during the trial. At screening, he had given incorrect information about his smoking habits.
Before discharge on Day 2, 12-OCT-2005 at 17:00 h, i.e.32.5 hours after dosing of imipramine only, vital signs were normal, and there were no adverse events. The trial CPRM agreed to discharge him on the afternoon of Day 2.

On 14-OCT-2005 investigator was notified that the subject was found unconscious at the Nijmegen train station at about 09:00 h on 13-OCT-2005. Another subject from this same trial reported that subject 08 regained consciousness spontaneously, the exact time is unknown, but within 5 minutes after falling. The subject was transported by ambulance to the Radboud Hospital in Nijmegen. Policemen were involved due to aggressive behaviour of the subject. The ambulance arrived at the emergency department at 09:50 h, the subject was conscious at that time. There is no information available about his state of consciousness during the ambulance ride. The start time of the syncope is 09:00 h, exact stop time unknown. On arrival at the hospital it was documented that the subject was conscious. Therefore, that time was chosen as the stop time of the event syncope. The subject was examined by a physician and released at 12:10 h with the diagnosis: collapse of unknown origin. ECG was normal, and comparable to the ones made at our site. The hospital physician stated that the subject smelled quite a bit, it is not specified which smell it was. As subject had been drinking, it was most probably the smell of alcohol. (On 14-OCT-2005, consent was given to retrieve this information.)

According to subjects' wife, he had called her at around 12:15 h on 13-OCT-2005 to inform her he was coming home. He told her that he had fainted that same morning due to the medication. Since then she had not heard from him and his whereabouts were unknown.

Before noon, on 14-OCT-2005, investigator was informed that subject 08 was again at the Nijmegen train station. He agreed to come to the trial site for medical examination.

Figure 220 Text from Imipramine DDI Study 25526 (Continued)

Subject said he drank a "few" beers, but denied drug abuse. However, we received reliable information that he did indeed use cannabis after discharge.
Subject 08 remembered passing out at the train station on 13-OCT-2005, and waking up in the hospital. He could not recall how and when he left neither the hospital, nor a conversation with the physician about a diagnosis. He recalled walking around town in Nijmegen all day long, feeling "out off the world". He apparently spent the night in a nearby hotel.
He did not go home (as he had promised his wife) because: "He knew he was heading for trouble" because he had to inform her that he was dismissed for non-compliance.

Physical examination was performed; an agitated, drunk man with a few cuts and bruises. He smoked constantly; there were no signs of psychosis or neurologic abnormalities. ECG, standing and supine vital signs were normal, heart rate elevated (98 bpm).
Laboratory results were not clinically relevant abnormal, except for an alcohol promillage of 2.2.
Due to agitation, a urine drug screen was not performed.

In consultation with our independent medical consultant, it was decided that it was not necessary to have this subject evaluated by a psychiatrist.

Conclusion:

- Syncope e.c.i., but most probably due to alcohol intoxication, possibly facilitated by cannabis abuse and imipramine dosing (on 11-OCT-2005 at 08:35)
- In agreement with the trials' CPRM, it was not filed as an SAE as it was not potentially life threatening, nor a prolonged hospitalization
- No reason for suspicion of cardiac of neurologic origin of the syncope
- Relation to the study medication imipramine: doubtful, asenapine: none.

5.6.3.2.9 Other Studies

An additional factor that's worrisome is that a number of subjects are listed in these single dose studies of 5 mg SL tablets as dropouts from the studies due to noncompliance, and in some cases it's clear that these are the subjects with the highest exposures. It's hard to understand how compliance would be an issue with a single dose, and without additional information including inspection of the raw case report forms these subjects should be considered as possibly experiencing serious AEs.

Although the QT Team acknowledged a number of AEs and worrisome indicators in their review including effects on calcium channels which are expected to result in conduction defects, these were not highlighted.

On April 14, 2008 at 3 PM this reviewer spoke with Suchitra Balakrishnan the medical officer on the QT review. She told me she was new and had taken over the QT review from another medical officer Dr. Grant. She had spoken to Dr. Norm Stockbridge and he had told her to only look at the QT review, the Integrated Summary of Clinical Safety and Investigator's Brochure. When I pointed out the serious nature and consequences in the elderly population she stated that she also had concerns. Consequently, I suggested that in the future she might wish to highlight any concerns for us that might need further review as medical officers typically don't review the phase I studies for safety.

She offered to do another review for other than QT effects, however I indicated that this would not be necessary presently but the medical division may decide to request a consult if another review cycle is needed.

Table 192 Summary of Selected Cardiac AEs

Study		Subj	Dose	Time	AE	
25506	IV study	1/2	0.7 mg IV over 30 min	15 min after end of infusion	Repeated Asystole with AV block responsive to Atropine Not vasovagel	Young healthy male. No cardiac illness found
25501	SD	1/6	30 mg PO SD	2.5 hrs	Asystole 8.7 sec with junctional escape rhythm	Young healthy male. No cardiac illness found
A7501015	Pivotal BE study		5 mg		2 subjects with "hypotension"	
A7501016	Pivotal BE study		5 mg	Telemetry monitoring	10 bradycardia 8 tachycardia 7 sinus pause 3 junctional rhythm 1 bradycardi with junctional rhythm	
41026	Pivotal BE Study		5 mg		At least 4 subjects effected Claimed that it's vasovagel orthostatic hypotension in 3 but 1 subject clearly not orthostatic in nature, and no description of another. Thus only 1 conceivably orthostatic.	
25525	Paroxetine DDI Study		5 mg SL BID		Afib requiring cardioversion with sotalol MI's (possibly 2) Hepatotoxicity Hypertension and inc HR	
25526	Imipramine DDI				Collapse and LOC of Unknown origin. Questionable relationship to asenapine, but possible.	
TQT Review					One subject died of cardiac failure in an ongoing trial	
25517						

5.6.3.3 *Agranulocytosis and Pancytopenia*

After finding serious AEs due to drug-drug interactions in clinical pharmacology studies this reviewer checked the deaths (and was going to check the serious AEs) in the overview of clinical safety. In the 'ongoing studies' this reviewer found two deaths with no cause listed and suspicious laboratory values. Figure 221 and Figure 222 show plots of the hematology lab values over time. Based upon visual inspection of the lab sheets it was initially thought that these were potential cases of aplastic anemia, upon plotting the data this needs to be revised to neutropenia with a developing pancytopenia with death likely due to agranulocytosis.

When the number of subjects who have been on drug for 52 weeks or longer are considered, the rough incidence of death due to agranulocytosis is 2 / 626 (or 1 in 313). There are also several other deaths attributed to respiratory arrest and pneumonia that need to be investigated. If these other suspicious deaths are considered it's even higher (~ 1 in 150).

Figure 221 Hematology Values Prior to Death for Subject 132017 -Study P25520

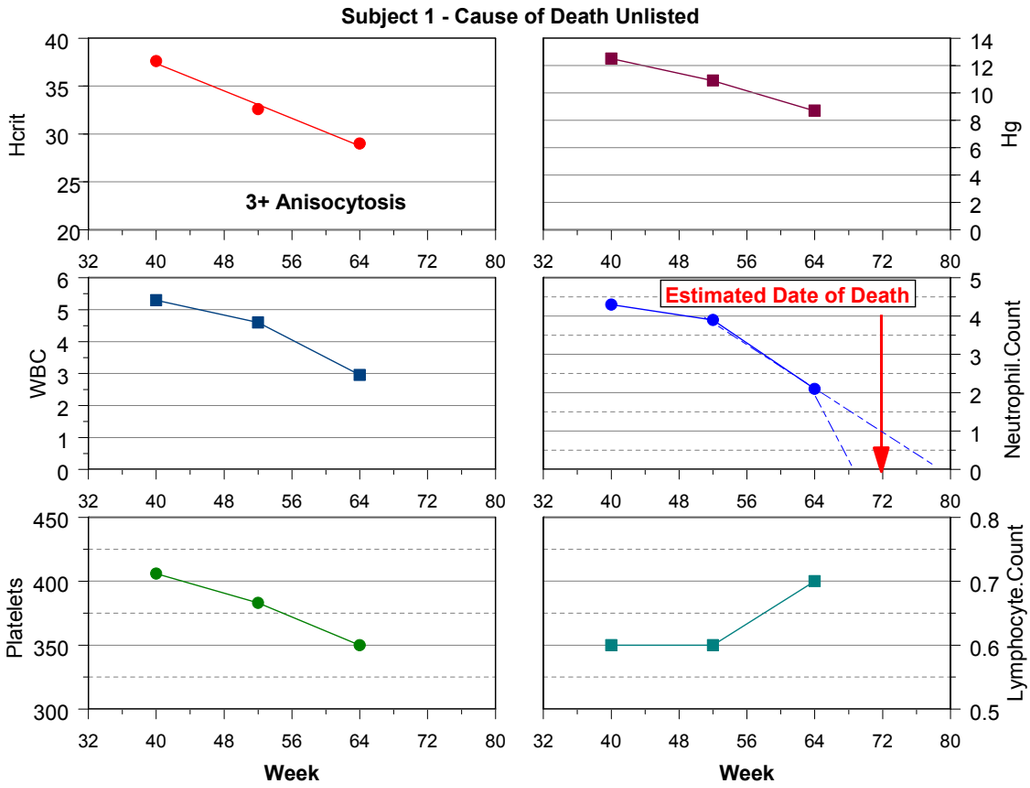
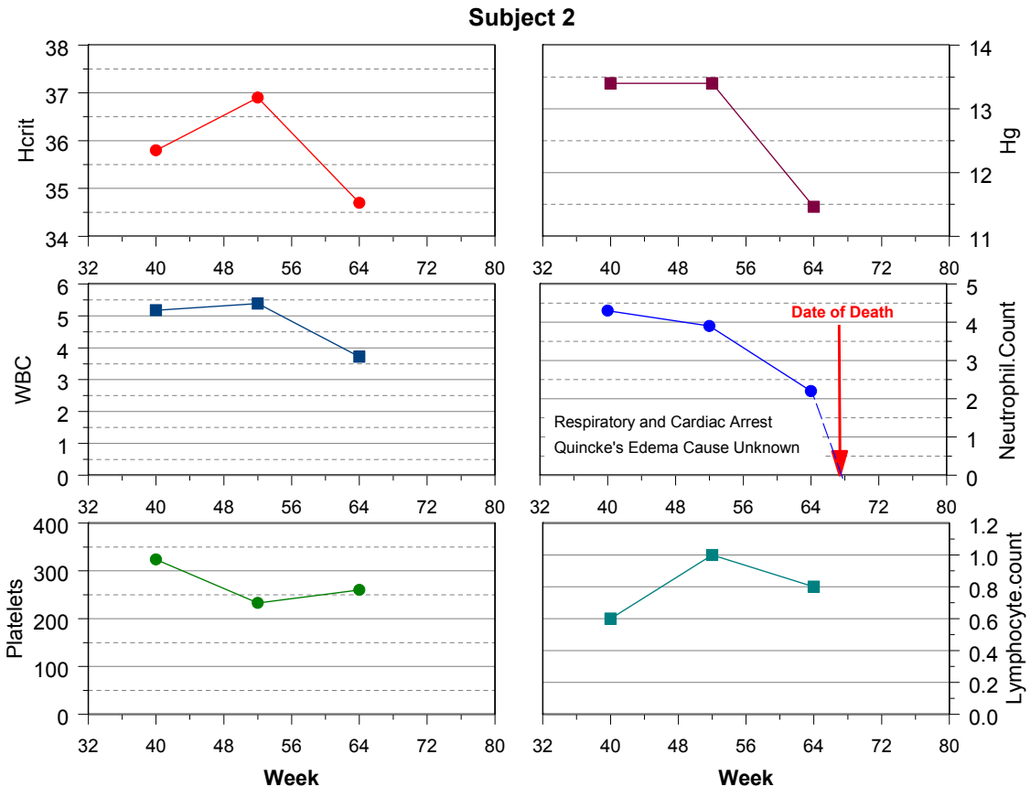


Figure 222 Hematology Values Prior to Death for Subject 241041 -Study P25520



5.6.3.4 Drug-Drug Interactions

Although not addressed in this review it was repeatedly observed that triglyderides were elevated with asenapine. In addition since asenapine has an N-oxide metabolite blood dyscrasias are a possibility. Both of these issues need to be addressed in future review cycles. For blood dyscrasias trends for trends for decreases in hematologic parameters may suggest the possibility and should be looked at.

In study 41009 one subject had an exascerbation of psychosis that may be due to an interaction between asenapine and over-the-counter allergy medications, specifically dextromethorphan and possibly pseudoephedrine. Other possibilities include an exascerbation of psychosis, also possibly due to these OTC drugs beginning prior to the treatment with the investigational agent, combined with use of a subtherapeutic dose or an experimental agent that would be ineffective for this patient.

STUDY AND TREATMENT DATA

Protocol number: 041009
Site Number: 01
Treatment: Org 5222, 10 mg
Test product: Org 5222, 5 mg

Subject number: **0012**
Subject initials: DAP

REASON FOR SUBJECT NARRATIVE SUMMARY

Serious Adverse Event: SAE# 0218-01D **Schizophrenic Reaction** *(Bipolar Schizoaffective Disorder)*

BASELINE DEMOGRAPHIC DATA

Date of birth: 22-Apr-69 (Age: 32 yrs)
Gender: Male
Height: 183 cm
Weight: 87.3 kg

EXPOSURE TO STUDY MEDICATION

Drug name	Total daily dose	Unit	Route	Day start	Day stop	Days on drug
Org 5222	10	mg	SL	24-Jun-01	02-Jul-01	9

DESCRIPTION OF EVENT

This 32-year-old Caucasian male took the study drug from 24-Jun-01 through 02-Jul-01. Current antipsychotic therapy was Geodon™. Prior to enrolment in the study, the subject presented with insomnia and increased anxiety. The symptoms were treated with Ambien® and Ativan®, respectively. Both symptoms continued until the follow-up period. The subject complained of having "racing thoughts" on 29-Jun-01, and on 30-Jun-01 was noted to be hyperverbal. On 01-Jul-01, the subject was reported to be intrusive and unable to maintain personal affairs outside a structured environment. The subject was admitted to the hospital with a diagnosis of bipolar schizoaffective disorder. The following day, the subject completed participation in the trial of Org 5222 and was restarted on Geodon™ at 40 mg BID. Moderate to severe increase in agitation and psychosis were noted in the follow-up period. In addition to Geodon™, treatment included Haldol®, Cogentin® and Depakote®. The event reportedly resolved on July 19, 2001.

ADDITIONAL RELEVANT INFORMATION

None

RELEVANT MEDICAL HISTORY

None

RELEVANT CONCOMITANT MEDICATION

Drug Name	Total Daily dose	Unit	Route	Start Date	Stop Date	Indication
Cardizem® CD	300	mg	PO	??-May-01	Cont	High Blood Pressure
acetylsalicylic acid	2	tab	PO	??-Jun-01	Cont	General body discomfort
ibuprofen	2	tab	PO	??-Apr-01	Cont	General body discomfort
Robitussin®	2	tsp	PO	??-??-1975	Unknown	Seasonal Allergies
Sudafed®	2	tab	PO	??-??-1975	20-Jun-01	Seasonal Allergies

Ativan®	2	mg	PO	23-Jun-01	Cont	Anxiety/Agitation
Ambien®	10	mg	PO	22-Jun-01	Cont	Insomnia
ziprasidone	80	mg	PO	??-Sep-99	21-Jun-01	Schizoaffective Symptoms

OTHER RELEVANT ADVERSE EXPERIENCES

Adverse experience	Day start	Day stop	Intensity	Action	Outcome	Causality
Insomnia	22-Jun-01	17-Jul-01	Moderate	None	Recovered	Unlikely
Increased anxiety	23-Jun-01	19-Jul-01	Moderate	None	Recovered	Unlikely
Racing thoughts	29-Jun-01	17-Jul-01	Moderate	None	Recovered	Unlikely
Hyperverbal	30-Jun-01	17-Jul-01	Moderate	None	Recovered	Unlikely
Increased agitation	14-Jul-01	14-Jul-01	Severe	None	Recovered	Unlikely
Increased psychosis	14-Jul-01	14-Jul-01	Severe	None	Recovered	Unlikely

RELATION TO STUDY DRUG
According to the investigator the event was **unlikely related** to trial medication.

Ziprasidone half-life 9 - 10 hr

There was also a neonatal death and a death due to complications 2 months status post of a hernia repair. No detailed information was submitted and needs to be requested however the possibility of interactions with narcotic analgesics and anesthetic agents needs to be kept in mind and evaluated.

6 Appendices

6.1 Filing Memo

Office of Clinical Pharmacology			
New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA Number	22-177	**Brand Name**	Sycrest®
OCPB Division (I, II, III, IV, V)	I	**Generic Name**	Asenapine Maleate
Medical Division	Psychiatry	**Drug Class**	Antipsychotic
OCPB Reviewer	Ron Kavanagh	**Indication(s)**	Schizophrenia Acute Bipolar I
OCP Team Leader	Ray Baweja	**Dosage Form**	SL Tablet
INDs	51,641	**Dosing Regimen**	BID
Date of Submission	August 31, 2007	**Route of Administration**	Sublingual
Estimated Due Date of OCP Review	March 4, 2008	**Sponsor**	Organon
PDUFA Due Date	June 30, 2004	**Sponsor's Agent**	N/A
Division Due Date		**Priority Classification**	S

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			**Also QBR**
Labeling	**X**			**Structured Product Labeling**
Reference Bioanalytical and Analytical Methods	**X**	16		**10 full 6 partial methods**
I. Clinical Pharmacology				
Mass balance:	**X**	1		
Isozyme characterization:	**X**	13		
Blood/plasma ratio:	**X**	1		
Plasma protein binding:	**X**	3		
Cell Transport:	**X**	1		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	7		
multiple dose:	**X**	4		
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	**X**	1		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**	7		
In-vivo effects of primary drug:	**X**	2		
In-vitro:				
Subpopulation studies -				
ethnicity:	**X**	1		
gender:				
pediatrics:	**X**	1		
geriatrics:	**X**			
renal impairment:	**X**	2		
hepatic impairment:	**X**	2		
PD:				
Phase 2:	**X**	**3**		
Phase 3:				
PK/PD:				

Phase 1 and/or 2, proof of concept:	**X**	7		
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	**X**	2		
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:	**X**	3		
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	1		
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	1		
replicate design; single / multi dose:				
Food-drug interaction studies:	**X**	1		
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies	**X**	**5**		
Genotype/phenotype studies:	**X**	1		
Chronopharmacokinetics				
Enantiomeric Interconversion	**X**	**1**		
Pediatric development plan	**X**	**1**		
Literature References	**X**	**30**		
Total Number of Studies		**>90**		

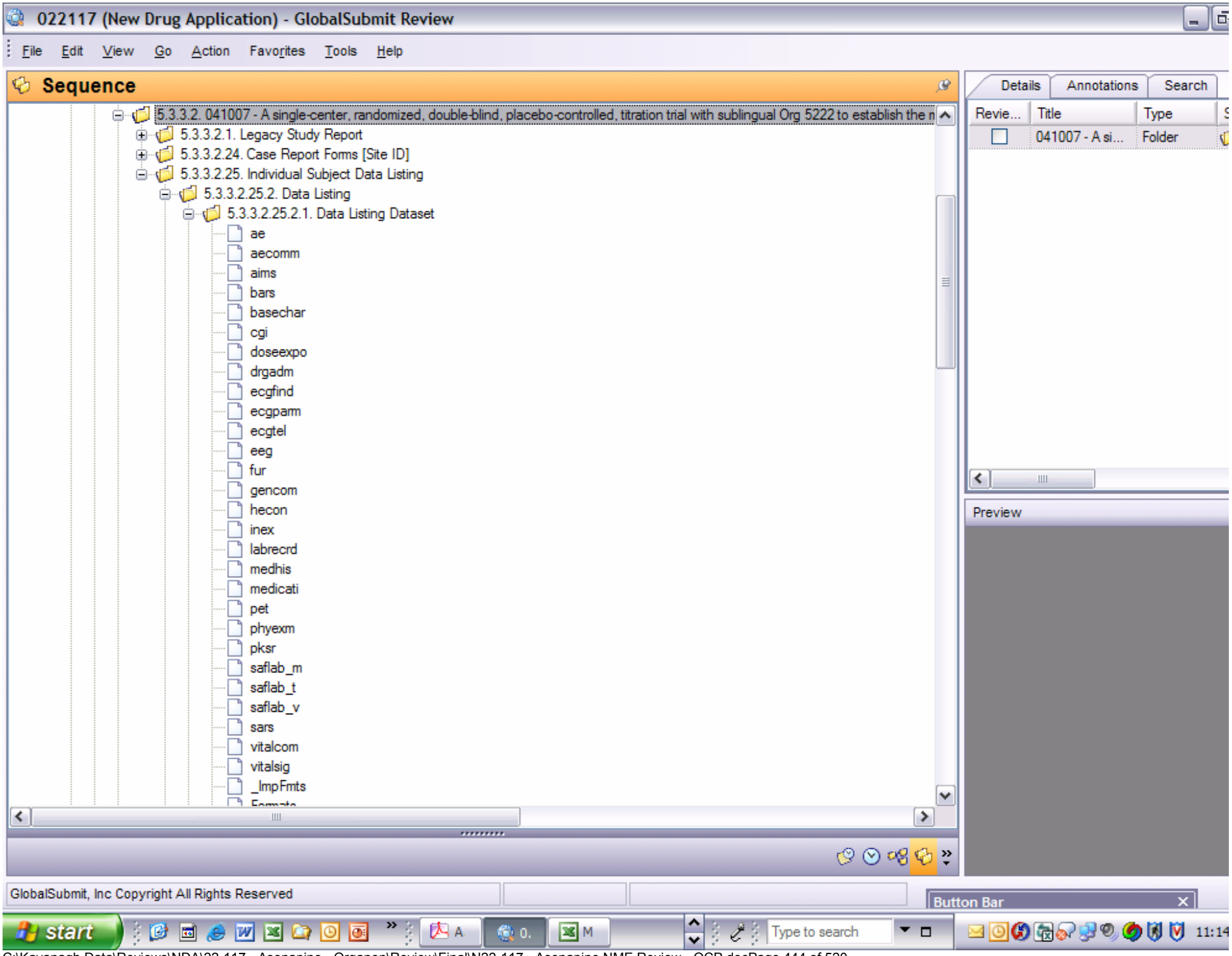
Filability and QBR comments

	"X" if yes	**Comments**
Application filable ?	**X**	
Comments sent to firm ?		
QBR questions (key issues to be considered)	**Gender Effect** **Age Effect** **Effect of Hepatic Impairment.** **Suicidality especially with dose and with maintenance therapy.** **Effect of Smoking. Especially in Bipolar Disorder.** **Minimum Effective Dose especially in bipolar disorder.**	
Other comments or information not included above	Pilot GRMP NDA See Attached Appendices for Comments and Additional Information.	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 22-077, HFD-850 (P. Lee, GobburuJ)
HFD-860 (KavanaghR, UppoorR, BawejaR, M. Mehta)
Psychiatry (KeidrowK, Updegraff), CDR

APPENDIX 1
Table 193

eCTD/GSReview Format	Number of Studies	Comments
Biopharmaceutic		
BA	6	
BE	6	
Bioanalytic	14	
Biomaterials		
Protein Binding	4	
Metabolism	14	
Cell Transport	1	
Pharmacokinetics		
Healthy Subjects	7	
Patients	3	
Intrinsic Factors	6	
Extrinsic Factors	6	
Pop PK	2	
PD & PK/PD	5	
Subtotal	***74***	54,976 Pages
Efficacy and Safety		
Schizophrenia		
Placebo	9	
Active Control no PBO	1	
Uncontrolled	1	
Integrated Study Reports		
ER	1	
ISE	1	
ISS	1	
Other Studies	25	Includes ER and PK Studies
Bipolar		
Placebo	2	
Active Control no PBO	1	
Uncontrolled	0	
Integrated Study Reports		
ER	2	
ISE	1	
ISS	0	
Other	3	
Subtotal	***48***	
Total Number of Studies to Check	**122**	


022117 (New Drug Application) - GlobalSubmit Review
File Edit View Go Action Favorites Tools Help
Sequence
5.3.3.2. 041007 - A single-center, randomized, double-blind, placebo-controlled, titration trial with sublingual Org 5222 to establish the n
5.3.3.2.1. Legacy Study Report
5.3.3.2.24. Case Report Forms [Site ID]
5.3.3.2.25. Individual Subject Data Listing
5.3.3.2.25.2. Data Listing
5.3.3.2.25.2.1. Data Listing Dataset
ae
aecomm
aims
bars
basechar
cgi
doseexpo
drgadm
ecgfind
ecgparm
ecgtel
eeg
fur
gencom
hecon
inex
labrecrd
medhis
medicati
pet
phyexm
pksr
saflab_m
saflab_t
saflab_v
sars
vitalcom
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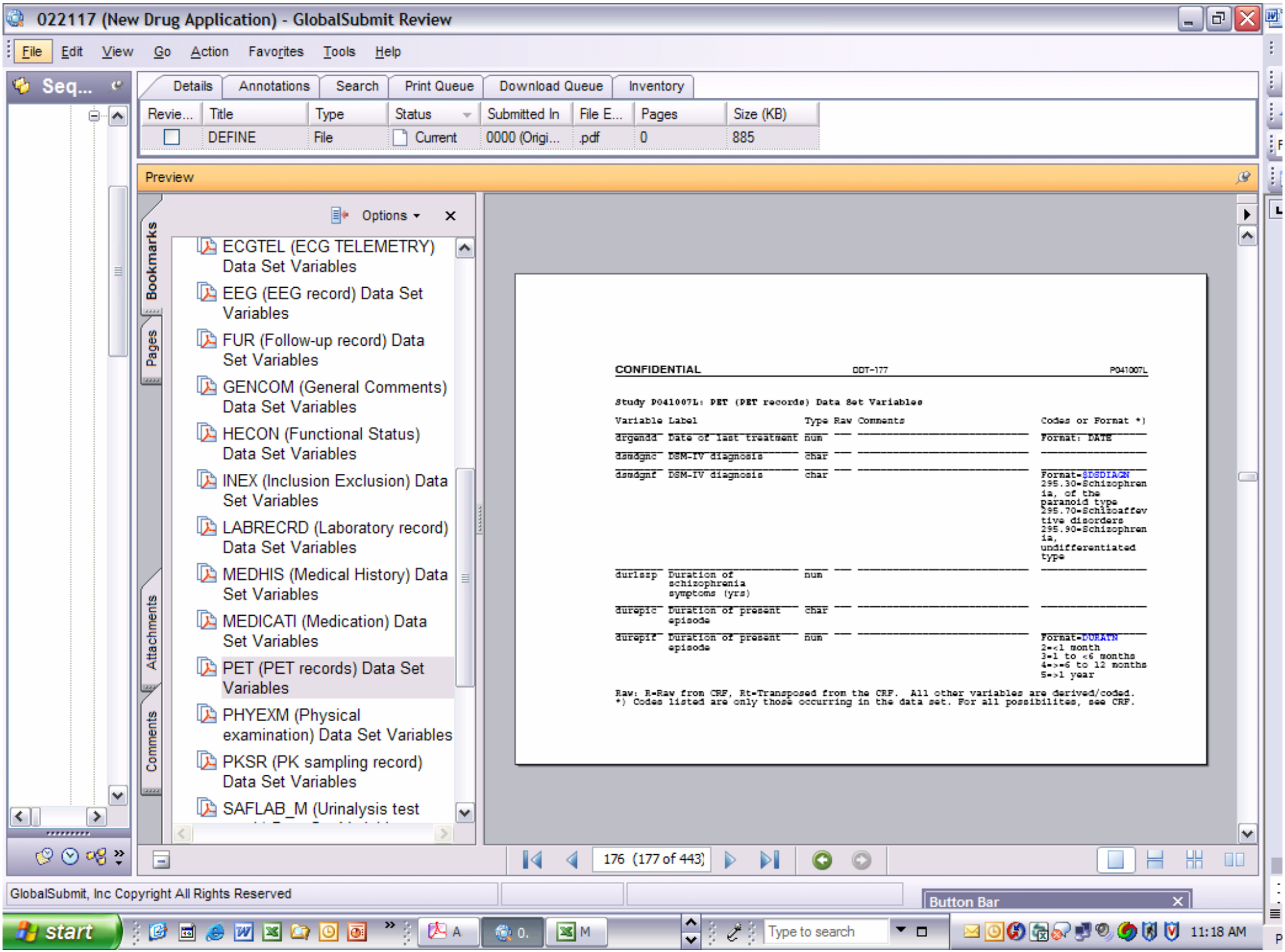
022117 (New Drug Application) - GlobalSubmit Review
File Edit View Go Action Favorites Tools Help
Details Annotations Search Print Queue Download Queue Inventory
Revie... Title Type Status Submitted In File E... Pages Size (KB)
DEFINE File Current 0000 (Origi... .pdf 0 885
Preview
Options
Bookmarks
Pages
Attachments
Comments
ECGTEL (ECG TELEMETRY) Data Set Variables
EEG (EEG record) Data Set Variables
FUR (Follow-up record) Data Set Variables
GENCOM (General Comments) Data Set Variables
HECON (Functional Status) Data Set Variables
INEX (Inclusion Exclusion) Data Set Variables
LABRECRD (Laboratory record) Data Set Variables
MEDHIS (Medical History) Data Set Variables
MEDICATI (Medication) Data Set Variables
PET (PET records) Data Set Variables
PHYEXM (Physical examination) Data Set Variables
PKSR (PK sampling record) Data Set Variables
SAFLAB_M (Urinalysis test
CONFIDENTIAL DDT-177 P041007L
Study P041007L: PET (PET records) Data Set Variables
Variable Label Type Raw Comments Codes or Format *)
drgendd Date of last treatment num Format: DATE
dsmdgnc DSM-IV diagnosis char
dsmdgnf DSM-IV diagnosis char Format-$DSDIAGN 295.30=Schizophrenia, of the paranoid type 295.70=Schizoaffective disorders 295.90=Schizophrenia, undifferentiated type
durlszp Duration of schizophrenia symptoms (yrs) num
durepic Duration of present episode char
durepif Duration of present episode num Format-DURATN 2=<1 month 3=1 to <6 months 4=>=6 to 12 months 5=>1 year
Raw: R=Raw from CRF, Rt=Transposed from the CRF. All other variables are derived/coded.
*) Codes listed are only those occurring in the data set. For all possibilities, see CRF.
176 (177 of 443)
GlobalSubmit, Inc Copyright All Rights Reserved
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11:18 AM

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: **Applicant:** **Stamp Date:**

Drug Name: **NDA Type:**

APPENDIX 2

	Content Parameter	Yes	No	Comment
Criteria for Refusal to File (RTF)				
1	Has the sponsor submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			
2	Has the sponsor provided metabolism and drug-drug interaction information?			
Criteria for Assessing Quality of an NDA				
	Data			
3	Are the data sets, as requested at the earlier meeting (e.g.: Pre-NDA meeting), submitted in the appropriate format (e.g. CDISC)?			
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			
	Studies and Analyses			
5	Has the Sponsor made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			
6	Did the sponsor follow the scientific advice provided regarding matters related to dose selection?			
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?			
8	Is there an adequate attempt by the sponsor to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			
10	Did the sponsor submit all the pediatric exclusivity data, as described in the WR?			
11	Is the appropriate pharmacokinetic information submitted?			

12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			
	General			
13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?			
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?			
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?			
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			
17	Was the translation from another language important or needed for publication?			

Any Additional Comments:

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

APPENDIX 3

Light Yellow not to be reviewed per OCP Management Instructions and Agreed to at November 9, 2007 Planning Meeting.

Light Green – May not need to be reviewed. However this needs to be confirmed.
Tan – Likely will only need superficial review.
Light Blue – Contains significant exposure response data

		N	Cohort						size	Datafiles							
										CDISC		Labeled	Location			Format	
										Any	PK			Raw Data	Comment	Metrics	Summary Stats
Bioanalytic		14															
Plasma & RBC binding		4															
In Vitro Metabolism		14															
Transport Study		1															
Studies With Sublingual Formulation																	
CP	Healthy Vol / Special Pop	29	F	29													
Biopharmaceutic	Particle Size				A7501016	Effect of Particle Size on BA of SL Tabs			922 106 75					T	Found via Hyperlink	T	T
	Organoleptic		(under other schizo ph III)		A7501024	Taste masking			565								
Bioavailability					25533	Absolute BA			375	Y	N	Y	App B	T		Text	T
					041026	Absolute BA											
					25506 (INT00035825)	Absolute BA (Combined 041036 & 25506		Not included in list of Safety Data Base in Summary Section	36 235 (5.3.5.4.1)	N		N	App A	T		Text	T
					041036	BE of Tablets vs. SL		Found in Table of all Clin Trials	555	N		No	App B	T		Text	T

					25537	Effect of Water on BA			2700	Y	N	N	App B	T	By individual	T	T
Bioequivalence					041009	2 way XO of 2 SL forms		Not included in list of Safety Data Base in Summary Section	1228 0113 0123 0083 0488				App B	T		T	T
					25512	3-Way XO sublingual, supralingual, buccal			1082 0133 0172	N	N	Part		Image		Image	Image
					041030	3-Way XO sublingual, supralingual, buccal			2099 0008 0135 0066	Y	N	No		T		T	T
					041014	1 x 15 mg vs. 3 x 5 mg	Not included in list of Safety Data Base in Summary Section		668 398 074	Y (30)				T	By Sequence	T	T
					A7501015	BE of 5 mg SL tabl Pivotal BE Study			1047 0076 0066 105 144			No	Found by hyperlink to BE metric summary table in CSR	T		T	T
SRD S/T					25509	SL 10 – 300 mcg			2474 0153 0124	Y	N			T	Tables and Figures not labeled	T	
MD S/T					25511	150 mcg SL BID			1671 0172 0321	Y	N			T		T	T
MD S/T					25514	200 mcg bid x 2 days then 300 mcg bid x 4.5 days			3193 0239 0218	Y	N			T		T	T
MD S/T					25542	Parallel 0.3 0.6 1 3 mg bid 0.3 1 3 5 mg bid 1 3 5 10 mg BID			1753 0168 0122 0112	Y	N			T		T	T

						1 3 5 10 15 mg bid 2 & 5 mg qd			0149 310								
					041028	SD Enantiomeric Interconversion			532 042 053	Y	N			T		T	T
					25532	MRD & 10 mg mass Bal			612 067 066 136 119	Y	N			T		T	T
Intrinsic Factors					25546	Japanese vs. Caucasian			4008 204 192 193 107 153 414	Y	N			T	Not laid out nice	T	T
					25522	Hepatic Impairment			875 82 66	Y	N			T		T	T
					A7501018	Hepatic Impairment			891 41 36 30 70 52	Y	N			T		T	T
					25521	Renal Impairment			766 82 58	Y	N			T		T	T
					A7501017	Renal Impairment			738 70 68								
Special Pops					A7501022	DB, Rand, Parallel Grp,PBO controlled MD S/T & PK study in Adolescents		1 – 10 mg bid	1131 70 73					No	Stamped Pfizer	NO	NO
Extrinsic Factors					041029	Effect of Food on BA			2141 0008 0134 0057	Y	N	Y	App B	T	T	T	
					25545	Effect of immediate			962	Y	N	N	App B	T	T	T	

						smoking by smokers on BA			0084 0107								
					25525	CYP2D6 DDI DM & Paroxetine			1965 66 69 86 86 76 139 206					T		T	T
					25526	CYP2D6 DDI Imipramine			1746 41 70					T		T	T
					25527	DDI Valproate			1468 59 43 59 31 96					T		T	T
					25528	DDI Induction CBZ			1603 53 58					T		T	T
					25529	DDI Cimetidine			1712 123 190					T		T	T
					041033	DDI 1A2 Fluvox			1254 140 153 184					T		T	T
					25540	Po vs. oral & charcoal			654 86 79 63 114					T		T	T
QTc					A7501001	DB, Parallel QTc Study of Asenapine, Quetiapine, and PBO			4500								
					754-0046	Comparative ER on QTc			72								
					INT00065	ER on QTc											
PD					25510	PET Study			194								

									219 15								
					25516	PET Study			329 132 13								
					86033	PET Study			52 227								
					25503	PET Study			54								
					041023												
	Pxts	8		8	041001	DB, pbo-ctrl MD MTD titration S/T study in subjs with Schizo and Schizoaffective		0.2 – 0.8 mg BID									
					041007	DB, pbo-ctrl MD MTD titration, S/T study in subjs with Schizo and Schizoaffective and a PD-PET subj-study in healthy vols		0.5 – 4.8 mg bid									
					041009	2- way XO rel BA of diff form SL tabs		2.5 mg & 5 mg bid									
					041012	Rand DB PBO Ctrl S.T study		20 mg bid									
					041014	2-way XO rel Bio and Safety Study		3 x 5 mg vs. 1 x 15 mg									
PK/PD					INT 39258	Dose Finding – Dose Response			85								
Ph II/III	Safety / Eff	14	Ph II Schizo		041002	Dose Finding – Dose Response			9363	0.8 mg	Y						
					041004(ext 041502)	Efficacy vs. Risperidone	Pop PK		6190	5 mg bid	Y						
					41502	“			1632	”	N						
					041013	Dose Finding – Dose Response	Ph II PK/PD		5034	1.6 mg? 2.4 mg?	Y						
					INT 00032958	Dose Finding – Dose Response											
					041500			0.2 mg bid 0.4 mg bid	2229		Y	trough					

								0.8 mg bid									
					(ext 041002) 041590 (ext 041500) (ext 041013)												
					041505		PK/PD	1.6 mg 2.4 mg	1884		Y	trough					
			Ph III Schizo Short Term	3	041021		PK/PD	5 mg bid 10 mg bid	4785		Y						
					041022	Vs. Olanzapine	PK/PD	5 mg bid 10 mg bid	4146		Y						
					041023	Efficacy vs. Haldol short	PK/PD	5 mg bid 10 mg bid	5161		Y						
			Ph III Schizo Long Term		25517		PK/PD Pop PK	5 mg bid 10 mg bid Flex dose	4628 18806 23663								
			Bipolor Mania 3 weeks	1	A7501004				2238	Y	Y				Pop PK Intensive Sampling		
			Bipolor Mania 3 weeks	1	A7501005				2155	Y	Y				Pop PK Intensive Sampling		
			Bipolor Mania 9 weeks		A7501006 (extension to the 2 short term studies A7501004 & A7501005)				3143 1037		N						
Pop PK					INT 00036661	Pop PK			228 6								
Pop PK					INT 00063719	Pop PK			63 3								
					INT 00039913	ER Model			56								
					INT 00043090	LOCF vs. MMRM			12								
					INT00039918	M&S ER			98 3								
Ongoing																	
	Schizo	12			25520 (ext 25517)				12								

					25543 25544 (ext 25543); A7501013 A7501014 (ext A7501013) A7501012 A7501021				12 10 13 10 8 5								
					041512 (ext 041021/022)	Long term extension vs. Olanzapine			10								
					041513 (ext 041023)	Long term extension vs. Haldol			7								
	Bipolar				A7501007 (ext A7501006); A7501008 A7501009 (ext A7501008)				12 11 8								
					25501	SD MD Tablets	30 mg		282								
					25506	Absolute BA Tablets			235								
					25507	SD PK Tabs			179								
					85029	SRD S/T Tabs			172								
					85136	RD Study of Tablets			376								
					25504	Efficacy Study Tablets			2135								
					87039	Efficacy Study Tablets			430								
					25505	Efficacy Study Tablets			944								
					CNS-9041	MRD PK tablets in Japanese			90								
					CNS-9141	MRD PK tablets in Japanese			36								
					CNS-9241	MD Parallel pilot efficacy in Japanese Tablets			38								
					041026	Rel BA Tablet vs. SL			235								
Total		**63**															

54 50 other studies

10 6 partials

REPORTS OF BIOANALYTICAL AND ANALYTICAL METHODS FOR HUMAN STUDIES

Protocol No. (Country)	**Trial Design and Objective**	**Treatment Groups**	**Trial Status; Type of Report**	
SDGRR 3569	Validation of the gas chromatographic mass spectrometric assay for the determination of Org 5222 in human plasma	Org 5222	Completed full	136
SDGRR 3570	Validation of the gas chromatographic assay for the determination of Org 30526 in human plasma	Org 30526	Completed full	69
R&DRR NL0012937	Method transfer validation of the GC-MS assay for the determination of Org 5222 in human plasma	Org 5222	Completed full	28
R&DRR NL0039449	Re-validation of the GC-MS assay for the determination of Org 5222 in human plasma	Org 5222	Completed full	21
R&DRR NL0054225	Validation of the LC-MS-MS assay for the determination of asenapine (Org 5222), Org 30526 and Org 31437 in human plasma	Org 5222 Org 30526 Org 31437	Completed full	67
R&DRR NL0061697	Amendment I to R&D RR NL0054255	Org 5222 Org 30526 Org 31437		14
R&DRR NL0058575	Re-validation of the LC-MS-MS assay for the determination of asenapine (Org 5222), Org 30526 and Org 31437 in human plasma	Org 5222 Org 30526 Org 31437		58
R&DRR NL0065058	Amendment I to R&DRR NL0058575	Org 5222 Org 30526 Org 31437		18
R&DRR INT00013367	Amendment II to R&DRR NL0058575	Org 5222 Org 30526 Org 31437		13
R&DRR NL0046846	Cross-validation of the LC-MS-MS assay for the determination of Org 5222 and Org 30526 in human plasma	Org 5222 Org 30526		80
R&DRR INT00003244	Validation of a method for the determination of asenapine-glucuronide (Org 216761-0) in human Li-heparin samples by LC-MS/MS	Org 216761-0		69
R&DRR INT00003248	Validation of a method for the determination of asenapine-glucuronide (Org 216761-0) in human urine samples by LC-MS/MS	Org 216761-0		103
R&DRR INT00006666	Validation of a Method for the Determination of Org 5222 and Org 30526 in Human Urine Samples by LC-MS/MS	Org 5222 Org 30526		131
R&DRR NL00005948	Validation of the LC-MS-MS assay for the determination of asenapine, Org 30526 and Org 214025 in human plasma	Org 5222 Org 30526 Org 214025		79
R&D RR INT00029604	Amendment 1 to NL00005948	Org 5222 Org 30526 Org 214025		

19 in vitro

REPORTS OF STUDIES PERTINENT TO PHARMACOKINETICS USING HUMAN BIOMATERIALS

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	
PLASMA PROTEIN BINDING STUDY REPORTS				
PK	SDG RR 2972	In vitro binding of [3H]-Org 5222 to male rat, dog and human plasma proteins and in vivo plasma protein binding after a single oral dose of [3H]-Org 5222 to male rats	Org 5222	15
PK	DM2005-005222-007	Plasma protein binding of asenapine (Org 5222) and N-desmethyl asenapine (Org 30526) in human, rat, dog, monkey, rabbit and mouse plasma, human alpha1-acid glycoprotein and human serum albumin	Org 5222 Org 30526	30
PK	DM2005-005222-015	Plasma protein binding of 11-hydroxyasenapinesul fate in human, rat and rabbit plasma	Org 214025 (asenapine 11-O-sulfate)	11
PK	R&DRR NL0029630	An in vitro binding study with Org 5222 by mouse, rat, rabbit, dog and human erythrocytes	Org 5222	23

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Trial Status; Type of Report	
REPORTS OF HEPATIC METABOLISM AND DRUG INTERACTIONS STUDIES					
PK	SDGRR 2874	In vitro metabolism of Org 5222 by rat, dog and human hepatic microsomes	Org 5222	Completed full	15
PK	SDGRR 5067	In vitro metabolism of Org 5222 by rat and human hepatocytes	Org 5222	Completed full	15
PK	R&DRR INT00003054	An in vitro metabolism study with Org 5222 by male mouse, rat, rabbit, dog and human liver microsomes	Org 5222	Completed full	33
PK	R&DRR NL0060905	An in vitro metabolism study with Org 5222 by male mouse, rat, dog and human and female rabbit hepatocytes	Org 5222	Completed full	36
PK	DM2006-005222-013	Determination of the Enzyme Kinetics and UGT Involved in the Metabolism of asenapine to the N-Glucuronide Conjugate of asenapine	Org 5222	Completed full	6
PK	R&DRR NL0010293	Characterization of human cytochrome P450 enzymes involved in the in vitro metabolism of Org 5222	substrate = asenapine inhibitor = fluvoxamine, ketoconazole	Completed full	28
PK	R&DRR NL0060848	A second characterization of the human cytochrome P450 enzymes CYP1A2, CYP2B6, CYP2C19, CYP2D6 and CYP3A4 involved in the in vitro metabolism of asenapine (Org 5222)	substrate = asenapine inhibitor = furafylline, orphenadrine, MPEP: 1-(1-methyl-1-phenylethyl)piperidi ne, tranylcypromine, benzylnirvanol, quinidine, ketoconazole	Completed full	37
PK	R&DRR NL0017588	The inhibition of the human cytochrome P450 enzymes CYP1A2 and CYP2D6 by Org 5222 (in vitro)	substrate = CEC: 7-ethoxy-3-cyanocoumarin, AMMC: 3-[2-(N,N-diethyl-N-methylamino)ethyl]-7-	Completed full	29

			methoxy-4-methylcoumarin inhibitor = asenapine, furafylline		
	R&DRR NL0048836	The assessment of the human cytochrome P450 enzyme CYP2D6 with Org 5222 and its metabolites Org 30526 and Org 31438 in vitro"	substrate = AMMC: 3-[2-(N,N-diethyl-N-methylamino)ethyl]-7-methoxy-4-methylcoumarin inhibitor = asenapine, N-desmethyl, N-oxide, quinidine coumarin, DBF: dibenzylfluorescein, MFC: 7-methoxy-4-trifluoromethylcoum arin, BzRes: benzyloxyresorufin, BQ: 7-benzyloxyquinoline		24
	R&DRR NL0050059	The assessment of inhibition of the human cytochrome p450 enzymes with asenapine (Org 5222) and its metabolites Org 30526 and Org 31437 in vitro	inhibitor = asenapine, N-desmethyl, N-oxide, furafylline, tranylcypromine, quercetin, sulfaphenazole, ketoconazole		50
PK	R&DRR NL0013163	The inhibition of the human cytochrome p450 enzymes CYP2C19 and CYP3A4 by Org 5222 (in vitro)	substrate -mephenytoin, testosterone inhibitor - asenapine, tranylcypromine, ketoconazole	Completed full	20
PK	R&DRR NL0050307	The assessment of inhibition of the human cytochrome P450 enzyme CYP2D6 with Org 10968 and Org 10969 (both enantiomers of asenapine (Org 5222)) in vitro	substrate - AMMC: 3-[2-(N,N-diethyl-N-methylamino)ethyl]-7-methoxy-4-methylcoumarin inhibitor - (R,R)-asenapine, (S,S)-asenapine, quinidine	Completed full	21
PK	DM2005-00522-009	Inhibition of P450 enzymes	substrate -phenacetin, bupropion, amodiaquine, diclofenac, S-mephenytoin, dextromethorphan, felodipine, midazolam, testosterone inhibitor - asenapine	Completed full	15
PK	RR 764-04914	Induction potential of asenapine (Org 5222) on Cytochrome P450 enzymes 1A2 and 3A4 in human hepatocytes	substrate: O-deethylase, testosterone 6beta- hydroxylase inducer: asenapine	Completed full	25
REPORTS OF STUDIES USING OTHER HUMAN BIOMATERIALS					
PK	DM2005-005222-008	In Vitro Transport Study of asenapine (ORG-5222) and N- Desmethyl asenapine (ORG-30526) in MDCK and MDR1 Cells	Org 5222 Org 30526	Completed full	22

APPENDIX 4

Size	**# Pages**
Only Phase I Clin Pharm Studies excluding Forrmulations not to be marketed.	74,976
Including ER Studies ~160,000	

21-999	Paliperidone OROS	~ 50,000

Familiar with
Minimal ER
Assistance

NDA	Drug	Start	TL	Duration
21-999	Paliperidone OROS	3.5 months		
22077	Bifeprunox	4 months		

Paliperidone OROS

Familiar with
Assistance Both QT and PM
They started in Feb and earlier not completed until and 8/3

Minimal ER
No Distractions – e.g. holidays, other submissions meetings.

Other

Bifeprunox

Metabolism Extremely Convoluted
Numerous Distractions

Original verbal agreement with timelines I had stipulated that it assumed there would be no meetings or other distractions

Asenapine

Large
Time
Distractions?
New computer format
Extensive ER
Not famailiar with computer software CDISC with take extra time to interpret convert reformat by hand

We can ignore QT because IRT will perform

Good opportunity for:

Training
Drug Disease State Modeling
E

Supposed to decrease Stresss

Reasonable Accommodation

Manuals and Library
Assistance – ER and training
New TL – direct all requests for timelines and status to RB, and not unduly stress.

CDISC Training

If don't follow standards Ireview etc. will spit it out.
Pseudo-CDISC
STDM Speak
2 day class
Chuck Cooper from Biostats: I "need significant support"

Need to include version no.

Shunting of other work Iloperidone & Asenapine who would take the work.

APPENDIX 5

ESTIMATION OF TIME REQUIRED

Comparative Size of NDA

NDA #	Drug	# Pages	Comments
21-999	Paliperidone OROS	~ 50,000	
22-117	Asenapine	74,976	Includes only Phase I Clin Pharm Studies and excludes forrmulations not to be marketed.
		~160,000	Including ER Studies

Prior Benchmarks

NDA	Drug	Duration
21-999	Paliperidone OROS	3.5 months
22077	Bifeprunox	4 months

Comments

Paliperidone OROS

Familiar with
Assistance Both QT and PM
They started in Feb and earlier not completed until and 8/3
Familiar with

Minimal ER
Assistance

Minimal ER
No Distractions – e.g. holidays, other submissions meetings.

Other

Bifeprunox

Metabolism Extremely Convoluted
Numerous Distractions

Original verbal agreement with timelines I had stipulated that it assumed there would be no meetings or other distractions

Asenapine

Large
Time
Distractions?
New computer format

Not famailiar with computer software CDISC with take extra time to interpret convert reformat by hand

Important and Key Features

We can ignore QT because IRT will perform

Extensive ER
Quasi-CDISC Format
Unfamiliar with CDISC format
Do not have any database programming skills needed to manipulate and extract datasets for analysis

Will Need Significant Training and Assistance

Miscoding of Data – e.g. SAEs

APPENDIX 6

Exposure Response Evaluations

EFFICACY

- Extent
- Time Course
- Disease Progression

Schizophrenia

- Short Term
- Long Term

PANSS
+
-

Other measures?

Bipolar

- Short Term
- Long Term

YMRS
Others?

SAFETY

Neuroendocrine
e.g Prolactin, ADH
QT
CV – e.g. orthostatic hypotension
HR

EPS
Tardive Dyskinesia
Akathesia
Pseudo parkinsonism
Acute Dystonia
All EPS

Agitation / Aggression / Suicidality / Self Injurious Behavior

EEG & Sleep Changes

Comments: vs. Active Control

APPENDIX 7 Scoping Meeting

Date: November 16, 2007
Time: 10:00 AM – 11:00 AM
Location: White Oak Rm 3560
Attendees: Ron Kavanagh
Ray Baweja
Ramana Uppoor
Joga Gobburu
Rob Levin
Gwen Zornberg
Mitch Mathis
Tom Laughren

The following issues were discussed:

- **Effect of Bioavailability on Efficacy**

Clinical Division: Concern over differences in bioavailability and efficacy with inadvertent oral (F ≈ 2%) and buccal as compared to sublingual administration (F ≈ 32%) and the effect on efficacy was raised.

OCP:

This reviewer indicated that if efficacy was seen in clinical trials then the effect of bioavailability on efficacy should not be an issue except in certain patients who are predisposed to swallow more drug.

Other issues noted by OCP included:

Smoking
Solubility
Bipolar
10 min wait

Post meeting note: Gender and Food Effect
And toxicity with swallowing

6.2 Mid-cycle Review Meeting

NDA Mid-Cycle Review - OCP Pre-Meeting

NDA:	22-117
Nonproprietary Name:	Asenapine SL Tablets
Submission Date:	August 30, 2007
PDUFA Due Date:	June 30, 2008
Indications:	Schizophrenia Acute manic or mixed episodes associated with bipolar I disorder
Mid-Cycle Review Meeting:	Friday, February 1, 2008
OCP Pre-meeting:	Friday, January 25, 2008
Attendees:	Dr. Ron Kavanagh - Reviewer Dr. Ray Baweja – TL Dr. Mehul Mehta - DD

Safety

Hepatotoxicity

Information from the pop PK analysis resulted in the identification of approximately ½ dz individuals with significantly elevated bilirubins (2 with bili's 2.5 ULN and 5 with bili's 10 x ULN). Most of these cases were associated with the TQT study where higher than anticipated clinical doses are used. Increases in transaminases were also reported in a large fraction of subjects in the early phase I studies with orally administered drug, at even low doses e.g. 1.5 mg. In addition, in the paroxetine DDI interaction study (asenapine 5 mg SL) there was a single individual with increases in transaminases 12x ULN that was followed by an increase in bili 1.7x ULN, i.e. a potential Hy's Law case indicating possible direct hepatotoxicity.

The medical reviewer has been informed of and directed toward all cases identified so far. Formation of an N-oxide metabolite may be the basis for many of these observations. All antipsychotics have a low incidence of cholestatic hepatic injury and the cases of elevated transaminases identified with asenapine so far may be associated with dose and route of administration (high doses result in swallowing of more drug) as well as other factors (e.g. body size, age, gender, and drug interactions). Further review and analysis is needed to determine how best to minimize risk as well as to make an informed risk:benefit analysis, and more information will likely need to be requested from the sponsor in the next few weeks. Thus it is premature to make any recommendations at this time.

Myocardial Infarction

A case of T-wave depression with chest pain temporally associated with asenapine's Tmax suggests the possibility of drug induced MI. (see latest labeling for clozapine).

QT Prolongation

Positive QT study. Maximum reported effect at 10 mg BID [ddQTcF 13.5 (3.9 – 17.1)] with an inverted U dose response. The dose response relationship is likely due to alteration in metabolic profile due to dose dependent first-pass effect.

Diabetes

Onset of diabetes mellitus presenting with ketoacidosis 3 – 4 months S/P asenapine. Although the timing would typically be thought of as arguing against it, delayed onset DM is known to occur, (e.g. pentamidine). However, no acute hypoglycemia was seen as is typically the case with pentamidine.

Suicidality

Preliminary ER analysis indicates that when time of exposure is placebo matched there is no clear difference in either direction from placebo.

Metabolism

Extremely high intrinsic clearance drug

4 Primary metabolic pathways
- N-desmethylation
- N-oxidation
- N-glucuronidation
- 11-oxidation (P450 vs. FMO)

CYP2D6 – Strong inhibitor
- Causes increased exposure to paroxetine (a potent CYP2D6 inhibitor in its own right).
- Average ~20 fold (up to ~45 fold) increase in dextromethorphan in urine (cough/cold products)
- CYP 2D6 PMs – maybe at increased toxicity and as there might be shunting to an N-oxide or other metabolites. Further analysis is needed to work out consequences.
- *In vitro* data indicates that it's a suicide substrate inhibitor, and may be dose and route dependent.

UGT1A4 – polymorphic
- Similar concerns as CYP2D6

CYP1A2 N-oxidation – May be CYP1A2
- Smoking study done in smokers
- Typically exposures to 1A2 drugs higher in women and elderly, however no studies performed in these populations

Clarifying information on structures of metabolites recovered in mass balance study has been requested and needs to be examined when it is eventually submitted

Biopharmaceutics and Route of Administration

Higher Doses – More Swallowed
More first pass effect
Appears to be important for hepatotoxicity

Food effect

High fat meal even 4 hours post dosing results in drop in AUC

Exposure Response

Schizophrenia
- Review not begun
- Appears to be flat dose response; 5 mg BID may be sufficient

Bipolar
- ER analysis indicates efficacy related to disease severity (as expected)
- May need limitation of efficacy claim based on disease severity. (Cut off based on YMRS).
- This may also effect maintainence claim – e.g. limitation to a subpopulation

Studies performed with 10 mg BID. Since efficacy in psychosis maxed out at 5 mg BID and there's a dose related safety issue, therefore limiting the dose should be considered. This may require an additional efficacy study at 5 mg BID.

PET studies

Information suggests old data may have been misinterpreted and may be better biomarker than currently thought. Needs further analysis.

Pop PK

Preliminary review indicates that cofactors used in analysis may not have been obtained at the appropriate time. More detailed analysis still needs to be performed.

Special Populations

Hepatic Impairment

Several fold increased exposures to total drug.
Increases in free drug exposures even higher.

Female

Not examined.

Elderly

Not examined.

Pediatrics

Preliminary report of PK in adolescents submitted with NDA.

As a pediatric indication was not included as part of this submission only a superficial examination of the study was performed to determine if the population was appropriate in order to provide advice to the sponsor as warranted so as to avoid unnecessary delays in the pediatric development program.

Pediatric population studied found to be non-representative of expected population and results of pediatric PK study is biased toward administration of possibly excessive and toxic doses.

Keep away from children due to potential dose related toxicity, (mg/kg basis), until adequate pediatric PK and efficacy studies performed.

6.3 Bioanalytical Assay Method Validation

Table 194 Assay Validation – Asenapine - GC/MS – Assay Method 3569

Laboratory	Scientific Development Group Dept of Drug Metabolism and Kinetics Organon The Netherlands
Method Validation Report Title	Validation of the Gas Chromatographic Mass Spectrometric Assay for the Determination of Org 5222 in Human Plasma
Method Validation Report #	3569
Date	05 December 1994
Analyst(s)	Maastrigt
Method Description	n-hexane Liquid –Liquid extraction.
Method Number	Included. No reference given.
Method Protocol Title	Ibid.
Matrix	Plasma
Analyte	Org 5222
Internal Standard	Org 5033 (different isomer)
Sample Extraction Volume	1 ml/
Injection Volume	
Sample Storage Method	- 20 °C
Structural Model	Linear Model
Error Model	1/ (conc^2)
Software	
Software Validation	
Range	0.02 - 2.0 ng/ml free base
LLOQ	0.02 ng/ml
Bias Overall	0.05 -7.84 0.4 -12.63 2 -4.42
Bias - Intra assay	0.05 -10.47 0.4 -9.1 2 -5.0
Bias - Inter assay	
Overall Precision	0.05 15.3 0.4 15.0 2 13.9
Intra assay Precision	0.05 17.2 0.4 4.5 2 4.0
Inter (Between) assay Precision	
Matrix Effects	*Not tested.*
Selectivity **Endogenous Substances** **Internal Standard** **Metabolites** **Incurred Samples** **OTC Drugs** **Dietary – e.g. Caffeine** **Drugs – Rx**	 Claimed no interference in 6 samples. (Inadequate description.) No interference. No interference with N-oxide. Others not tested. Not Tested.
Stability - Blood	
Stability - Plasma **RT** **Refrigerated** **Long Term (-20 °C)** **Stability Freeze/Thaw**	 Stable 2 weeks. Not Stable at 1 month. Contrary to Claims.
Stability - Extracted **RT** **Refrigerated** **On Machine**	

Table 195 Assay Validation – Asenapine - GC/MS – Assay Method 3570 MN136

Laboratory	Scientific Development Group Dept of Drug Metabolism and Kinetics Organon The Netherlands
Method Validation Report Title	Validation of the Gas Chromatographic Assay for the Determination of Org 30526 in Human Plasma
Method Validation Report #	3570 MN136
Date	December 1994
Analyst(s)	M. Gross
Method Description	SPE
Method Number	
Method Protocol Title	Ibid.
Matrix	Plasma
Analyte	Org 30526 (N-desmethyl)
Internal Standard	Org 30491 (different isomer)
Sample Extraction Volume	1 ml
Injection Volume	
Sample Storage Method	
Structural Model	Quadratic
Error Model	1/ (conc)^2
Software	
Software Validation	
Range	0.2 - 10.0 ng/ml free base
LLOQ	0.2 ng/ml 1.56% 5.9% CV
Bias Overall	0.75 -2.9 2.0 3.3 7.5 -2.4
Bias - Intra assay	0.75 0.4 2.0 4.2 7.5 0.75
Bias - Inter assay	
Overall Precision	0.75 6.3 2.0 6.3 7.5 9.8
Intra assay Precision	0.75 2.7 2.0 7.2 7.5 10.7
Inter (Between) assay Precision	
Matrix Effects	*Not tested.*
Selectivity **Endogenous Substances** **Internal Standard** **Metabolites** **Incurred Samples** **OTC Drugs** **Dietary – e.g. Caffeine** **Drugs – Rx**	Pooled plasma from 6 sources.
Stability - Blood	
Stability - Plasma **RT** **Refrigerated** **Long Term (-20 °C)** **Stability Freeze/Thaw**	2- 3 cycles
Stability - Extracted **RT** **Refrigerated** **On Machine**	

Table 196 Assay Validation – Asenapine - GC/MS – Assay Method NL0039449 (NL0012937)

Laboratory	Not Mentioned.
Method Validation Report Title	A Revalidation of the GC-MS assay for the determination of Org 5222 in human plasma
Method Validation Report #	NL0039449
Date	June 2002
Analyst(s)	
Method Description	Increase in upper limit of assay range.
Method Number	See validation report NL0039449
Method Protocol Title	Ibid.
Matrix	Plasma
Analyte	Org 5222
Internal Standard	Org 5033 (different isomer)
Sample Extraction Volume	
Injection Volume	
Sample Storage Method	
Structural Model	quadratic
Error Model	1/ (conc^2)
Software	
Software Validation	
Range	0.02 – 20.0
LLOQ	0.02 -0.9% CV 6.4%
Bias Overall	0.06 0.1% 0.8 -2.2% 1.6 -5.8% 16 0.5%
Bias - Intra assay	
Bias - Inter assay	
Overall Precision	0.06 13.7% 0.8 11.1% 1.6 7.3% 16 6.8%
Intra assay Precision	
Inter (Between) assay Precision	
Matrix Effects	
Selectivity **Endogenous Substances** **Internal Standard** **Metabolites** **Incurred Samples** **OTC Drugs** **Dietary – e.g. Caffeine** **Drugs – Rx**	
Stability - Blood	
Stability - Plasma **RT** **Refrigerated** **Long Term (-20 °C)** **Stability Freeze/Thaw**	
Stability - Extracted **RT** **Refrigerated** **On Machine**	

Table 197 Assay Validation – Asenapine - GC/MS – Assay Method NL00542055

Laboratory	Organon Walthrop Germany
Method Validation Report Title	Validation of the LC-MS-MS assay for the determination of Asenapine (Org 5222), Org 30526 and Org 31437 in human plasma
Method Validation Report #	NL00542055
Date	May 2004
Analyst(s)	Dingler E
Method Description	
Method Number	See validation report NL0054255
Method Protocol Title	Ibid.
Matrix	Plasma
Analyte	Org 5222 (Asenapine) Org 30526 (N-Desmethyl-asenapine) Org 31437 (Asenapine N-oxide)
Internal Standard	^{13}C-Org 5222 Org 5649 (DeHalogenated N-Desmethyl-asenapine)
Sample Extraction Volume	SPE
Injection Volume	
Sample Storage Method	
Structural Model	quadratic
Error Model	1/ (conc^2)
Software	
Software Validation	
Range	0.1 – 20.0
LLOQ	0.02 -0.9% CV 6.4%
Bias Overall	0.06 0.1% 0.8 -2.2% 1.6 -5.8% 16 0.5%
Bias - Intra assay	
Bias - Inter assay	
Overall Precision	0.06 13.7% 0.8 11.1% 1.6 7.3% 16 6.8%
Intra assay Precision	
Inter (Between) assay Precision	
Matrix Effects	*Ion suppression of greater t*
Selectivity **Endogenous Substances** **Internal Standard** **Metabolites** **Incurred Samples** **OTC Drugs** **Dietary – e.g. Caffeine** **Drugs – Rx**	
Stability - Blood	
Stability - Plasma **RT** **Refrigerated** **Long Term (-20 °C)** **Stability Freeze/Thaw**	
Stability - Extracted **RT** **Refrigerated** **On Machine**	

Claims it's Validated but also states.

"The validation was performed in ten anaytical runs of which five were accepted.
Run 1 – 7 were used before the method was slightly adapted which is described in Amendment I (R&D RR no. NL0053679) to protocol R&D RR no. NL0051303. Run 11, 13, 15 and 16 did not meet the acceptance criteria which can be explained with crosstalk between the samples for run 15. In run 13 the technician spitted a sample over the others. Run 12 was used to determine the stability in processed samples.
All QC samples with a deviation >30% from the nominal value were omitted from statistics.
The results of the validation experiments are tabulated in Table 1 up to Table 10."

Need to come back to.

Table 198 Assay Validation – Asenapine - GC/MS – Assay Method NL0058575

Laboratory	Organon Walthrop Germany
Method Validation Report Title	Re-validation of the LC-MS-MS assay for the determination of Asenapine (Org 5222), Org 30526 and Org 31437 in human plasma – Amendment I
Method Validation Report #	NL0058575
Date	January 2005
Analyst(s)	Dingler E
Method Description	Lowering limit of detection.
Method Number	See validation report NL0054255
Method Protocol Title	Ibid.
Matrix	Plasma
Analyte	Org 5222 (Asenapine) Org 30526 (N-Desmethyl-asenapine) Org 31437 (Asenapine N-oxide)
Internal Standard	^{13}C-Org 5222 Org 5649 (DeHalogenated N-Desmethyl-asenapine)
Sample Extraction Volume	SPE
Injection Volume	
Sample Storage Method	
Structural Model	
Error Model	
Software	
Software Validation	
Range	
LLOQ	
Bias Overall	
Bias - Intra assay	
Bias - Inter assay	
Overall Precision	
Intra assay Precision	
Inter (Between) assay Precision	
Matrix Effects	
Selectivity **Endogenous Substances** **Internal Standard** **Metabolites** **Incurred Samples** **OTC Drugs** **Dietary – e.g. Caffeine** **Drugs – Rx**	
Stability - Blood	
Stability - Plasma **RT** **Refrigerated** **Long Term (-20 °C)** **Stability Freeze/Thaw**	
Stability - Extracted **RT** **Refrigerated** **On Machine**	

Problem 7 validation runs of which 5 were accepted.

Table 199 Assay Validation – Asenapine - GC/MS – Assay Method NL00542055 (NL0061697)

Laboratory	Organon Walthrop Germany
Method Validation Report Title	Validation of the LC-MS-MS assay for the determination of Asenapine (Org 5222), Org 30526 and Org 31437 in human plasma – Amendment I
Method Validation Report #	NL00542055
Date	April 2005
Analyst(s)	Dingler E
Method Description	Addition of Long term stability results Addition of stock solution stability.
Method Number	See validation report NL0054255
Method Protocol Title	Ibid.
Matrix	Plasma
Analyte	Org 5222 (Asenapine) Org 30526 (N-Desmethyl-asenapine) Org 31437 (Asenapine N-oxide)
Internal Standard	^{13}C-Org 5222 Org 5649 (DeHalogenated N-Desmethyl-asenapine)
Sample Extraction Volume	SPE
Injection Volume	
Sample Storage Method	
Structural Model	
Error Model	
Software	
Software Validation	
Range	
LLOQ	
Bias Overall	
Bias - Intra assay	
Bias - Inter assay	
Overall Precision	
Intra assay Precision	
Inter (Between) assay Precision	
Matrix Effects	
Selectivity **Endogenous Substances** **Internal Standard** **Metabolites** **Incurred Samples** **OTC Drugs** **Dietary – e.g. Caffeine** **Drugs – Rx**	
Stability - Blood	
Stability - Plasma **RT** **Refrigerated** **Long Term (-20 °C)** **Stability Freeze/Thaw**	
Stability - Extracted **RT** **Refrigerated** **On Machine**	

Due to confusion regarding the sponsor's validation reports this reviewer stopped reviewing with # TM130 and due to time constraints was unable to finish review of the Assays Validations and the performance of the analytic methods used.

6.4 Identification of Elevated Bilirubins and Medical Reviewer Notification

6.4.1 E-mail Notification and Request to Obtain Lab Records from Sponsor

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From: Kavanagh, Ronald E
Sent: Friday, November 30, 2007 1:27 PM
To: Levin, Robert
Cc: Zornberg, Gwen; Baweja, Raman K; Mathis, Mitchell
Subject: Asenapine - Potential Safety Signal

Bob,

Sorry to make more work for you but I was going through the PET studies yesterday and saw a mention of a dose response for increases in LFTs in their early phase I studies. Also I was looking at the POP PK today and saw the range on Bili's went up to 11 mg/dL. I did a check of the data and found 20 subjects in the studies in the pop PK analysis with Bili's > 1.4 and 6 subjects with bili's of ≥10. This is in the TQT study and they didn't submit any labs with the study report so I've asked Keith to get them for the TQT study. The doses of asenapine in this study was 15 - 20 mg bid but I don't know if these subjects were on asenapine or quetiapine or PBO yet.

There's also a subject with Afib and another with Vtach in that study, and there was a mention of Afib in a healthy vol in another study. (I need to verify which study).

Since the mention of a dose response with LFTs is with the early studies when they were still using oral tabs, swallowing the tabs might be more of a safety issue rather than an efficacy issue due to the high first pass effect.

I'm attaching the information of the subjects from the POPPK analysis.

Have fun.

Ron

<< File: Study ID in Pop PK Analysis.doc >>

<< File: Study ID in Pop PK Analysis.doc >>

Study ID in Pop PK Analysis	Study ID	Study Description	Dose	Subject	Bilirubin
42, 46	ORG25542 ORG25546	RMD MTD	3 – 15 mg BID	1	1.46
42, 46	ORG25542 ORG25546			1	2.28
46	ORG25546	Caucasians & Japanese	10 mg BID	3	1.52
46	ORG25546			10	1.75
46	ORG25546			14	1.7
46	ORG25546			19	2.34
46	ORG25546			25	1.52
46	ORG25546			26	1.64
42	ORG25546			28	1.7
46	ORG25546			31	1.52
42, 46	ORG25542 ORG25546			37	1.46
42,46	ORG25542 ORG25546			37	1.64
46	ORG25546			41	1.52
46	ORG25546			144	1.46
16	A751016	BA particle size	5 mg SL SD	10011009	1.6
15	A751015	BE SL	5 mg SL SD	10011022	1.7
16	A751016	BA particle size	5 mg SL SD	10011058	1.7
15	A751015	BE SL	5 mg SL SD	10011069	1.7
1	A751001	TQT Study	15 - 20 mg BID MD	10050003	10
1				10050006	10
1				10050007	10
1				10050009	11
1				10050010	10
1				10050013	10

TQT study subj with Afib and one with Vtach

Also another study with Afib 25520?

Figure 223 Sponsor's Report of Dose Related Hepatotoxicity in Study SDGRR 2086 (1987) noted in PET Study Report

SDGRR 2086 (1987)

In a multiple dose safety study in healthy male volunteers, four dose levels have been used: 1,5 mg b.i.d.; 5 mg b.i.d.; 10 mg b.i.d. and 15 mg b.i.d. The scheduled duration of each dosing was 14 days. Orally administered Org 5222 15 mg b.i.d. induced time dependent abnormalities in liver function tests, predominantly a rise in plasma ALAT and ASAT levels, in 3 out of 6 subjects starting after 6 days dosing. The abnormalities were reversible and declined, after treatment was stopped on day 8 or 9, to normal levels by day 20 to 27. There are signs of some liver function disturbance in the 10 mg b.i.d. treatment with one out of 6 subjects showing raised plasma ALAT and ASAT levels. One out of 4 subjects in the 5 mg b.i.d. group showed a small increase in the plasma ALAT level. No ALAT or ASAT level changes were observed in the 1,5 mg b.i.d. group. No other effects were found

6.5 Requests to Sponsor

A telephone conference was held with the sponsor on December 5, 2007, regarding clarification and timing of a request for datafiles. In addition the sponsor was requested to provide the chemical structures of all metabolites, along with any codes, (e.g. HPLC-2 U27, F18), their chemical names, and to include the percentage recoveries. The sponsor asked for the reason and this reviewer explained that it was simply to make certain that this reviewer had made assignments correctly and he could not be certain of their accuracy without confirmation. The sponsor agreed to this request, however in their response which was included in the cover letter for Amendement 011 BB submitted December 28, 2007, the sponsor was nonreponsive and simply referred to the reviewer to the same information already provided, (see Figure 224,).

Figure 224 Sponsor's Response to OCP Data Request from Cover Letter of Amendment 011 BB

Please provide chemical structures of metabolites from human in vivo studies including percent recoveries.

Reference is made to the metabolite profiling analysis of the human ADME trial (25532). This analysis is reported in Report INT00003211 titled *Profiling of a metabolism study with [^{11}C]-labelled asenapine in healthy volunteers*. The report was submitted in the NDA as part of Module 4, Section 4.2.2.5 and provides a complete overview of all isolated and identified metabolites of asenapine following sublingual administration, including chemical structures. Recoveries of metabolites were quantitatively assessed in urine and feces and are presented per individual in Table 9-6 and Table 9-7 of this report. A summary of the structures of the major metabolites and the proposed biotransformation scheme of asenapine can be found in Module 2.7.2, Figure 6.

6.6 April 11, 2008 Consult Request from Medical Team Leader

From: Zornberg, Gwen Sent: Fri 4/11/2008 11:03 AM
To: Kavanagh, Ronald E; Baweja, Raman K
Cc: Laughren, Thomas P; Mathis, Mitchell; Kiedrow, Keith; Zornberg, Gwen
Subject: NDA 22117 Asenapine Study A7501022

Dear Ron, Dear Ray,

I am certain that you are aware of this pediatric study for your NDA review, however, to be thorough though for your easy reference, I'm just following up from the wrap-up meeting to give you the study number of the blinded 3- week, pediatric (ages 12-17 years) tolerability, safety, PK study, which was reduced to 10 days after notification form Steve on 7 September 2005 that I had noted in our meeting for easy reference.

Thanks,

Gwen

6.7 Consults

6.7.1 Pharmacometrics Consult

In early November 2007 prior to the scoping meeting a pre-meeting was held with Drs. Kavanagh, Baweja, Uppoor, and Gobburu[14]. Dr. Kavanagh requested assistance from pharmacometrics due to the size and complexity of the NDA and in particular the extensive amount of pharmacometrics submitted including modeling and simulation for drug disease state modeling. Dr. Gobburu declined stating that pharmacometrics did not have the resources however Dr. Uppoor suggested to Dr. Gobburu that this could be revisited at a later date.

6.7.2 Pharmacogenomics Consult

Since none of the samples collected for pharmacogenetics were analyzed and no pharmacogenomic information was submitted a formal consult was not requested. This reviewer however did provide an overview of the possible pharmacogenetic issues to the pharmacogenomic reviewer early in the review cycle and recent publications regarding the pharmacogenomics of agranulocytosis and aplastic anemia in Ashkenazi Jews and Thai with clozapine were presented verbally during the briefing. In addition Dr. Urs Meyers graciously provided comments regarding the high incidendence of agranulocytosis with clozapine in Finland on May 12, 2008 after the OCP briefing.

6.7.3 Required Thorough QT Study Consult

The review of the thorough QT study that was performed by the Interdisciplinary QT team may be found in DFS folder N 022117 N000 30-Aug-2007 in file U:\PDF Reviews\QTIRT. NDA 22117(29Feb08).pdf

[14] Personal files with a formal justification for assistance are dated November 13, 2007 and were begun after the meeting.

6.8 OCP Briefing Slides

N.B. this version of slides contains corrections to slides 10, 13 and 62 requested by OCP management at the briefing. Otherwise slides are unchanged. These corrections include correction of labeling on effect on dextromethorphan and correction of dose correction in total radioactivity calculation (34.3 x from 33 x).

Slide 1

N22-117
Asenapine Sublingual Tablets

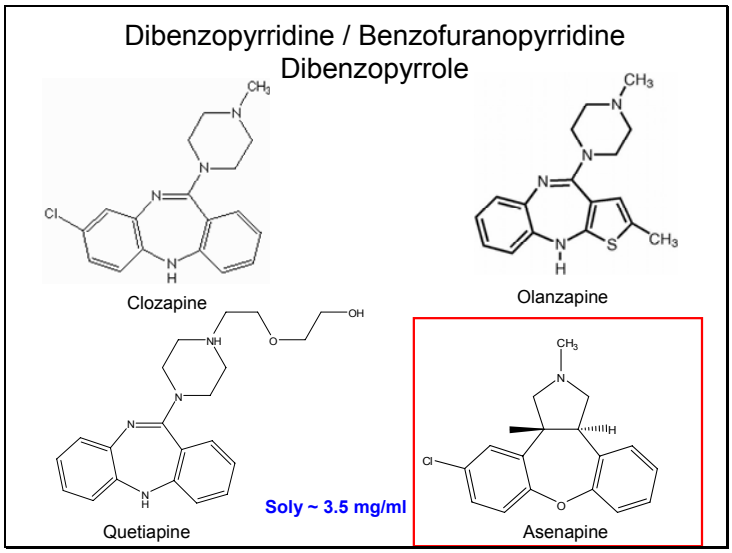
OCP Briefing
Ron Kavanagh, B.S.Pharm,. Pharm.D., Ph.D.
May 12, 2008

Slide 2

Background

- Antipsychotic
  - Very potent receptor antagonist
    - All Dopamine, Serotonin, α-Adrenergic, Histamine tested
- Proposed Indications
  - *"for the treatment of schizophrenia" (Acute 6 weeks)*
  - *For the treatment of acute manic or mixed episodes associated with Bipolar I disorder with or without psychotic features (acute 3 weeks)*
- Proposed Regimens
  - Schizophrenia: 5 mg – 10 mg BID SL
  - Bipolar I: 10 mg BID SL
    - No eating or drinking for 10 minutes after administration

Slide 3



Slide 4

	Olanzapine	Clozapine	Quetiapine
Elderly	BB	BB	BB
Suicidality			BB
Agranulocytosis / Neutropenia		BB	
Allergic rxn			
Cardiac and Circulatory Arrest		BB	
First Degree Heart Block			With OD
Tachycardia			
Heart Failure			
Myocarditis		BB	
Cardiac Arrest			
Extrasystoles			
Afib			
Brady			
CVA			
Liver Injury (LFTs)			
Jaundice			
Seizures		BB	
SJS			X
SIADH			
Wt Gain			
Diabetes			
Dyslipidemias			
Rhabdomyolysis			
Neuroleptic Malignant Syndrome			

BB = Black Box warning.

Except for SJS virtually all AEs are included in labeling for all 3 drugs.

Appears that these are class effects based on structure however they varying in frequency between drugs.

Slide 5

Receptor Class	Receptor Subtype IC50 for binding (nMol/L)							
Serotoninergic	**5-HT1A**	**5-HT1B**	**5-HT2A**	**5-HT2B**	**5-HT2C**	**5-HT5A**	**5-HT6**	**5-HT7**
IC50 nMol/L	2.5	4	0.1	0.2	0.03	1.4	0.3	0.1
Dopaminergic	**D1**	**D2L**	**D2S**	**D3**	**D4**	**D4.7**		
IC50 nMol/L	1.4	1.3	1.4	0.4	1.1			
Alpha Adrenergic	**α1A**	**α2A**	**α2B**	**α2C**				
IC50 nMol/L	1.2	1.1	0.3	1.2				
Muscarinic	**M1**	**M2**	**M3**	**M4**	**M5**			
IC50 nMol/L	8,128	31,623	21,380	9,120	2.5			
Histaminic	**H1**	**H2**						
IC50 nMol/L	1	6.17						
Reuptake Transporters	**SERT**	**NET**	**DAT**					
IC50 nMol/L	4	0.1	0.2					
Beta Adrenergic	?							
IC50 nMol/L								
Nicotinic	?							
IC50 nMol/L								

	Approx Conc / IC_{50}
Red	≥10
Pink	1 to 10
Maroon	0.5 - 1

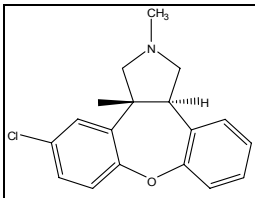
Only Binding
Virtually NO Information on agonism / antagonism

5HT2B – Agonists associated with Phen-fen cardiac valvulopathy

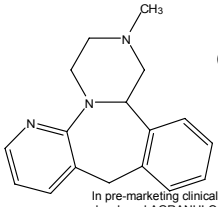
5HT2A and 5HT5A associate with appetitie

D4 associated with akathesia

Slide 6



Asenapine

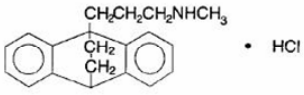


Mirtazapine
(Remeron – Organon 1994)
Antidepressant
excessive sedation with alcohol or benzodiazepines
Agranulocytosis
DDI – MAOIs
CL dec 40% in elderly males
10% in elderly Females

In pre-marketing clinical trials of mirtazapine, 2 out of 2796 patients developed AGRANULOCYTOSIS (absolute neutrophil count (ANC) less than 500 cells/cubic millimeters with symptoms) and 1 patient developed severe NEUTROPENIA (ANC less than 500 cells/cubic millimeters without symptoms).
All 3 patients recovered after mirtazapine was discontinued.
The incidence based on these 3 cases was approximately 1.1 per 1000 patients.

Discontinue therapy if the patient develops a sore throat, fever stomatitis, or signs of infection, along with a low white blood cell (WBC) count.

Other events rarely (incidence less than 1 in 1000 patients) reported in pre-marketing evaluation were PANCYTOPENIA, THROMBOCYTOPENIA, LEUKOPENIA, ANEMIA, LYMPHOCYTOSIS, lymphadenopathy, and petechia (Prod Info Remeron(R), 02a).

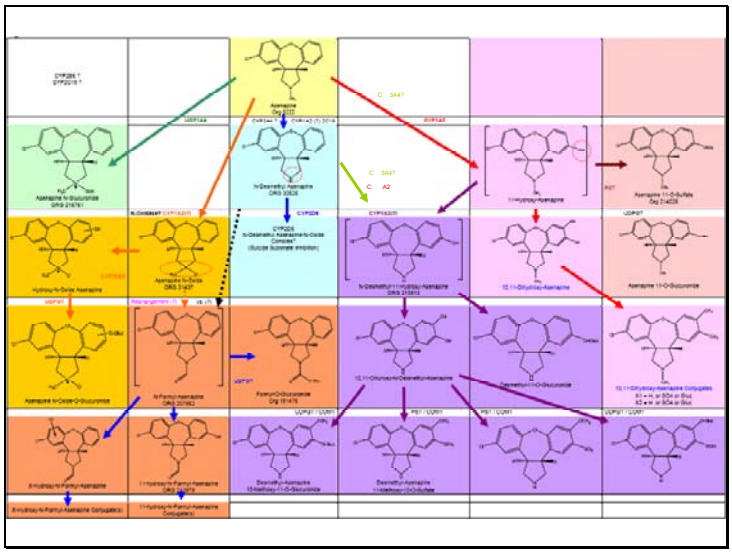


Maprotiline - Ludiomil – Ciba Geigy

Extreme caution should be used when this drug is given to:
patients with a history of myocardial infarction; a history or presence of cardiovascular disease because of the possibility of conduction defects, arrhythmias, myocardial infarction, strokes and tachycardia.
Agranulocytosis
CYP2D6 MAOIs

Ludiomil because of case of possible DDI with CHF

Slide 7



Olanapine formyl metabolite via hydroxyl intermediate

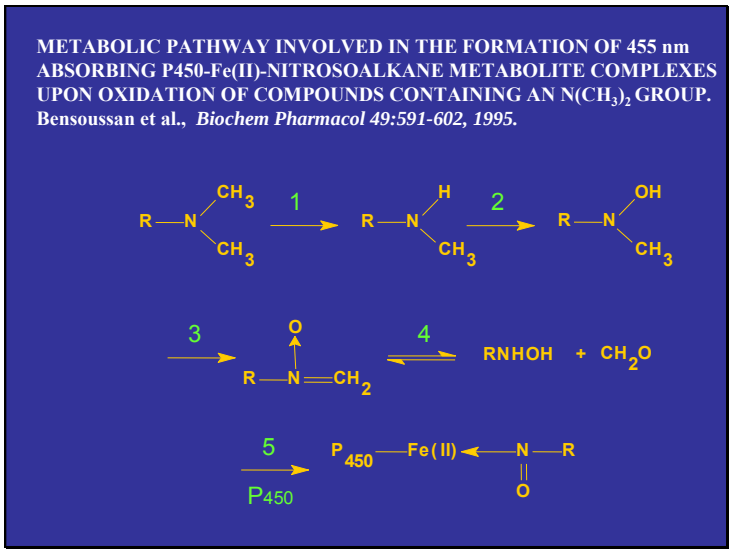
Slide 8

Table 1 Summary of Results of *In Vitro* Cytochrome P450 Inhibition Studies with Asenapine and Selected Metabolites

Study	Date	Test System	Isozyme	Inhibitor	Ki	Claimed Type of Inhibition
NL0017588	Dec 1999	Supersomes	1A2	Asenapine	2.6 µMol	Competitive
			2D6		6.76 nMol	Competitive
NL0013163	April 1999	Supersomes	2C19	Asenapine	25.18	Uncompetitive
			3A4 (a) 3A4 (b)		51.4 125.59	Mixed-competitive ? ?
NL0048836	Aug 2003	Supersomes		Asenapine	15.7 nMol	Competitive
			2D6	30626 N-Desmethyl	62.08 nMol	Noncompetitive
				31437 N-Oxide	82.82 nMol	Competitive
NL0050059	Oct 2003	Supersomes	1A2	Asenapine (N.B. CYP2D6 not studied)	1.5 µMol	Competitive
			2C8		350.44 µMol	Noncompetitive
			2C9		105.10 µMol	Uncompetitive
			2C19		2.0 µMol	Competitive
			3A4 (1)		33.24 µMol	Noncompetitive
			1A2	30626 N-Desmethyl-Asenapine (N.B. CYP2D6 not studied)	1.4 µMol	Noncompetitive
			2A6		70.31 µMol	Competitive
			2C8		80.33 µMol	Noncompetitive
			2C9		172.34 µMol	Noncompetitive
			2C19		1.78 µMol	Competitive
			3A4 (1)		3.53 µMol	Competitive
			1A2	31437 N-oxide (N.B. CYP2D6 not studied)	No inhibition	
			2A6			
			2C8			
			2C9			
			2C19			
			3A4 (1)			
			3A4 (2)			
NL0060807	Oct 2003	Supersomes	2D6	10650 N(2)-Oxide	28.72 nMol	Competitive
			2D6	10650 N(2)-Oxide	12.40 nMol	Competitive
DM2006-005222-000	Dec 2006	Pooled Human Liver Microsomes (HLM)	CYP1A2	Asenapine	0.9 µMol*	
			CYP2B6		> 30 µMol*	
			CYP2C8		> 30 µMol*	
			CYP2C9		> 30 µMol*	
			CYP2C19		> 30 µMol*	
			CYP2D6		44 nMol*	
			CYP3A		> 30 µMol*	
			CYP3A		> 30 µMol*	

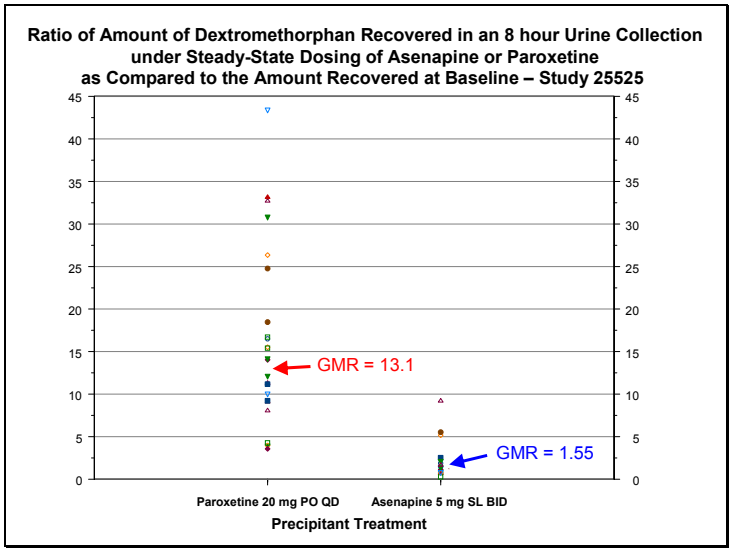
a IC50

Slide 9

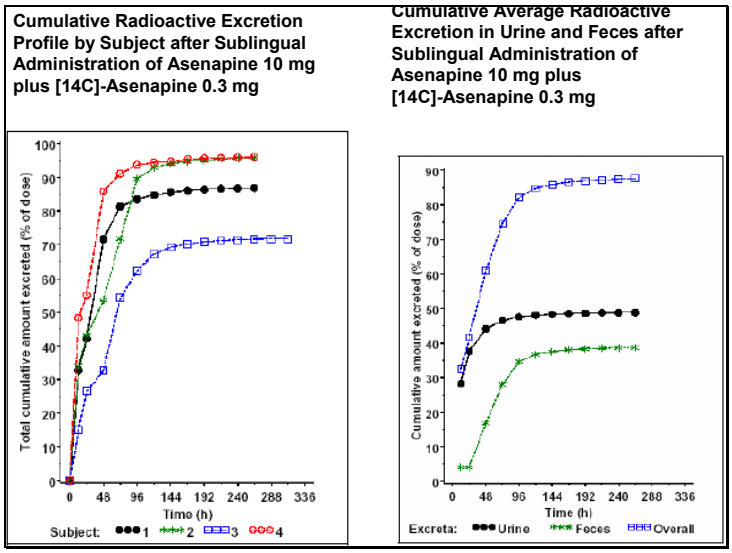


From FDA presentation 1999

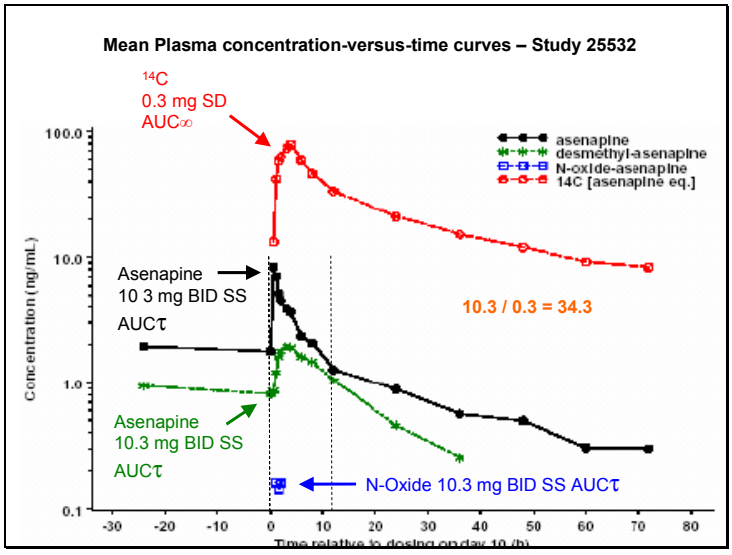
Slide 10



Slide 11



Slide 12



Slide 13

Table 1 Plasma Exposures to Asenapine and Selected Metabolites Relative to Total ^{14}C Radioactivity after Asenapine 10 mg and 0.3 mg 14-C-Asenapine at Steady-State - Study 25532

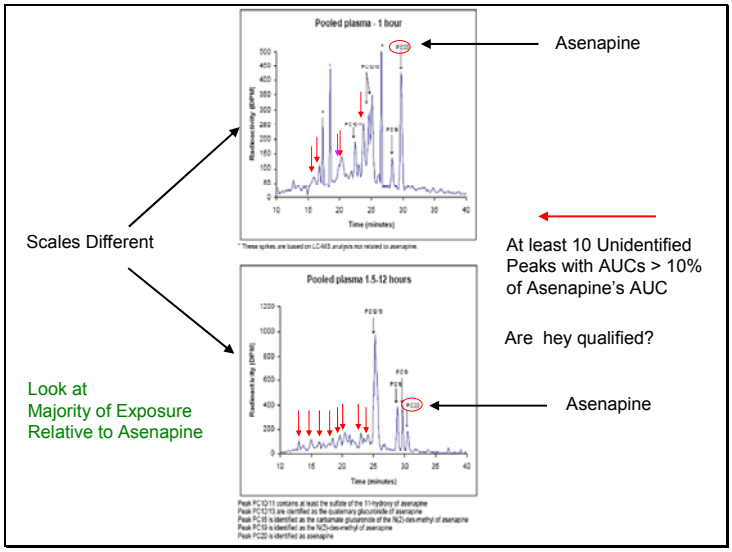
Dose		10.3 mg			0.3 mg	10.3 mg	
Metric	Subject	Asenapine	Desmethyl – Asenapine	Asenapine N–oxide	^{14}C [asenapine equivalents]	Dose Normalized ^{14}C [asenapine equivalents]	% extrap
AUCτ [a] (ng/mL x hr^{-1})	1	33.3	12.8	0.2	1523.2	52297	11.5
	2	27.8	13.6	0.9	1282.6	44036	25.6
	3	50.6	27.7	0.7	1952.8	67046	16.5
	4	35.7	17.7	0.6	1470.0	50470	8.5
Fraction of ^{14}C (%)	1	2.2	0.8	0.01	–	–	–
	2	2.2	1.1	0.07	–	–	–
	3	2.6	1.4	0.04	–	–	–
	4	2.4	1.2	0.04	–	–	–
	Mean[b]	2.3	1.1	0.04	–	–	–
Fraction of Dose Normalized ^{14}C (%)	1	0.06	0.02	0.000	–	–	–
	2	0.06	0.03	0.002	–	–	–
	3	0.08	0.04	0.001	–	–	–
	4	0.07	0.04	0.001	–	–	–
	Mean[c]	0.067	0.032	0.001	–	–	–

Total 0.1%

99.9% of Circulating Radioactivity Unidentified

Even if only look at unnormalized data 96.6% unidentified

Slide 14



Slide 15

Possible 11-Hydoxylation
17% - 27% Mixed
Can't Identify Relative Amounts

Possible N-Desmethylation
Based on Lilly Olanzapine Publication
Formyl Metabolite may be formed via hydroxylation and not desmethylation
Only 3% – 4% definitively via desmethylation

12%% – 21% definitively via glucuronidation

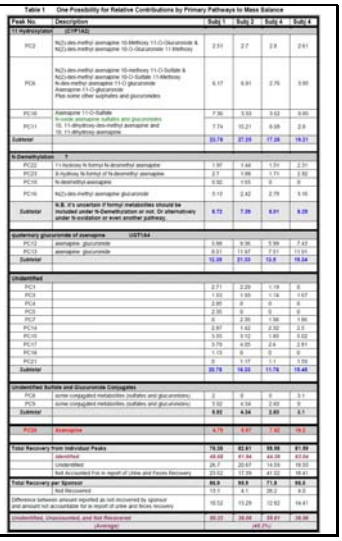
12% - 21% not identified

3% - 6% Mixture of Conjugates

Unchanged Asenapine 5% - 16%

17.2% - 33.5% Identified

64.5% - 82.8% Unknown



Slide 16

Dose and Time Dependent Drug Induced Liver Injury*

***Oral* Multiple Rising Dose PK S/T Study – Feb 1988**

Group No.	Subject No & Initials	Dose	Abnormal Tests	Day of Onset of rise	Time of Peak of rise	Day of 1st subsequent normal value	Severity	
II	14.JT	3 mg bd	ALT	10	10	14	++	1/ 4
III	18.A3	10 mg bd	ALT	10	11	21	++	1/ 4
			AST	10	11	13	+	
IIIA	101.PB	20 mg bd	T.bili	2 & 10	2 & 10	5 & 14	+ & +	
	102.TT	Placebo	Alk Phos	Raised at screening and throughout			+	1-2 / 6
			ALT	14	14	21	+	
	104.HB	20 mg bd	ALT	10	15	-	++	
			AST	0	2 & 14	5 & 21	+	
IV	28.DG	30 mg bd	ALT	9	9	-	+++	
			AST	9	9	- 3.75x ULN	+++	
	29.AM	30 mg bd	ALT	0	12	15	+++	3 / 6
			AST	10	12	14 2x ULN	+	
			GGT	0	6	15	+	
	30.NB	30 mg bd	ALT	6	11	- 8.33x ULN	+++	
			AST	6	9	17	+++	

\+ = 0-49%
++ = 50-99%
+++ = 100%+

9 of 20 given asenapine had elevated LFTs

PK included in study design but not reported.

* D LI – differentiated from hepatotoxicity by increase in bilirubin indicating end-stage injury

Slide 17

Other Signals - DILI

- BE study 41026 – (b) (4) Tab
  - Inc LFTs star ing day 2 (synopsis)
  - Study Report Available only on request
- Paroxetine Interaction Study
  - (Asenapine 5 mg BID)
  - 4 subjects Inc. LFTs
    - 2 after single dose of paroxetine added
    - 1 after 3 days of asenapine
    - 1 inc AST after 6 days Rx; ALT Max 9.5 x ULN; declined to WNL 8 days after d/c
- BE Study – Different (b) (4)
- TQT Study
  - Pop PK study reported 6 subjects wi h Total Bilirubin ≥ 10 mg/dL
  - CSR only reports summary statistics for labs prior to & after Rx (how long?)
  - Labs during Rx note reported

Slide 18

Asystole with 0.7 mg IV over 30 minutes

Dec 1991

Cardiac investigations - including a 24 hour Holter ECG, echocardiogram, exercise ECG and carotid sinus massage - revealed no cardiac pathology that may have predisposed to the event.

Org 5222 has alpha-blocking activity. It is possible that the drug aggravated hypotension (during sitting) and this precipitated an inappropriate vagal response in a vagotonic (athletic) subject. However, this does not adequately explain the persistence of the sinus arrest and the lack of response to lying supine.

Secondly, this almost certainly has to be classed as a drug induced effect with a serious adverse effect on the conducting system of the heart.

If you require any further report or details from me please let me know.

Kind regards,

Yours sincerely,

Graham Jackson
CONSULTANT CARDIOLOGIST

$Fabs^{SL} \approx 0.35$
0.7 mg IV ≈ 2.1 mg SL

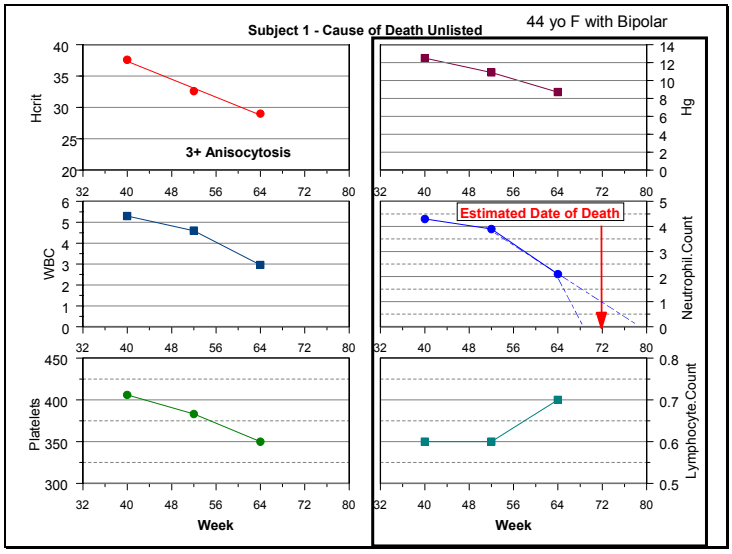
Slide 19

Other Cardiac Safety Signals

- Study 25509
  - sponsor indicates that the asenapine is unsafe at drug exposures obtained with clinical dosages and due to cardiotoxicity and direct hepatotoxicity and should not be dosed chronically at greater than 4 mg daily
- PO MRD Study
  - 1 subj with asystole for 8.7 seconds with a junctional escape rhythm with single 30 mg dose (~ 3 – 10 mg SL)
- 5 mg SD Pivotal BE Study – (b) (4)
  - *20 of 35 healthy subjects had observed cardiac effects on telemetry*
  - 10 subjects experienced bradycardia, 8 tachycardia, 7 sinus pause, 3 junctional escape rhythms, and 1 bradycardia with junctional rhythm
- 5 mg SD Pivotal BE Study – Direct Compression vs. Lyophilized
  - *"One subject (Subject 20) had a neurally mediated reflex bradyca without sciousness) in supine position after treatment with the (b) t (b) (4) n tablet."*
- Paroxetine nteraction Study (5 mg BID)
  - Afib 1 5 hr post dose requiring sotalol for cardioversion 24 hours later
  - Subject 09 dropped out due to ECG changes (negative T in II, III and AVF, main reason), "non-cardiac" chest pain, pain between scapulae and shortness of breath at Day 7. (Day 2 of asenapine)
- MI in Safety Database
- Study 246021
  - Death due to cardiac failure 2 months after maprotiline was added.

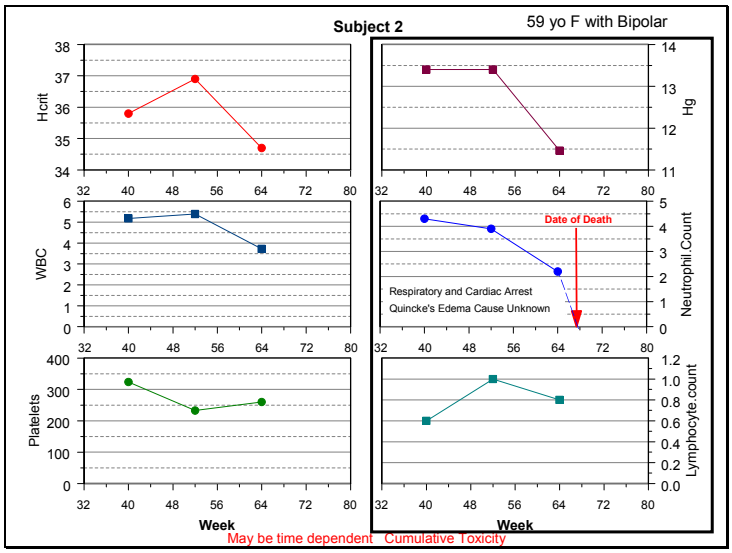
This does not include the cases of cardiac effects in the safety data base from the phase III trials and vica versa (except for MI as noted).

Slide 20



Based on initial lab sheets thought that might be aplastic anemia, however after plotting it appears platelets might not have been dropping fast enough, however microhemorrhages were noted in the brain on autopsy. Consequently this is definitely neutropenia with RBC anemia, with presumptive death due to agranulocytosis and possible aplastic anemia.

Slide 21



Slide 22

Suicidality in Acute Psychosis in Schizophrentics

Week	1	2	3	4	5	6	Total
Placebo	N 503	N 439	N 372	N 301	N 263	N 233	N 503
Suicidal and self−injurious behaviours NEC	1 (0.2)	–	1 (0.3)	2 (0.7)	–	1 (0.4)	5 (1.0)
Suicidal ideation	1 (0.2)	–	1 (0.3)	2 (0.7)	–	–	4 (0.8)
Suicide attempt	–	–	–	–	–	2 (0.9)	2 (0.4)
Total	**2 (0.4)**	–	**2 (0.5)**	**4 (1.3)**	–	**3 (1.3)**	**11 (2.2)**
Asenapine 5 mg BID (fixed)	N 274	N 247	N 215	N 186	N 167	N 159	N 274
Suicidal and self−injurious behaviours NEC	–	–	–	–	2 (1.2)	–	2 (1.2)
Suicidal Ideation	–	–	–	–	1 (0.6)	–	1 (0.36)
Suicide attempt	–	–	–	–	1 (0.6)	1 (0.6)	2 (1.2)
Total	–	–	–	–	**4 (2.4)**	**1 (0.6)**	**3 (1.1)**
Asenapine 10 mg BID (fixed)	N 274	N 208	N 183	N 147	N 132	N 126	N 274
Suicidal and self−injurious behaviours NEC	–	–	–	–	1 (0.8)	–	1 (0.8)
Se f−injurious ideation	–	–	–	–	1 (0.8)	–	1 (0.8)
Total	–	–	–	–	**2 (1.5)**	–	**2 (0.73)**
Asenapine 5 10 mg BID (fixed & Flexible)	N 870	N 758	N 663	N 529	N 455	N 424	N 870
Suicidal and self−injurious behaviours NEC	1 (0.1)	–	1 (0.2)	2 (0.4)	3 (0.7)	1 (0.2)	8/870 (0.92%)
Se f−injurious ideation	–	–	–	–	1 (0.2)	–	1 (0.1)
Intentional self−injury	–	–	1 (0.2)	–	–	–	1 (0.1)
Suicidal ideation	1 (0.1)	–	–	2 (0.4)	1 (0.2)	1 (0.2)	5 (0.6)
Suicide attempt	–	–	–	–	1 (0.2)	1 (0.2)	2 (0.2)
Total	**2 (0.2)**	–	**2 (0.3)**	**4 (0.8)**	**6 (1.32)**	**3 (0.7)**	**17 (2.0%)**
Olanzapine 10−20 mg QD	N 194	N 161	N 146	N 124	N 110	N 102	N 194
Suicidal and self−injurious behaviours NEC	–	–	–	1 (0.8)	–	–	1 (0.8)
Se f−injurious ideation	–	–	–	–	1 (0.8)	–	1 (0.8)
Suicidal ideation	–	–	–	1 (0.8)	–	–	1 (0.8)
Total	–	–	–	**2 (1.6)**	**1 (0.9)**	–	**3 (1.5)**

Slide 23

Prevalence of AEs Indicative of Suicidality over Time by Treatment in Acute Bipolar I Trials During Inpatient Period

	Week 1	Week 2	Week 3	Total Weeks 1 3
Placebo	N 203	N 166	N 131	203
Suicidal and self−injurious behaviours NEC				
Se f−injurious ideation				
Intentional self−injury				
Suicidal ideation				
Suicide a tempt				
Completed Suicide				
Total				0 (0.0)
All Asenapine 5−10 mg BID (fixed and flexiible)	N 379	N 317	N 260	379
Suicidal and self−injurious behaviours NEC				
Se f−injurious ideation				
Intentional self−injury		1 (0.3)	1 (0.4)	2 (0.53%)
Suicidal Ideation			1 (0.4)	
Suicide a tempt				
Completed Suicide		1 (0.3)		
Total		2	2	4 (1.06%)
Olanzapine 5−20 mg QD	N 394	N 358	N 323	394
Suicidal and self−injurious behaviours NEC		2 (0.6)		2 (0.51%)
Se f−injurious ideation				
Intentional self−injury				
Suicidal ideation				
Suicide a tempt		1 (0.3)		
Completed Suicide		1 (0.3)		
Total		4		4 (1.02%)

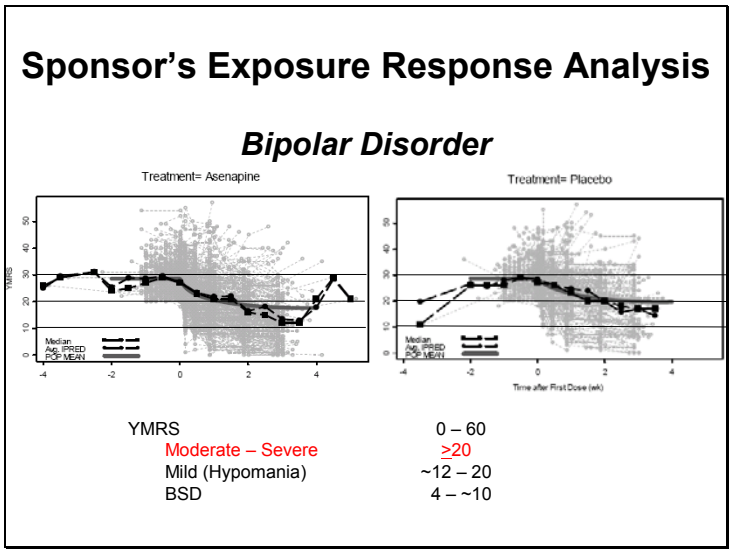
Slide 24

Safety Summary

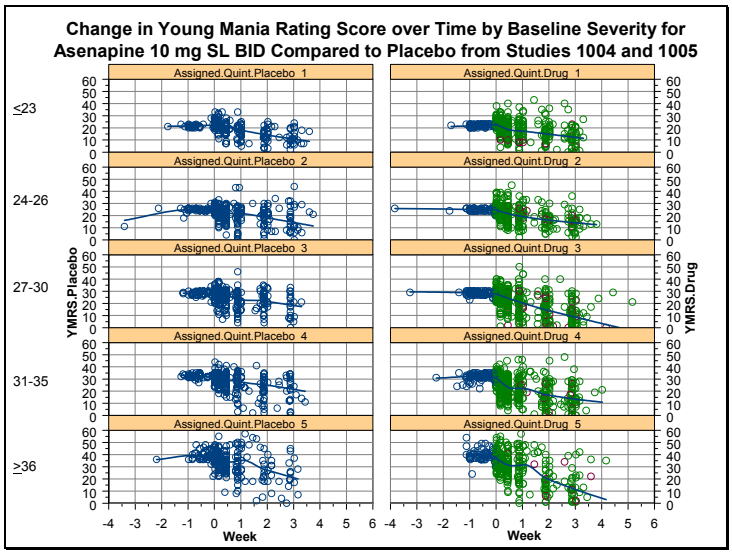
- Death due to Presumptive Agranulocytosis
  - 1 / 313 to 1 / 156 with 1 - 1.2 years of Rx (0.32% - 0.65%)
- Death due to Suicide in Acute Bipolar
  - 1 / 317 (0.32%)
- Deaths due to Cardiotoxicity
  - MI, CHF, Arrhythmias (?)
- Potential Total Incidence in Similar Population
  - > 1 / 117 – 1 / 158 – 1 / (~ 1%)
- Deaths in Actual Population of Use
  - (Greater exposures, DDIs, Comorbid Disorders, less intensive monitoring)
  - Expected to be higher (< 1%)

The higher range for death due to agranulocytosis is based on assuming that at least 2 other cases of death due to respiratory arrest are due to infection secondary to agranulocytosis.

Slide 25



Slide 26



Only works with YMRS > 27

Similar results with active control ziprasidone

Information from other reviews and submissions (olanzapine, paliperidone) indicate similar findings

Slide 27

Racial and Ethnic Characteristics by Treatment and Disease Severity - Study A7501004

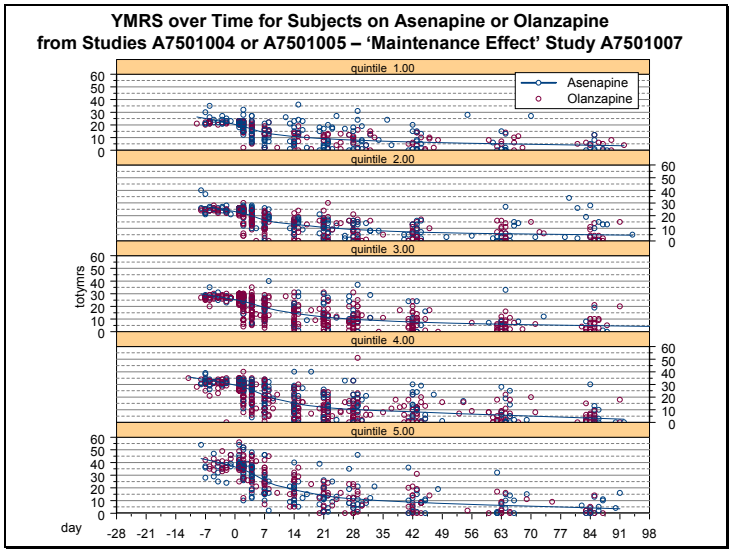
Treatment	Group	% of Subjects					
	Quintile	Asian	Black	Caucasian	Ethiopian	Hispanic	Puerto Rican
Placebo	1	12.5	3.1	78.1	0.0	6.3	0.0
	2	18.8	18.8	50.0	0.0	12.5	0.0
	3	15.8	26.3	57.9	0.0	0.0	0.0
	4	38.5	7.7	46.2	0.0	7.7	0.0
	5	43.8	31.3	25.0	0.0	0.0	0.0
	Total	22.9	15.6	56.3	0.0	5.2	0.0
Asenapine	1	15.2	10.9	73.9	0.0	0.0	0.0
	2	15.6	15.6	65.6	0.0	3.1	0.0
	3	15.9	25.0	56.8	0.0	2.3	0.0
	4	28.6	28.6	39.3	0.0	3.6	0.0
	5	38.2	26.5	35.3	0.0	0.0	0.0
	Total	21.7	20.7	56.0	0.0	1.6	0.0
Olanzapine	1	15.9	18.2	59.1	0.0	6.8	0.0
	2	6.1	3.0	81.8	0.0	9.1	0.0
	3	18.0	24.0	56.0	0.0	0.0	2.0
	4	34.2	21.1	42.1	0.0	2.6	0.0
	5	35.1	24.3	35.1	2.7	2.7	0.0
	Total	21.8	18.8	54.5	0.5	4.0	0.5

Slide 28

Ethnic Characteristics by Treatment and Disease Severity Study A7501005

Treatment	Group	% of Subjects						
	Quintile	Asian & Oriental	Asian Indian	Black	Caucasian	Hispanic	Latino	NA & American Indian
Placebo	1	0.0	0.0	15.0	70.0	15.0	0.0	0.0
	2	0.0	0.0	33.3	55.6	0.0	5.6	5.6
	3	5.0	0.0	20.0	75.0	0.0	0.0	0.0
	4	25.0	0.0	20.0	55.0	0.0	0.0	0.0
	5	50.0	3.8	7.7	38.5	0.0	0.0	0.0
	Total	18.3	1.0	18.3	57.7	2.9	1.0	1.0
Asenapine	1	8.5	0.0	19.1	68.1	4.3	0.0	0.0
	2	11.4	0.0	17.1	71.4	0.0	0.0	0.0
	3	11.6	0.0	16.3	65.1	2.3	2.3	2.3
	4	17.5	0.0	12.5	70.0	0.0	0.0	0.0
	5	51.9	3.7	14.8	29.6	0.0	0.0	0.0
	Total	17.7	0.5	16.1	63.0	1.6	0.5	0.5
Olanzapine	1	11.8	0.0	15.7	64.7	5.9	2.0	0.0
	2	15.4	2.6	20.5	53.8	5.1	0.0	2.6
	3	12.5	0.0	17.5	67.5	2.5	0.0	0.0
	4	28.0	0.0	16.0	56.0	0.0	0.0	0.0
	5	30.3	3.0	12.1	51.5	3.0	0.0	0.0
	Total	18.1	1.1	16.5	59.6	3.7	0.5	0.5

Slide 29



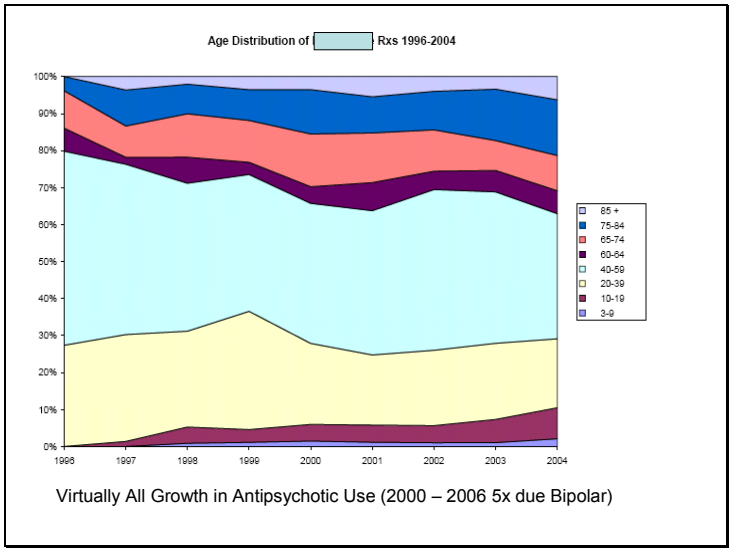
Not placebo controlled.

Noninferiority inappropriate.

Even Olanzapine with Placebo Control only had median time to release a few days longer as compare to placebo.

Question. If continue Rx and inpatient stay for 4 – 6 weeks would there be any diff with maint Rx

Slide 30



Slide 31

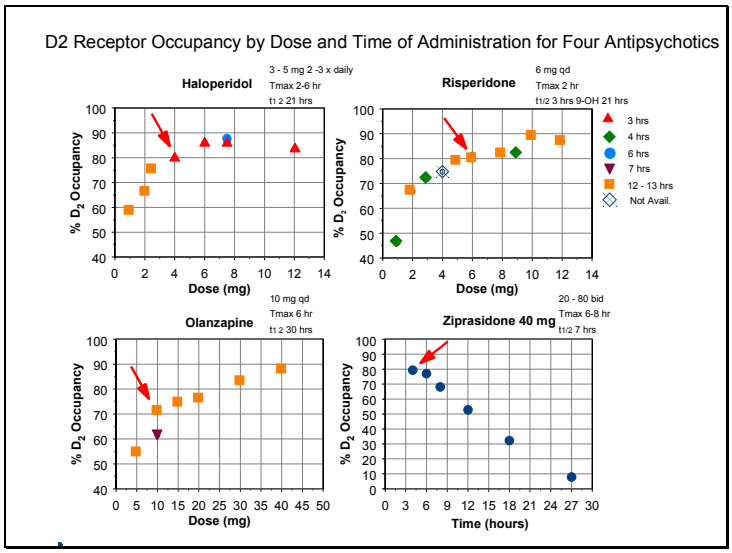
- BSD
  - NIMH May 2007
  - 2.5%
  - Rec. Rx with antipsychotics
- Pediatric Bipolar
  - Full DSM IV criteria
  - Bipolar vs. ADHD
  - Easy to Misdiagnose
- APA – Washington DC; May 2007
  - 43% of Patients Coming to NYU Hospital with Dx Bipolar did not have Bipolar per DSM-IV
  - Overdiagnosed
- Concerns
  - Misuse (inappropriate use)
  - High Risk to Benefit even with appropriate use

Slide 32

Exposure Response

Schizophrenia

Slide 33



Slide 34

Study		041004			041021			
Treatments		Placebo	Asenapine 5 mg BID	Risperidone 3 mg BID	Placebo	Asenapine 5 mg BID	Asenapine 10 mg BID	Olanzapine 15 mg QD
Rx Arm (tcaf)		3	2	1	1			
N		60	58	6	93	102	96	95
Baseline		92.4 (1 9)	96.5 (2.2)	92.2 (2.1)	93.7 (1 1)	90.8 (1.0)	93.2 (1.1)	92.6 (1.1)
A to:	Day 4				-3.9 (.8)	-4.0 (0.8)	-5.5 (0.8)	-3.3 (0.8)
	Day 7	-3.9 (1.5)	-6.2 (1.7)	-5.6 (1.8)	-6.5 (1.0)	-7.8 (1.0)	-8.8 (1.0)	-7.1 (1.0)
	Day 14	-5.5 (1.6)	-11.3 (2.0)*	-8.3 (2.4)	-9.8 (1.3)	-13.1 (1.3)	-11.5 (1.3)	-11.6 (1.3)
	Day 21	-6.4 (2.1)	-16.9 (2.4)*	-10.8 (2.8)	-10.5 (1.4)	-12.9 (1.4)	-11.9 (1.4)	-12.8 (1.4)
	Day 28	-6.6 (2.3)	-16.9 (2.5)*	-10.3 (2.7)	-10.7 (1.5)	-14.0 (1.)	-12.0 (1.)	-14.6 (1.5)
	Day 35	-4.7 (2.2)	-16.0 (2.6)*	-10.5 (2.7)	-10.2 (1.6)	-14.5 (1.)*	-13.1 (1.6)	-15.8 (1.6)*
	Day 42	-5.3 (2.3)	-15.9 (2.6)*	-10.9 (2.7)	-11.1 (1.6)	-14.4 (1.6)	-13.5 (1.6)	-16.5 (1.6)*
	Endpoint	–	–	–	-11.1 (1.6)	-14.5 (1.6)	-13.4 (1.6)	-16.5 (1.6)*

Study		041022			041023			
Treatments		Placebo	Asenapine 5/10 mg BID	Olanzapine 10-20 mg QD	Placebo	Asenapine 5 mg BID	Asenapine 10 mg BID	Haloperidol 4 mg BID
Rx Arm (tcaf)								
N		89	85	85	122	109	105	112
Baseline		84.7 (1 1)	86.8 (1.1)	86.5 (1.1)	89.0(0.9)	88.9 (1.0)	89.4 (1.0)	88.5 (1.0)
A to:	Day 4	-2.9 (0.7)	-4.2 (0.7)	-3.7 (0.7)	-3.4 (0.7)	-2.9 (0.8)	-4.4 (0.8)	-3.4 (0.8)
	Day 7	-4.8 (1.2)	-4.9 (1.2)	-5.0 (1.1)	-5.9 (0.9)	-7.2 (1.0)	-7.7 (1.0)	-7.3 (1.0)
	Day 14	-7.1 (1.5)	-8.7 (1.5)	-9.2 (1.5)	-8.3 (1.1)	-10.5 (1.2)	-10.4 (1.2)	-11.0 (1.2)
	Day 21	-8.8 (1.6)	-9.5 (1.6)	-9.9 (1.6)	-9.1 (1.3)	-13.2 (1.4)*	-11.6 (1.4)	-13.8 (1.4)*
	Day 28	-8.9 (1.6)	-10.0 (1.6)	-10.7 (1.6)	-9.4 (1.4)	-14.2 (1.)*	-11.7 (1.)	-14.4 (1.5)*
	Day 35	-9.3 (1.7)	-10.1 (1.7)	-11.2 (1.7)	-10.2 (1.5)	-15.3 (1.6)*	-13.3 (1.6)	-14.7 (1.5)*
	Day 42	-10.1 (1.7)	-9.1 (1.7)	-11.4 (1.7)	-10.8 (1.6)	-16.2 (1.7)*	-14.7 (1.7)	-15.6 (1.6)*
	Endpoint	-9.9 (1.7)	-9.4 (1.7)	-11.5 (1.7)	-10.7 (1.6)	-16.2 (1.7)*†	-14.9 (1.7)	-15.4 (1.6)*

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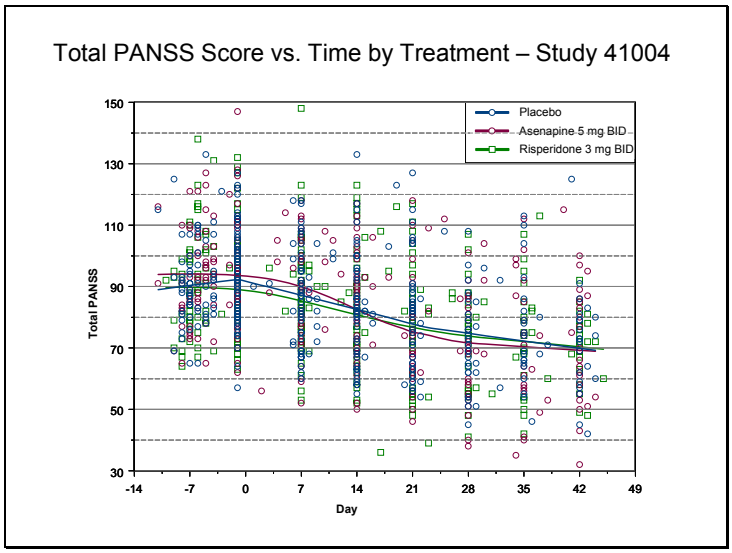
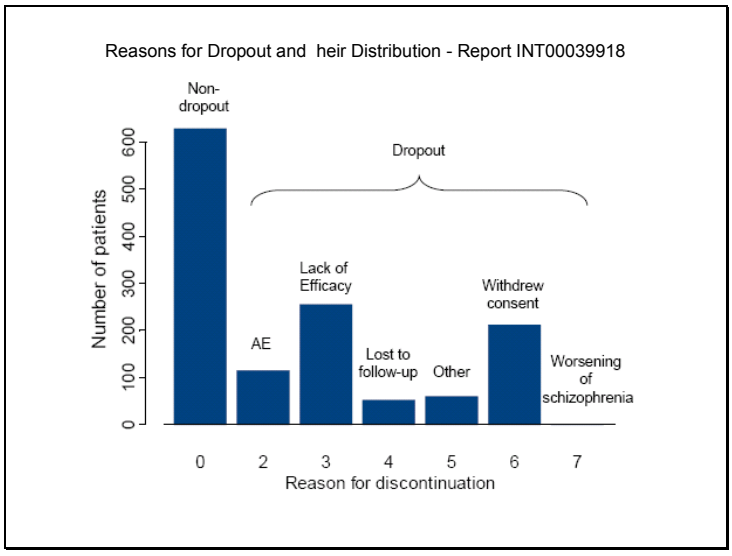
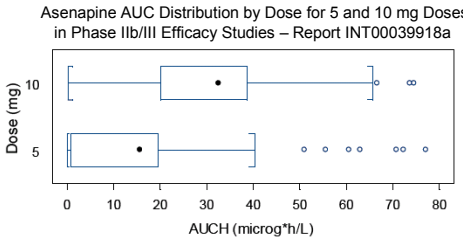


Slide 36

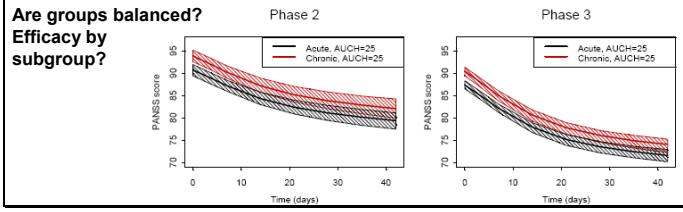


Slide 37

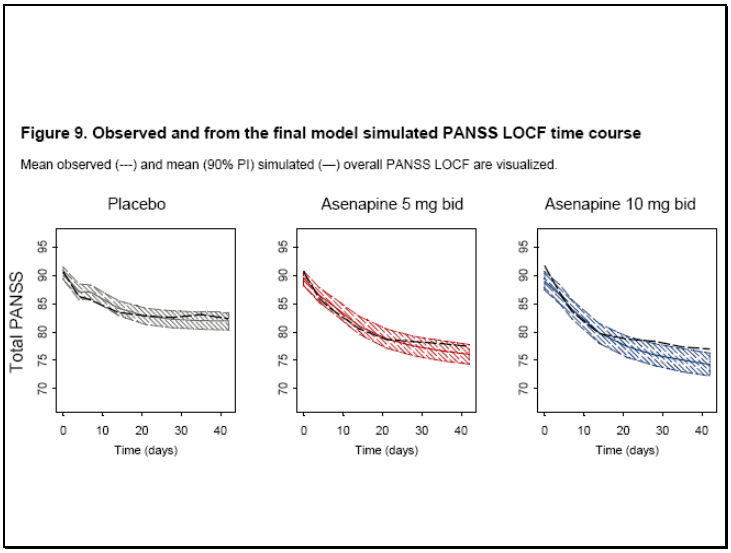
Effect of Duration Of Episode



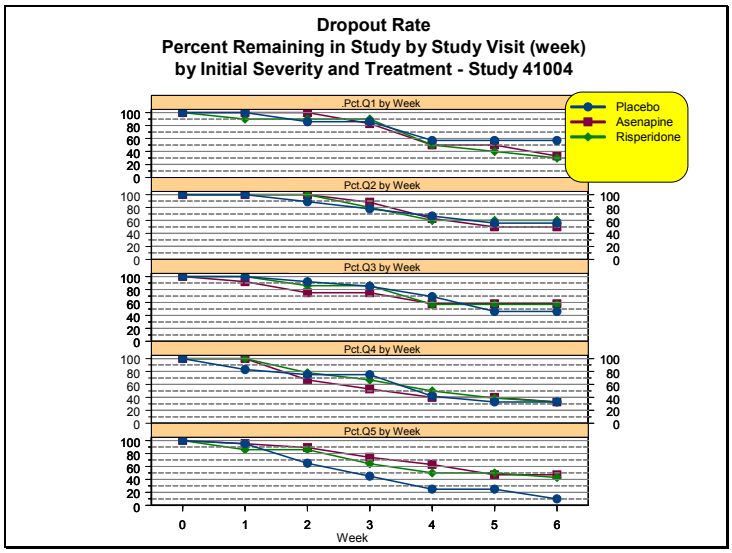
Are groups balanced? Efficacy by subgroup?



Slide 38



Slide 39



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Drop out Rates and Odds Ratio by Treatment
and Initial Disease Severity – Study 41004

Treatment	Duration of Rx	Odds Ratio of Remaining on Active Drug Treatment Compared to Placebo					
		Q1	Q2	Q3	Q4	Q5	Total
Asenapine	Baseline	1.0	1.0	1.0	1.0	1.0	1.0
	Screen	1.0	1.0	1.0	1.0	1.0	1.0
	Visit 1	1.0	1.0	0.92	1.20	1.0	1.02
	Visit 2	1.17	1.13	0.81	0.89	1.38	1.06
	Visit 3	0.97	1.13	0.89	0.71	1.64	1.04
	Visit 4	0.88	0.94	0.84	0.96	2.53	1.16
	Visit 5	0.88	0.90	1.26	1.20	1.89	1.23
	Visit 6	0.58	0.90	1.26	1.00	4.74	1.31
Risperidone	Baseline	1.0	1.0	1.0	1.0	1.0	1.0
	Screen	1.0	1.0	1.0	1.0	1.0	1.0
	Visit 1	0.90	1.0	1.0	1.2	0.90	1.00
	Visit 2	1.05	1.13	0.93	1.04	1.32	1.10
	Visit 3	1.05	1.03	1.01	0.89	1.43	1.08
	Visit 4	0.88	0.90	0.83	1.20	2.00	1.11
	Visit 5	0.70	1.08	1.24	1.17	2.00	1.21
	Visit 6	0.53	1.08	1.24	1.00	4.29	1.23

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Drop out Rates and Odds Ratio by Treatment and Initial Disease Severity – Study 41023

Treatment	Duration of Rx	Odds Ratio of Remaining on Active Drug Treatment Compared to Placebo					
		Q1	Q2	Q3	Q4	Q5	Total
Asenapine 5 mg BID	Baseline	1.00	1.00	1.00	1.00	1.00	1.00
	Visit 1	1.04	0.93	0.88	1.00	1.00	0.96
	Visit 2	1.08	1.01	0.86	0.97	0.97	0.98
	Visit 3	0.90	1.06	0.76	1.02	0.73	0.91
	Visit 4	1.04	0.97	0.73	1.18	0.70	0.93
	Visit 5	1.04	1.03	0.77	1.60	0.67	1.01
	Visit 6	1.04	1.03	0.91	1.50	0.74	1.06
Asenapine 10 mg BID	Baseline	1.00	1.00	1.00	1.00	1.00	1.00
	Visit 1	1.04	1.00	0.96	0.91	0.96	0.98
	Visit 2	1.23	1.09	0.97	0.99	0.96	1.03
	Visit 3	1.46	1.07	0.89	0.93	1.03	1.04
	Visit 4	1.78	0.99	0.80	0.96	1.03	1.04
	Visit 5	1.70	0.86	0.85	1.30	0.98	1.07
	Visit 6	1.70	0.90	1.00	1.30	1.08	1.14
Haloperidol 4 mg BID	Baseline	1.00	1.00	1.00	1.00	1.00	1.00
	Visit 1	1.01	0.81	1.00	0.95	1.00	0.96
	Visit 2	1.10	0.78	1.02	0.94	0.99	0.95
	Visit 3	1.18	0.76	0.87	0.88	1.01	0.91
	Visit 4	1.43	0.70	0.81	1.02	0.86	0.91
	Visit 5	1.35	0.71	0.85	1.38	0.81	0.96
	Visit 6	1.28	0.69	1.01	1.22	1.03	1.00

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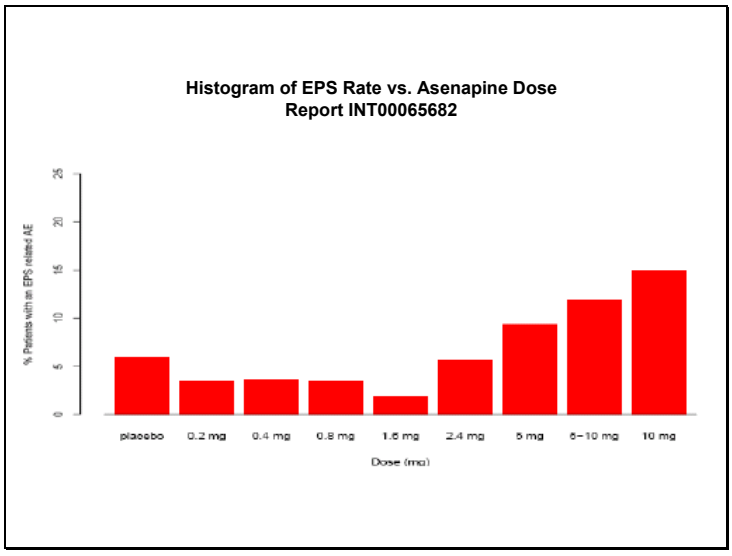

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Psychometric Testing in Healthy Young Adults
PO MRD PK S/T Study

a) Immediate Recall (Session 1)

Change 0-13	II	3	0.5	(0.71)	0.3	(3.40)	2.6	>0.2
	III	10	0.0	(0.00)	1.8	(0.96)	0.8	0.072
	IIIa	20	-1.0	(1.41)	2.0	(1.55)	1.2	0.053
	+P value		>0.2		>0.2			

b) Delayed Recall (Sessions 2 & 3)

Change 0-13	II	3	0.8	(1.06)	-0.9	(3.20)	2.4	>0.2
	III	10	0.5	(1.41)	2.5	(2.12)	1.7	>0.2
	IIIa	20	-1.8	(1.06)	1.6	(1.83)	1.4	0.056
	+P value		>0.2		0.15			

- Significance in Dementia Associated Psychosis (particularly Alzheimer's)? Class Effect?

This is in contrast to a recent publication from the sponsor in on effect on neurotransmitters in brains of rats that they claim indicates it might improve cognition. This would be significant for demented patients and could be used for promotion of off-label claims.

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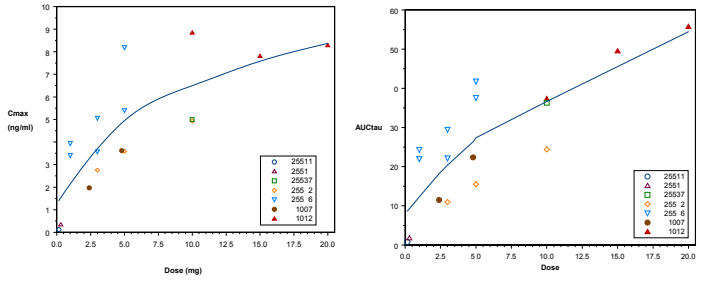
MD Linearity



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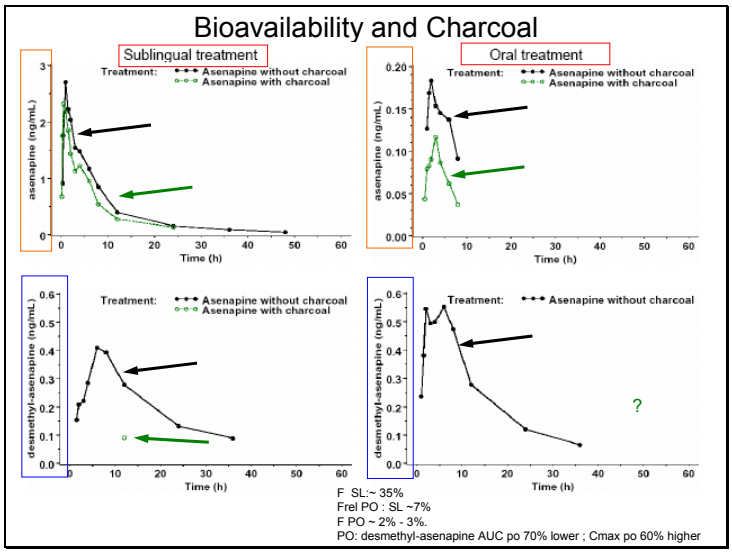

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Intrinsic Factors

- Race and Ethnicity
  - Caucasian vs. Japanese (n = 6 / group)
    - Higher Desme hyl-asenapine in caucasians
      - Likely due to swallowing
- Gender
  - Not studied
  - Data might be extractable
  - 1A2 substrate
    - Exposures likely higher in women
- Elderly
  - Not studied
  - Found abbreviated study report hidden in 4 mo safety update
- Adolescents
  - Abbreviated study report
  - NDA not for adolescents
  - Risk Management Strategy (REMS) for Off Label Use

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Asenapine BID Pharmacokinetics in Adolescents receiving Antipsychotics - Study A7501022

Asenapine

Dose	1 mg	3 mg	5 mg	10 mg
N (n)	8 (7)	8 (5)	8 (8)	8 (8)
Tmax (hr)	0.705 (0.25 - 1.5)	0.890 (0.0 - 1.5)	1.04 (0.0 - 2.8)	1.28 (0.0 - 3.0)
Cmax (ng/mL)	1.03 (49.6)	2.64 (55.6)	3.54 (47.9)	2.77 (81.8)
Cmin (ng/mL)	0.253 (53.8)	0.793 (49.8)	1.02 (41.9)	0.901 (55.8)
AUC(0 τ) (ng/mL x hr ^{1})	6.56 (60.8)	15.8 (49.5)	22.9 (47.5)	19.7 (54.0)
CL/F (L/min)	3.21 (43.5)	4.53 (83.5)	6.81 (138)	10.3 (42.8)
Vd/F (L)	7750 (64.4)	12100 (90.0)	14700 (79.5)	19700 (47.3)

Desmethyl-Asenapine

N (n)	8 (5)	8 (5)	8 (8)	8 (6)
Tmax (hr)	3.04 (0.50 - 12)	1.82 (0.28 - 6.0)	4.00 (0.0 - 11)	3.59 (0.78 - 4.0)
Cmax (ng/mL)	0.430 (67.7)	1.04 (63.2)	1.40 (37.4)	2.96 (74.5)
Cmin (ng/mL)	0.219 (57.5)	0.621 (67.8)	0.800 (37.6)	1.07 (83.5)
AUC(0 τ) (ng/mL x hr ^{1})	4.03 (60.2)	10.1 (72.9)	13.3 (38.2)	25.8 (63.2)
t½ (hr)	23.0 (28.1)	31.2 (100.9)	21.1 (36.1)	15.2 (23.1)

N = Number of subjects.
n = N for t½ and Vd/F

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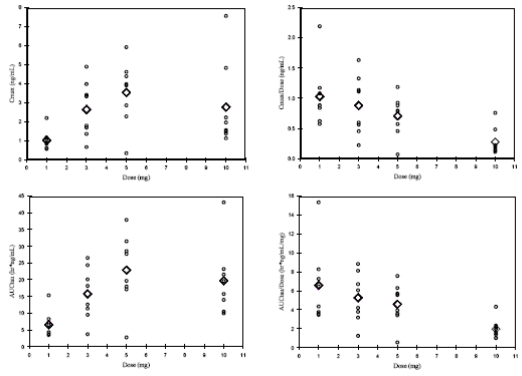
Unnormalized and Dose-normalized Asenapine Cmax and AUCs by Dose in Adolescent Subjects – Study A7501022

Figure 4. Asenapine Cmax (Upper Panel) and AUC(0-∞) (Lower Panel)Values Following q12h Administration of Sublingual Asenapine Tablet Doses to Adolescent Subjects With A Psychotic Disorder, Study A7501022



Left panels show observed values; right panels show dose-normalized values. Circles are individual subjects, diamonds are arithmetic means.

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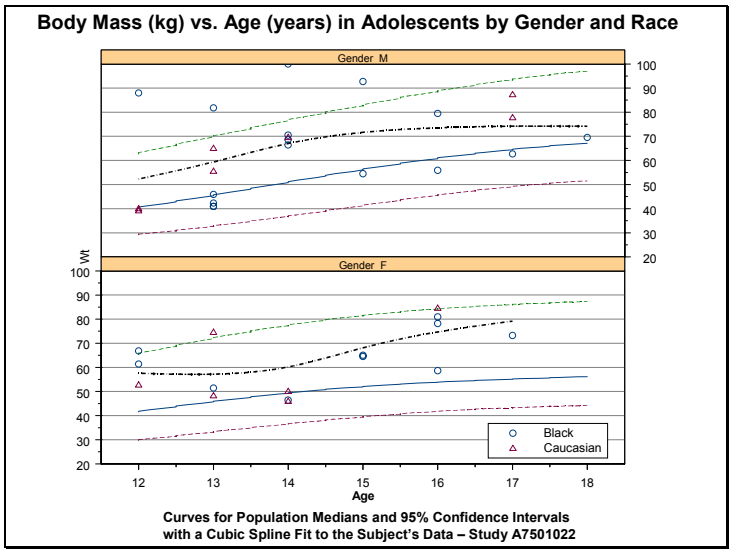
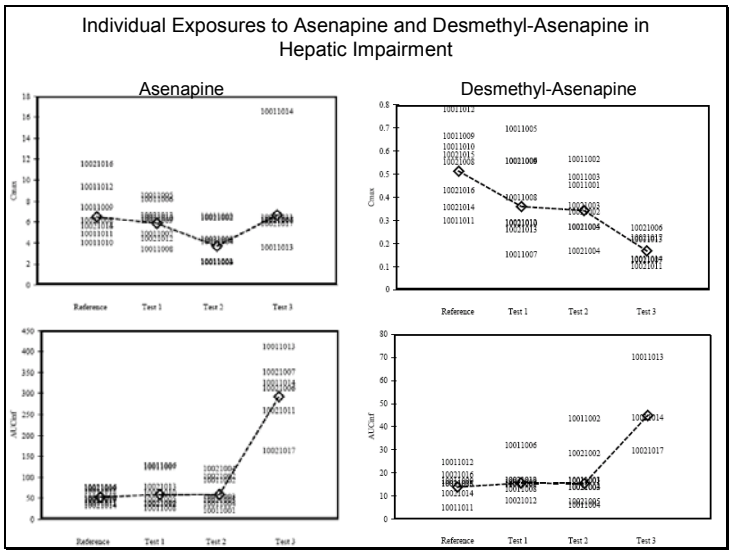
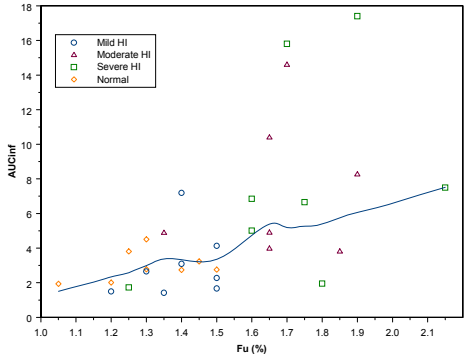


Slide 50



Slide 51

AUC vs. Free Fraction in Subjects with Hepatic Impairment



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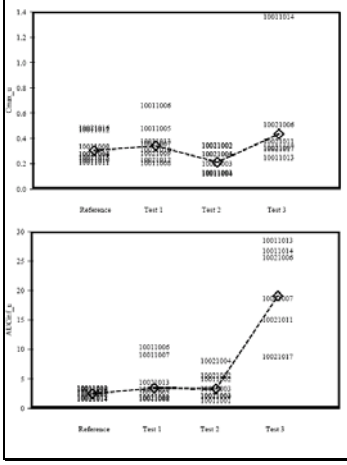
Unbound Asenapine following Single 5-mg Sublingual Doses in Subjects with Various Degrees of Liver Impairment - Study A7501018



	Normal	Mild	Moderate	Severe
N	8		8/7	6
Cmaxu (ng/mL)	0.317 ± 0.105 (33.1) 0.217-0.487 [0.278]	0.364 ± 0.148 (40.6) 0.206 - 0.659 [0.330]	0.229 ± 0.0948 (41.4) 0.119 - 0.347 [0.238]	0.524 ± 0.419 (80.1) 0.248 - 1.36 [0.303]
AUCu(0 - tlqc) (ng/mL x hr^{-1})	2.38 ± 0.686 (28.8) 1.55-3.17 [2.38]	3.65 ± 2.45 (67.1) 1.52 - 8.38 [2.78]	3.64 ± 2.16 (59.5) 1.20 - 7.69 [3.00]	16.5 ± 5.06 (30.7) 8.44 - 22.5 [16.4]
AUCu(0-∞) (ng/mL x hr^{-1})	2.57 ± 0.717 (27.9) 1.65-3.42 [2.61]	4.38 ± 3.44 (78.6) 1.61 - 10.4 [2.93]	3.93 ± 2.41 (61.2) 1.30 - 8.09 [3.34]	20.6 ± 7.71 (37.5) 8.83 - 28.4 [22.1]
CL/Fu (mL/min)	35000 ± 10400 (29.9) 24300-50600 [32200]	29400 ± 16900 (57.3) 8020 - 51600 [29600]	29900 ± 18900 (63.2) 10300 - 64100 [25000]	4790 ± 2480 (51.9) 2030 - 9430 [3860]
fu (%)	0.047 ± 0.005 0.040 - 0.057	0.059 ± 0.012 0.046 - 0.080	0.057 ± 0.007 0.046 - 0.067	0.066 ± 0.013 0.053 - 0.082

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Renal Insufficiency

- No clear effect on Asenapine or Desmethyl-asenapine kinetics
- CYP2D6 and Transporters Effected in Severe Renal Failure
- Other metabolites not examined
  - Expected that conjugates and possibly N-oxides and may be effected

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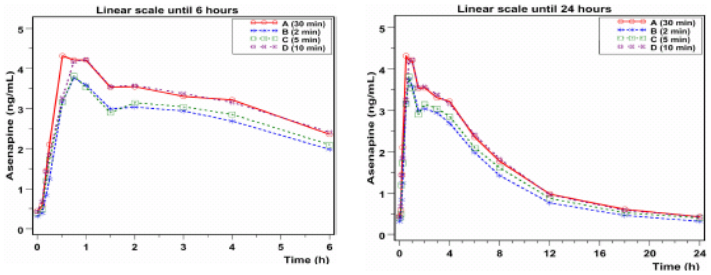
Extrinsic Factors

Effect of Water at Various Times after Drug Administration – Study 25537



Desmethyl-asenapine 90% CI for Cmax Indicates Higher Peaks in some subjects at 2 min

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Smoking

- CYP1A2 Substrate
  - smoking should induce
- Study conducted in Smokers
  - Effect of a single cigarette smoked concurrently
- Possibly applicable to schizophrenics Not other populations
  - Different Frequency of AEs?
  - Different Risk : Benefit Ratios?
- No clear effect on asenapine or desmethyl-asenapine
- Other metabolites not studied
- Applicable

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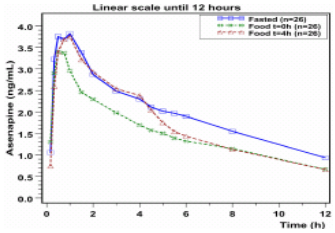
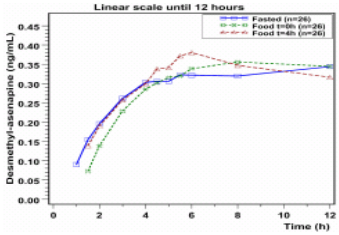
Effect of Food Administration at Various Times on Asenapine Mean Concentration vs. Time Profiles – Study 41029





NOT Truly Fasted
High Energy Supplement

Analyte (n)	Metric	Summary Statistics (A) Fasted	(B) Fed t=0h	(C) Fed t=4h	Geometric Mean Ratios (90% CI) B : A	C : A
Asenapine (n=26)	Tmax (h)	0.98 0.38 - 3.00	0.75 0.32 - 4.00	0.76 0.33 - 4.00	–	–
	Cmax (ng/mL)	4.46 ± 2.57	3.89 ± 2.24	4.27 ± 2.10	0.90 0.73 - 1.11	1.02 0.83 - 1.26
	AUC∞ (ng/mL x hr^{-1})	38.5 ± 15.6	30.8 ± 14.1	32.6 ± 11.7	0.79 0.66 - 0.94	0.87 0.73 - 1.03
N - Desmethyl - Asenapine (n=26)	Tmax (h)	7.00 4.00 - 12.0	7.9 8.00 - 12.0	6.00 3.00 - 12.0	–	–
	Cmax (ng/mL)	0.395 0.167	0.402 ± 0.139	0.407 ± 0.192	–	–
	AUC∞ (ng/mL x hr^{-1})	10.9 ± 3.68	11.0 ± 3.30	10.9 ± 4.23	–	–

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Drug-Drug Interactions

- Studied
  - CYP2D6 – noncompetitive inhibitor
    - Single Dose Asenapine 5 mg & Imipramine 75 mg
    - Multiple Dose Asenapine & Paroxetine
    - Single and Multiple Dose Dextromethorphan
  - CYP1A2
  - UDPGT1A4
- Expected - Not Studied - Likely Clinically Significant
  - CYP2C9 ?
  - COMT
- Possible - Significance?
  - PST
  - FMO

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Asenapine and Imipramine

Table 1 Asenapine and Desmethyl-Asenapine Pharmacokinetic Metrics in the Presence and Absence of Imipramine - Study 25526

Analyte	Asenapine					Desmethyl-Asenapine				
Metrics	Summary Statistics		Geometric Means		Geometric Mean Ratio (90% CI)	Summary Statistics		Geometric Means		Geometric Mean Ratio (90% CI)
Parameter (unit)	Asenapine	Asenapine + Imipramine	Asenapine	Asenapine + Imipramine		Asenapine	Asenapine + Imipramine	Asenapine	Asenapine + Imipramine	
n	24	24	--	--	23	24	24	23	--	--
Tmax (h)	0.75 0.50 - 3.0	0.975 0.50 - 2.0	--	--	--	6.00 2.00 - 8.05	3.0 1.5 - 12.0	--	--	--
Cmax (ng/mL)	4.87 (34.1) 2.67 - 9.01	5.39 (36.6) 0.974 - 10.6	4.56	5.33	1.17 1.05 - 1.30	0.490 (33.5) 0.212 - 1.09	0.641 (28.3) 0.299 - 0.881	0.476	0.521	1.09 1.03 - 1.17
AUC∞ (ng/mL x hr^{-1})	38.1 (29.4) 21.9 - 63.8	39.2 (25.2) 10.3 - 54.6	36.1	39.7	1.10 1.01 - 1.20	11.7 (34.8) 7.04 - 25.2	12.1 (29.1) 7.13 - 20.0	11.1	11.6	1.04 0.98 - 1.11

Values are mean (%CV) range except for Tmax where values are median and range.

Table 2 Imipramine and Desmethyl- Imipramine Pharmacokinetic Metrics in the Presence and Absence of Asenapine - Study 25526

Analyte	Imipramine					Desipramine				
Metrics	Summary Statistics		Geometric Means		Geometric Mean Ratio (90% CI)	Summary Statistics		Geometric Means		Geometric Mean Ratio (90% CI)
Parameter (unit)	Imipramine	Asenapine + Imipramine	Imipramine	Asenapine + Imipramine		Imipramine	Asenapine + Imipramine	Imipramine	Asenapine + Imipramine	
n	24	24				24	24			
Tlag (h)	1.0 0.5 – 2.0	2.0 1.0 – 4.0				1.5 0.75 – 3.0	2.0 1.0 – 4.0			
Tmax (h)	2.50 1.50 - 4.00	2.00 1.50 - 4.00				3.00 1.50 - 24.0	4.00 1.50 - 24.2			
Cmax (ng/mL)	44.6 (47.1) 10.4 - 98.7	45.0 (44.4) 17.7 - 83.8	41.9	42.6	1.00 0.91 - 1.11	12.6 (45.4) 3.45 - 25.3	13.4 (37.1) 6.22 - 23.4	12.2	12.7	1.04 0.98 - 1.11
AUC∞ (ng/mL x hr^{-1})	542 (58.2) 91.4 - 1175	571 (56.7) 183 - 1364	483	501	1.04 0.97 - 1.10	801* (102) 154 - 3223	859 (105) 133 - 3461	521	560	1.08 0.99 - 1.17
t½ (h)	12.3 (37.7) 4.68 - 23.1	13.7 (44.5) 6.87 - 31.7				32.9* (58.1) 12.6 - 82.8	41.4 (96.1) 13.7 - 190			

Values are mean (%CV) range except for Tmax where values are median and range.

75 mg SD first followed by 5 mg SL SD

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DDI Study

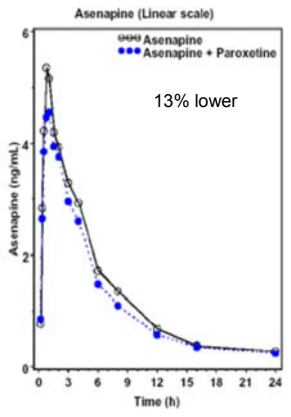
Asenapine / Paroxetine / DM

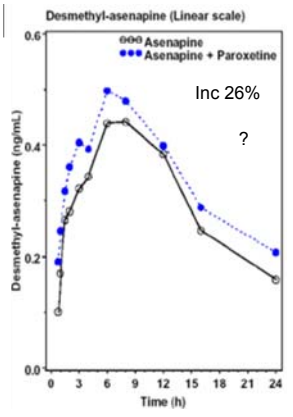
Table 1 Study Design for Paroxetine / Asenapine Drug-Drug Interaction Study - Study 25525

Objective		Effect of Asenapine on Paroxetine & Dextromethorphan		Effect of Paroxetine on Asenapine & Dextromethorphan	
Nominal Designations Used	*Treatment Sequence*	A		B	
	CSR Statistical Analysis Arm	B		A	
	PK Report SAS Analysis Arm	A		B	
	Treatment Arm	A		A	
	Pharmacokinetic Arm	A		A	
Treatments	*Screening*	DM 30 mg PO to determine 8 hour DX:DM UMR		DM 30 mg PO to determine 8 hour DX:DM UMR	
	Day 1		Paroxetine 20 mg SD		Placebo
	Day 2				Asenapine 5 mg SL
	Day 3		Placebo		
	Day 4	Asenapine 1 mg SL BID			
	Day 5	Asenapine 3 mg SL BID			
	Day 6	Asenapine 5 mg SL BID		Paroxetine 20 mg PO QD	
	Day 7				
	Day 8				
	Day 9				
	Day 10				
	Day 11				DM 30 mg PO to determine 8 hour DX:DM UMR
	Day 12		DM 30 mg PO to determine 8 hour DX:DM UMR		
	Day 13		Placebo Paroxetine		Placebo Asenapine
	Day 14		Paroxetine 20 mg SD		Asenapine 5 mg SL
	Day 15				
	Day 16				

Slide 60

Effect of Paroxetine on Asenapine

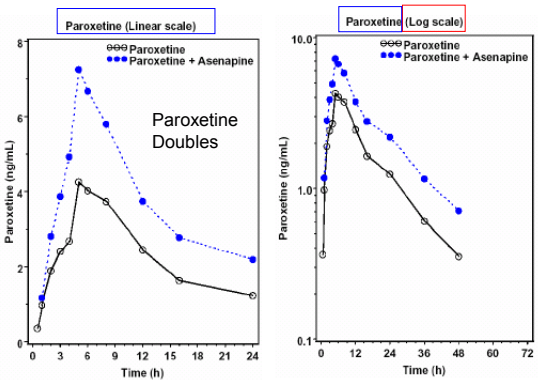




20 mg QD & 5 mg SL SD

Slide 61

Effect of Asenapine on Paroxetine



5 mg SL BID & 20 mg SD

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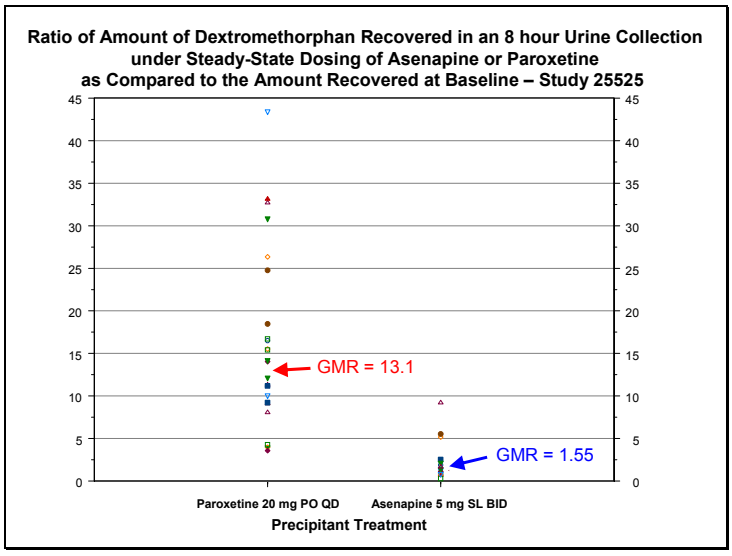
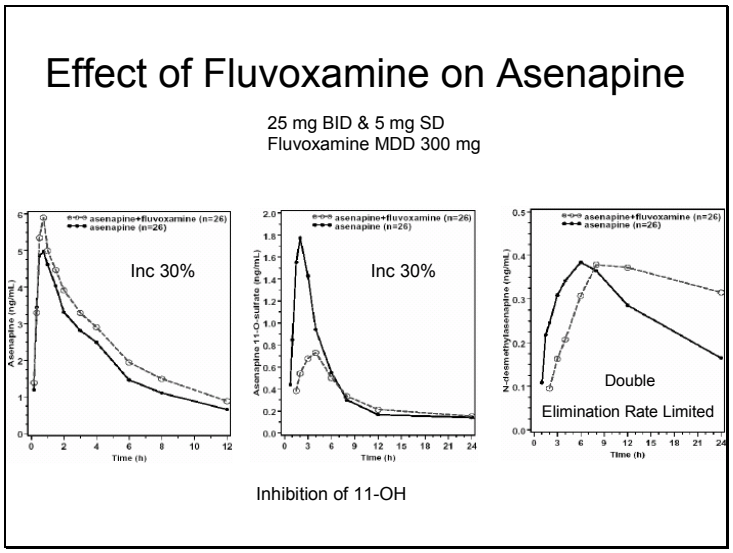
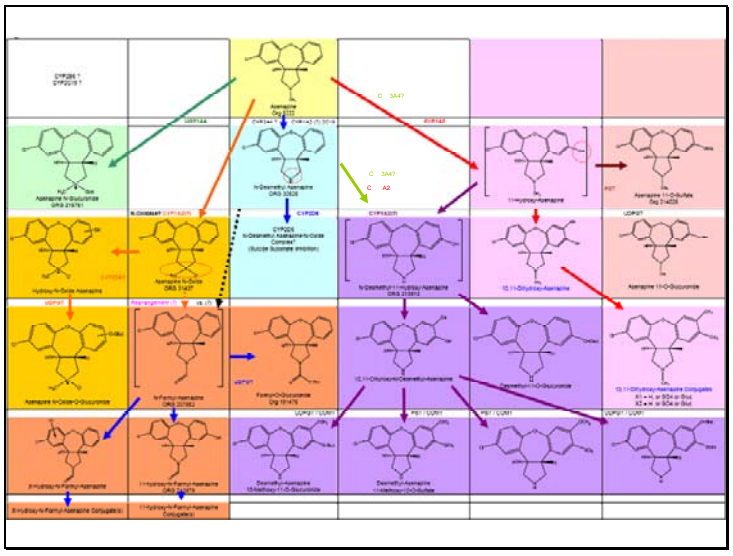


Slide 63



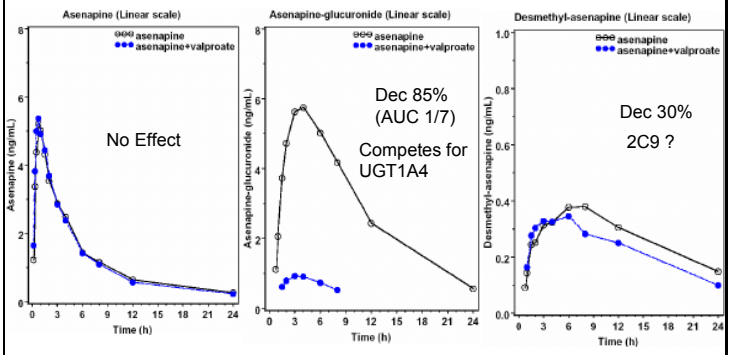
Slide 64



Slide 65

Effect of Valproate on Asenapine

500 mg PO BID & 5 mg SL SD

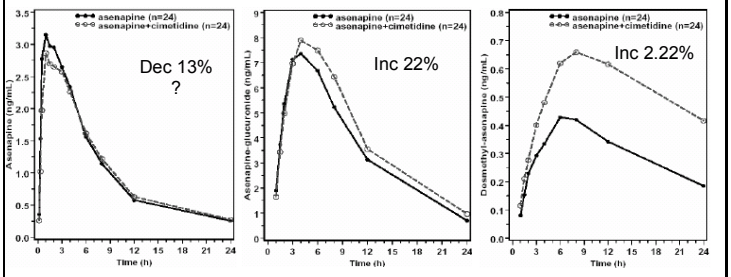


Shun ing to N-Oxide and / or 11-OH

Slide 66

Effect of Cimetidine on Asenapine

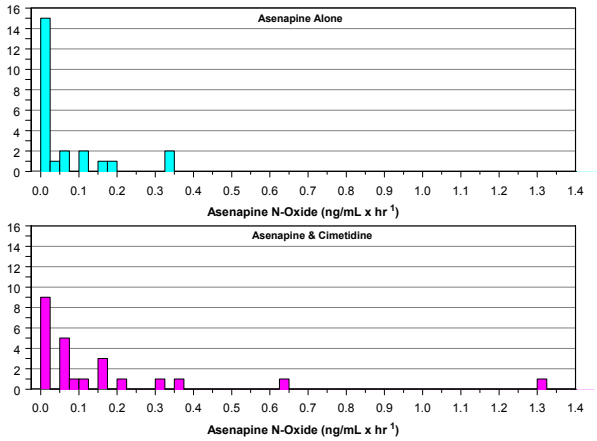
800 mg PO BID & 5 mg SD



Cimetidine Imidazole
Agranulocytosis 1 : 100,000
Reported to increase incidence with structurally similar antipsychotics

Slide 67

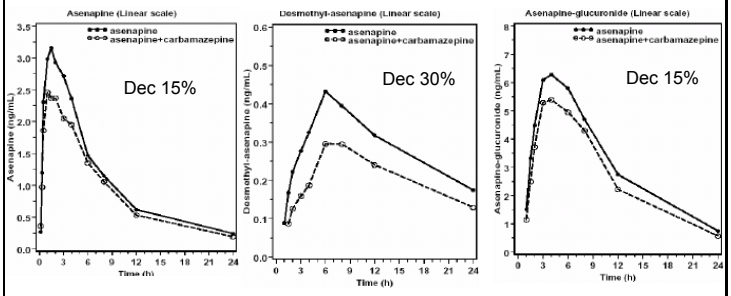
Effect of Cimetidine on Asenapine N-Oxide Exposure



Slide 68

Effect of Carbamazepine on Asenapine

200 mg BID & 5 mg SD



3A4 11-OH ?

Slide 69

Table 1 Difference in Least Square Means from Placebo of Time Matched Change from Baseline in QTcF (ΔΔQTcF) – Study A7501001

Treatment Day	Treatment Comparison	Statistical Reviewer's Analysis					Sponsor's Analysis of Manually Read ECGs				
		N	Time Post-Dose (hour)	Difference (SE)	Lower Limit 90% CI	Upper Limit 90% CI	N	Time Post-Dose (hour)	Difference (SE)	Lower Limit 90% CI	Upper Limit 90% CI
Day 10	Asenapine 5 mg b.i.d. vs Placebo	30	1	0.9 (4.2)	-6.0	7.9	30	1	0.9	-5.0	6.9
		30	2	2.6 (3.4)	-3.0	8.2	30	2	2.6	-3.3	8.6
		30	3	5.0 (3.9)	-1.5	**11.4**	30	3	5.0	-1.0	**10.9**
		30	4	5.8 (3.0)	0.8	**10.8**	30	4	5.8	-0.2	**11.7**
		30	6	4.1 (3.0)	-0.8	8.9	30	6	4.1	-1.9	**10.0**
		29	8	5.8 (3.4)	0.3	**11.3**	29	8	5.9	-0.1	**11.9**
		29	12	0.8 (3.8)	-5.1	6.6	29	12	0.9	-5.1	6.8
	Asenapine 15 mg b.i.d. vs Placebo	33	1	5.6 (3.7)	-0.6	**11.7**	33	1	5.6	-0.2	**11.4**
		33	2	6.4 (3.4)	0.9	**12.0**	33	2	6.4	0.6	**12.3**
		33	3	8.7 (3.5)	3.0	**14.4**	33	3	8.7	2.9	**14.5**
		33	4	8.0 (3.4)	2.5	**13.6**	33	4	8.0	2.2	**13.8**
		33	6	5.1 (2.5)	0.9	9.2	33	6	5.1	-0.8	**10.9**
		33	8	6.2 (3.2)	0.9	**11.3**	33	8	6.1	0.3	**12.0**
		32	12	1.2 (3.2)	-4.1	6.5	32	12	1.0	-4.8	6.9
Day 16	Asenapine 10 mg b.i.d. vs Placebo	27	1	3.4 (3.3)	-2.0	8.8	27	1	3.4	-3.13.9	**10.0**
		27	2	10.5 (3.6)	4.5	**16.5**	27	2	10.5		**17.1**
		27	3	-0.4 (3.8)	-6.6	5.9	27	3	-0.4	-6.9	6.2
		27	4	9.3 (4.4)	2.0	**16.5**	27	4	9.3	2.7	**15.9**
		28	6	6.0 (3.8)	-0.3	**12.3**	28	6	6.2	-0.4	**12.8**
		28	8	5.0 (4.3)	-2.0	**12.1**	28	8	5.2	-1.4	**11.9**
		26	12	0.2 (4.9)	-7.8	8.3	26	12	0.4	-6.2	7.1
	Asenapine 20 mg b.i.d. vs Placebo	29	1	2.6 (3.5)	-3.2	8.4	29	1	2.6	-3.8	9.1
		29	2	5.2 (3.6)	-0.7	**11.2**	29	2	5.2	-1.2	**11.7**
		29	3	-1.1 (4.3)	-8.1	5.9	29	3	-1.1	-7.5	5.4
		28	4	4.9 (4.1)	-1.9	**11.6**	28	4	5.1	-1.4	**11.6**
		29	6	-1.3 (3.8)	-7.5	4.9	29	6	-1.3	-7.8	5.1
		29	8	-1.8 (4.1)	-8.5	5.0	29	8	-1.8	-8.2	4.7
		29	12	-1.4 (4.6)	-9.0	6.2	29	12	-1.4	-7.9	5.0

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Sponsor's Table of Categorical QTcF by Gender and Treatment

		Number (Percent) of Subjects by Maximum Post-dose QTcF (msec)								
		Males					Females			
		<430	430-<450	450-<500	≥500		<450	450-<470	470-<500	≥500
Treatment	N	n(%)	n(%)	n(%)	n(%)	N	n(%)	n(%)	n(%)	n(%)
Baseline										
Placebo	28	27 (96.4)	1 (3.6)	0 (0.0)	0 (0.0)	7	7 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asenapine 5 mg	33	33 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	5	5 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asenapine 15 mg	26	26 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	12	12 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Quetiapine 375 mg	27	27 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	10	10 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Day 1[a] through Day 10										
Placebo	28	27 (96.4)	0 (0.0)	1 (3.6)	0 (0.0)	7	6 (85.7)	0 (0.0)	1 (14.3)	0 (0.0)
Asenapine 5 mg	33	29 (87.9)	4 (12.1)	0 (0.0)	0 (0.0)	5	5 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asenapine 15 mg	26	24 (92.3)	1 (3.8)	1 (3.8)	0 (0.0)	12	9 (75.0)	2 (16.7)	1 (8.3)	0 (0.0)
Quetiapine 375 mg	27	26 (96.3)	1 (3.7)	0 (0.0)	0 (0.0)	10	9 (90.0)	1 (10.0)	0 (0.0)	0 (0.0)
Day 11 through Day 16										
Placebo	27	26 (96.3)	1 (3.7)	0 (0.0)	0 (0.0)	5	5 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asenapine 10 mg	24	21 (87.5)	3 (12.5)	0 (0.0)	0 (0.0)	4	4 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asenapine 20 mg	20	20 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	10	8 (80.0)	1 (10.0)	1 (10.0)	0 (0.0)
Quetiapine 375 mg	22	22 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	7	6 (85.7)	1 (14.3)	0 (0.0)	0 (0.0)

Source: 11.1.2.01.01.05
[a] Post dose

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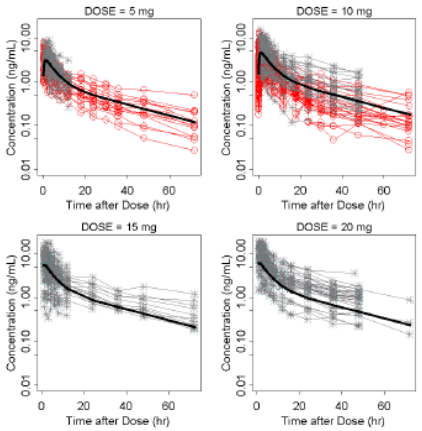
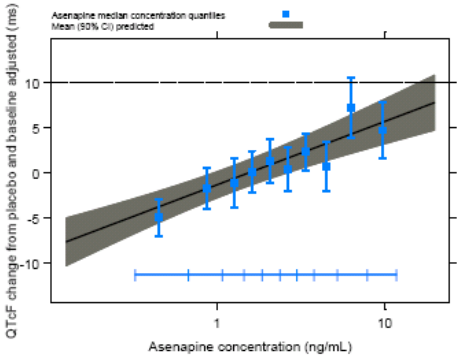
Phase I/II Pop PK Predicted Asenapine Steady State Concentration-Time Profiles
(Base Model) for Selected Doses with Overlaid Observed Concentra ions



Slide 72

**Linear Model of ΔΔQTcF vs. Asenapine Concentration
Overlaid with Mean QT Prolongation with 90% CIs
at the Median-of the 10% Quantiles for Asenapine Concentration**



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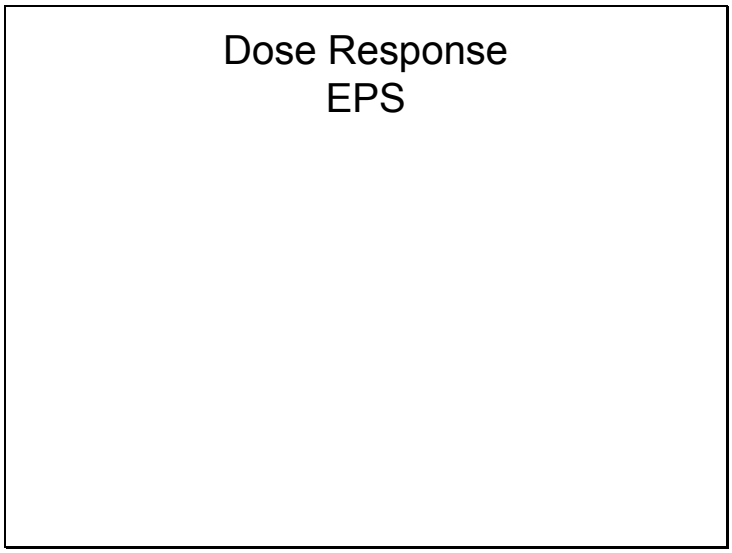

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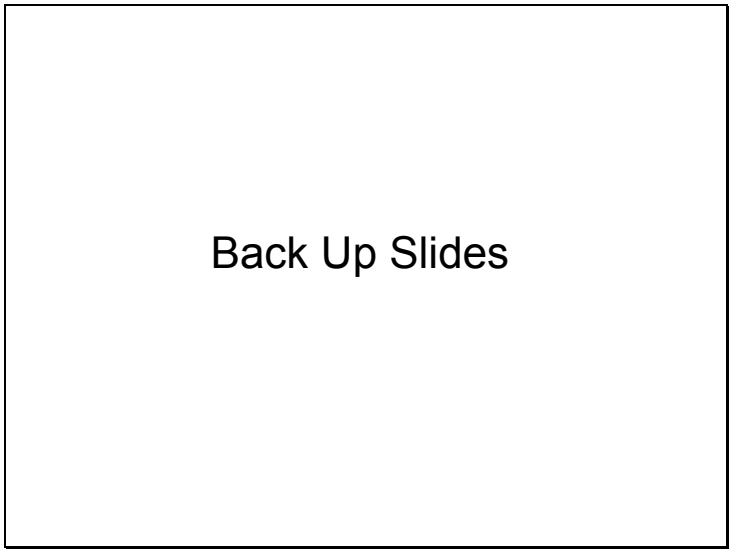
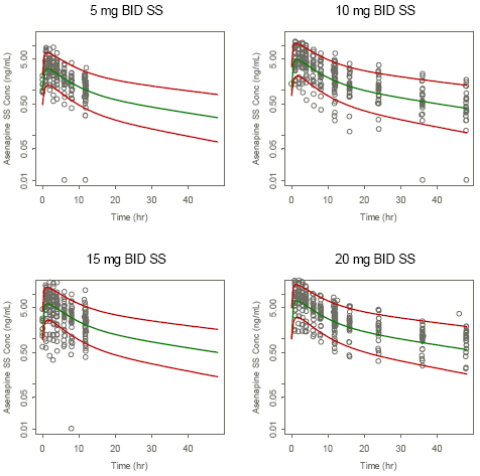


Slide 75

Asenapine Pop PK from TQT Study



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Medians of the Typical Individual Model Predictions of the YMRS Response, Median Differences in the Typical Individual YMRS Response (ΔYMRS) and 90% CIs

	Week	Placebo		5 mg BID		10 mg BID	
		Median	90%CI	Median	90%CI	Median	90%CI
YMRS[a]	0	28.5	(28.1, 28.9)	28.5	(28.1, 28.9)	28.5	(28.1, 28.9)
	0.5	24.4	(23.8, 26.1)	22.9	(22.5, 24.4)	22.0	(21.5, 23.5)
	1	21.8	(21.2, 24.3)	20.3	(19.8, 22.3)	19.5	(18.9, 21.3)
	1.5	19.8	(19.0, 22.8)	18.4	(17.8, 20.9)	17.6	(17.0, 19.8)
	2	18.1	(17.2, 21.4)	16.8	(16.1, 19.6)	16.1	(15.4, 18.7)
	2.5	16.6	(15.7, 20.2)	15.4	(14.7, 18.4)	14.8	(14.0, 17.6)
	3	15.3	(14.4, 19.0)	14.2	(13.4, 17.4)	13.6	(12.8, 16.6)
	Week	10 mg BID–5 mg BID		5 mg BID–Placebo		10 mg BID–Placebo	
		Medianb	90%CI	Medianb	90%CI	Medianb	90%CI
ΔYMRS[b c]	0	0 [0]	--	0 [0]	--	0 [0]	--
	0.5	-0.8 [-3.7]	(-1.1,-0.4)	-1.5 [-6.3]	(-2.1, -0.7)	**2.4 [9.7]**	(-3.2, -1.2)
	1	-0.8 [-4.1]	(-1.2,-0.4)	-1.5 [-7.0]	(-2.3, -0.7)	**2.4 [10.8]**	(-3.5, -1.1)
	1.5	-0.8 [-4.2]	(-1.2,-0.4)	-1.4 [-7.0]	(-2.2, -0.7)	**2.2 [10.9]**	(-3.4, -1.0)
	2	-0.7 [-4.2]	(-1.1,-0.3)	-1.3 [-7.0]	(-2.1, -0.6)	**2.0 [10.9]**	(-3.2, -1.0)
	2.5	-0.6 [-4.2]	(-1.1,-0.3)	-1.2 [-7.0]	(-2.0, -0.6)	**1.8 [10.9]**	(-3.1, -0.9)
	3	-0.6 [-4.2]	(-1.0,-0.3)	-1.1 [-7.0]	(-1.9, -0.5)	**1.7 [10.9]**	(-2.9, -0.8)

a Medians of the typical individual predictions with parameter uncertainty on the YMRS scale
b Median of the differences between the typical individual predictions for treatments.
c The numbers in brackets, [ ], represent median percent changes (i.e., median of 100×ΔYMRS/YMRS).

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Table 1 Summary of Asenapine Pharmacokinetic Parameter Values Following Administration of Asenapine 5 mg Micronized Tablets (Reference) and 5 mg Milled Tablets (Test) (Study A7501016)

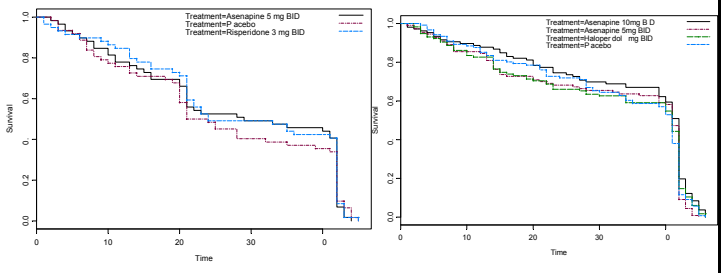
Parameter	Least-Squares Mean Parameter Values		Ratio	90% Confidence Interval
	(b)(4) Tablet (Test)	(b)(4) Tablet (Reference)		
N	35	34		
Cmax ng/mL	2.95	3.25	90.6	80.80 to 101.65
AUC(0-tlqc) ng*hr/mL	21.2	23.0	92.1	83.62 to 101.45
AUC(0-∞) ng*hr/mL	23.1a	25.1b	92.0	83.69 to 101.18
Tmax hr	1.13	1.12		Not Applicable
t½ hr	18.7a	19.1b		Not Applicable

a N=33;
b N = 32 (t½ could not be determined for all subjects)
Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference). 90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean.

AEs

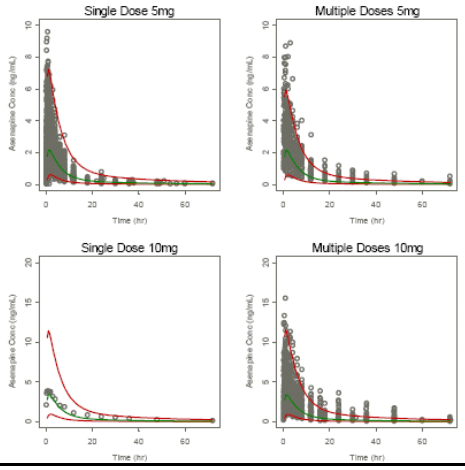
Slide 78

Kaplan-Meir Plots
Survival over Time by Treatment Group - Study 41023



Slide 79

Sponsor's Plot of Phase I/II Pop PK
Unconditional 95% Prediction Interval wi h Overlaid Observations



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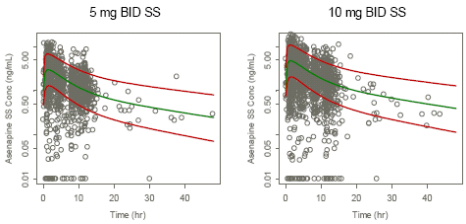
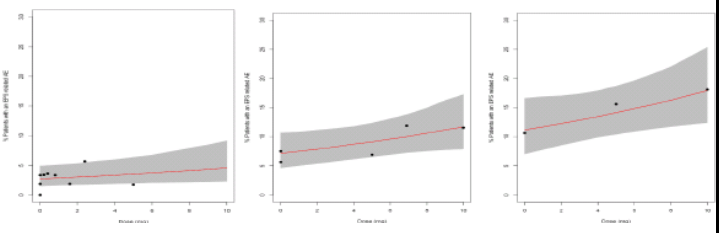
Observed Asenapine Concentrations from All
Phase 2/3 Studies by Dose Overlaid on Unconditional 90% Prediction Interval



Slide 81

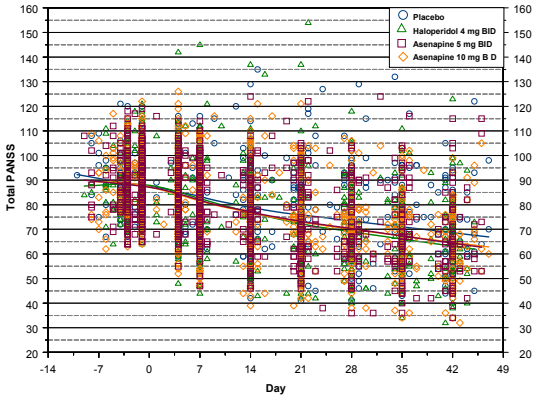
Proportion of Subjects with an EPS-Related Adverse Event in the Different Acute Schizophrenia Trials vs. Dose in Milligrams Report INT00065682



Left: 041-002,041-004 and 041-013. Middle: 041-021 and 041-022.
Right: 041-023. Observed (.), Median predicted (-) and95% confidence interval.

Slide 82

Total PANSS Score vs. Time by Treatment - Study 41023



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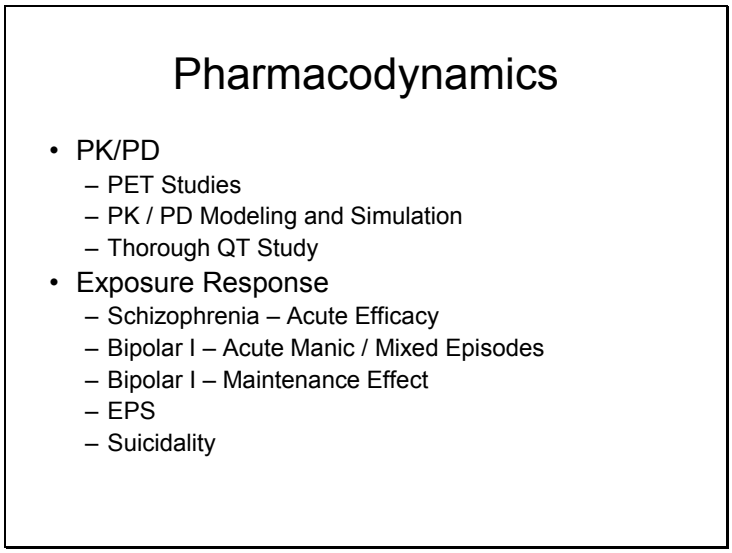

6.9 Submission Quality

This will be provided as an amendment to this review.

6.10 Good Review Management Practice – Pilot Program - Critique

This will be provided as an amendment to this review.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ron Kavanagh
5/15/2008 11:32:55 AM
BIOPHARMACEUTICS
Please see amendment(s) for labeling and other comments per review

Raman Baweja
5/15/2008 03:53:55 PM
BIOPHARMACEUTICS
I plan to have a Memo to File as OCP TL.

New Drug Application
Memo to File - Clinical Pharmacology
Change in Recommendation

NDA:	22-117
Type of Submission:	Original NDA
Submission Date:	August 30, 2007
Associated INDs:	51,641 September 30, 1996 (Treatment of Psychosis) 70,329 August 3, 2004 (Treatment of Acute Mania in Bipolar I)
Generic Name:	Asenapine Maleate
Formulation: **Strengths:**	Sublingual Tablets 5 mg, 10 mg
Route:	Sublingual (N.B. Route is mislabeled in Application Form 356h)
Brand Name:	Sycrest®
Sponsor:	Organon / Schering-Plough
Reviewer:	Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D.

Kavanagh, Ronald E

From: Kavanagh, Ronald E
Sent: Friday, May 16, 2008 10:21 AM
To: Mehta, Mehul U
Cc: Baweja, Raman K; Laughren, Thomas P; Temple, Robert
Subject: NDA 22-117 Asenapine Change in Recommendation

Mehul,

Per my 9 AM verbal notification I am changing my recommendation for asenapine (NDA 22-117) to nonapproval per FD&CA Sec. 505 d) 1) b; d) 2); d) 5; and c) 7.

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All of the cardiac and respiratory toxicities can potentially be explained by this, and appears to be the mechanism for the death 2 months after adding an antidepressant and may be an alternative mechanism for several deaths including the patient with Quincke's edema and the death of the neonate.

I'm also afraid that the nasal congestion and respiratory symptoms seen in many patients will be self mediated with OTC decongestants and will increase toxicity.

It appears that this toxicity is mediated by agonism at the 5HT2B receptor and is likely due to an active metabolite produced in the 11-hydroxylation cascade. Based on the sponsor's receptor binding information the metabolite involved might be the 11-O-Sulfate but it could be others.

The metabolic scheme, the mechanism, and the observed toxicities along with the study designs used by the sponsor in the drug-drug interaction studies, and the lack of many specific pieces of information in the submission as well as other things indicate that the sponsor knew about this toxicity and specifically tried to prevent our detecting it.

The potentially toxic metabolites are formed via CYPs 3A4 and 1A2, and based upon the use of this medication it will be used in subjects who have increased formation via these pathways and the long term toxicities may be subtle and not appreciated until well after marketing. Although based on the asenapine paroxetine drug interaction study at least ~60% of the patients taking this drug may be at risk and it is likely even higher in African Americans and children. (AA due to expression of 3A5 and children due to factors already mentioned.)

I simply do not believe there is anything we can do that would adequately educate physicians and patients to the risks and that with off-label use we will be looking at an epidemic of potentially lethal cardiac and pulmonary toxicities in children several years from now.

I believe that the pop PK findings in blacks are likely either erroneous or spurious and a dedicated PK study in appropriate subjects will demonstrate why pop PK studies are unreliable.

This only a brief summary and I intend to amend my review to include more details and request adequate time to fully document my concerns.

Ron

Tracking:

Recipient	Delivery	Read
Mehta, Mehul U	Delivered: 5/16/2008 10:21 AM	
Baweja, Raman K	Delivered: 5/16/2008 10:21 AM	Read: 5/16/2008 10:31 AM
Laughren, Thomas P	Delivered: 5/16/2008 10:21 AM	Read: 5/16/2008 10:28 AM
Temple, Robert	Delivered: 5/16/2008 10:21 AM	Deleted: 5/16/2008 4:35 PM

Kavanagh, Ronald E

From: Laughren, Thomas P
To: Kavanagh, Ronald E
Sent: Friday, May 16, 2008 10:28 AM
Subject: Read: NDA 22-117 Asenapine Change in Recommendation

Your message

To: Mehta, Mehul U
Cc: Baweja, Raman K; Laughren, Thomas P; Temple, Robert
Subject: NDA 22-117 Asenapine Change in Recommendation
Sent: 5/16/2008 10:21 AM

was read on 5/16/2008 10:28 AM.

Kavanagh, Ronald E

From: Temple, Robert
To: Kavanagh, Ronald E
Sent: Friday, May 16, 2008 4:35 PM
Subject: Not read: NDA 22-117 Asenapine Change in Recommendation

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was deleted without being read on 5/16/2008 4:35 PM.

Kavanagh, Ronald E

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To: Kavanagh, Ronald E
Cc: Baweja, Raman K; Laughren, Thomas P; Temple, Robert; Lesko, Lawrence J; Huang, Shiew Mei; Uppoor, Ramana S
Subject: RE: NDA 22-117 Asenapine Change in Recommendation

Ron,

Please go ahead with your plan to undertake further evaluation of this new safety issue that has just been identified. Please send me a brief e mail COB Wednesday, May 21st, describing your progress, whether more time is needed and if so, how much more and to evaluate what remaining information.

Mehul

Note: New Address

Mehul Mehta, Ph.D.
Director
Division of Clinical Pharmacology I
Office of Clinical Pharmacology
OTS, CDER, FDA
Building 51, Room 2178
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301)796-2140
fax (301)847-8712
mehul.mehta@fda.hhs.gov

From: Mehta, Mehul U
Sent: Friday, May 16, 2008 1:37 PM
To: Kavanagh, Ronald E
Cc: Baweja, Raman K; Laughren, Thomas P; Temple, Robert; Lesko, Lawrence J; Huang, Shiew Mei; Uppoor, Ramana S
Subject: RE: NDA 22-117 Asenapine Change in Recommendation

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Sent: Tuesday, May 20, 2008 4:54 PM
To: Mehta, Mehul U
Cc: Baweja, Raman K; Laughren, Thomas P; Temple, Robert; Lesko, Lawrence J; Huang, Shiew Mei; Uppoor, Ramana S
Subject: RE: NDA 22-117 Asenapine Change in Recommendation

Mehul,

As you are aware from previous discussions I do not believe it is possible to write labeling with the present lack of information, and I was excused from writing labeling.

Today Ray told me that he is writing labeling. Since this must be based on the current version of my review prior to any amendment that you indicated I have until COB tomorrow to write, I must indicate my objection.

Ron

From: Mehta, Mehul U
Sent: Friday, May 16, 2008 1:37 PM
To: Kavanagh, Ronald E
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ron Kavanagh
5/20/2008 05:10:26 PM
BIOPHARMACEUTICS

New Drug Application
Clinical Pharmacology Review – Amendment # 1

NDA:	22-117
Type of Submission:	Original NDA
Submission Date:	August 30, 2007
Associated INDs:	51,641 September 30, 1996 (Treatment of Psychosis) 70,329 August 3, 2004 (Treatment of Acute Mania in Bipolar I)
Generic Name:	Asenapine Maleate
Formulation: **Strengths:**	Sublingual Tablets 5 mg, 10 mg
Route:	Sublingual (N.B. Route is mislabeled in Application Form 356h)
Brand Name:	Sycrest®
Sponsor:	Organon / Schering-Plough
Reviewer:	Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D.
Acting Team Leader:[1]	John Duan, Ph.D.

1 Table of Contents

[1] Usual Team Leader: Raman Baweja, Ph.D.

1.1 List of Tables

1.2 List of Figures

2 Executive Summary

2.1 Introduction

Asenapine is a heterocyclic dibenzo-oxepino pyrrole antipsychotic, i.e. a tetracyclic D2 antagonist that includes a pyrrole as the fourth ring that is proposed for the treatment of schizophrenia or acute episodes of bipolar I disorder. Dosages are 5 – 10 mg BID SL for schizophrenia, and 10 mg BID SL for the acute treatment of mania.

After the completion of the original OCP review, it was realized that the clinical pharmacology program appeared to be designed to minimize the ability to detect and mitigate risks. Consequently this reviewer believed it was not possible to make appropriate labeling recommendations. Thus on May 16th 2007 the recommendation for NDA 22-117 was changed to not approvable as required by the Food Drug and Cosmetics Act, (sections 505 d) 1) b; d) 2) 5, and c) 7).

On June 13, 2008 the sponsor submitted an amendment to the NDA (amendment no. 27 modification type BB). The EDR notification was received just as this review was about to be finalized so this reviewer included a review of this amendment in the present amendment.

2.2 Summary of Major Conclusions

Amendment 027 submitted June 13, 2008 fails to address the concerns raised regarding metabolism and mass balance as outlined in the original NDA review and clearly cannot address concerns regarding metabolism raised in this amendment. A critique of this amendment may be found in § 4.6 Appendix 6 - Review of Amendment 027 Submitted June 13, 2008

Asenapine causes serious cardiovascular toxicities including death due to pulmonary arterial hypertension and both direct and indirect effects on the myocardium, and also likely via indirect effects on platelet aggregation. These toxicities may either manifest acutely or chronically.

Pharmacology / Toxicology data indicates that asenapine affects bone remodeling and ossification and this may be of concern during pregnancy, in growing children, and in other populations where bone remodeling is an issue, e.g. elderly women and renal failure patients.

Asenapine appears likely to cause pulmonary arterial hypertension in neonates, resulting in death and maiming of children, and may even cause death simply by breast feeding infants by exposed mothers to drug postnatally.

There is also a probability that asenapine causes other connective tissue disorders, such as hernias and rupture of tendons in addition to other problems.

Animal studies indicate that there may be an increase in motor activity. For a drug that may be used to treat bipolar disorder or 'off-label' for bipolar II, bipolar depression, or bipolar spectrum disorder in children increased motor activity could be mistaken for a symptom of the illness and not drug toxicity and could induce prescribers to inappropriately increase the dose, which would increase the risk of chronic cardiopulmonary toxicity.

Asenapine also appears to cause agranulocytosis and there is a possible risk of aplastic anemia.

Mechanistically effects on platelet aggregation and strokes are also expected.

Death from asenapine can come suddenly and without warning in otherwise young healthy individuals due to arrhythmias or strokes with symptoms easily misattributed to something else such as orthostatic hypotension. More likely most serious cardiovascular toxicities are cumulative resulting in a Phen-Fen

type toxicity especially when dosed for over a year, although symptoms which are likely to be misattributed to something else, (e.g. fatigue), may occur as soon as the first dose.

The entire development program appears designed to minimize detection and quantification of risks and thereby precludes the ability to write appropriate labeling. In fact it is this reviewer's opinion that in several instances the sponsors' actions clearly rise to the level of unlawful conduct and must be reported to the criminal investigators.

Preliminary review indicates that it is also less safe than competing agents and offers few if any advantages.

With respect to benefit there is insufficient data to presently support use in schizophrenia and as for bipolar disorder the data indicted that only the most severely ill (YMRS > 27) may benefit with a few weeks of treatment but possibly not beyond that. Thus even efficacy in bipolar disorder I needs to be confirmed.

After further review this reviewer believes that asenapine is unacceptably dangerous at this time, there was inadequate information submitted to assess safety and such information was expected. There is insufficient information to determine if it will have the effects it purports to as suggested in the labeling.

In conclusion the Food Drug and Cosmetics Act require that asenapine not be approved based on the following subsections and criteria:

505 d)

1) Investigations do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling

2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions;

4) Upon the basis of the information submitted as part of the application, and upon other information with respect to asenapine, there is insufficient information to determine whether asenapine is safe for use under suggested conditions of use

5) On the basis of the information submitted as part of the application and based on other information, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling

7) Based on a fair evaluation of all material facts, such labeling is false and/or misleading in several particulars

In this reviewer's opinion the only way to potentially salvage this drug to redo the entire phase I and phase II programs with some additional phase III work including long term toxicity data. In addition, appropriate and complete preclinical pharmacology and toxicology data must be submitted that will allow a full vetting of the mechanistic bases of asenapine's toxicities and how they can be mitigated.

2.3 Recommendations

2.3.1 Recommendations re: Asenapine

It is recommended that asenapine N22-117 submitted on August 30, 2007 not be approved per the Federal Food Drug and Cosmetics Act under Sections 505 [21 USC 355] d) (1); (2); (3); (4); (5); and (7).

2.3.2 Recommendations re: Class Effects

As the toxicities also appear to be class effects for a variety of different classes of drugs re-evaluation of other drugs and drug classes should be undertaken and a communication to the public of an emerging public safety issue that is an imminent threat to the public health be communicated with maximum haste.

2.3.2.1 Nonphenothiazine Antipsychotics

Nonphenothiazine[2] antipsychotics that are at the top of the list with regards to the degree of concern regarding cumulative long term (**> 1 year**) cardiopulmonary toxicities include the following structurally similar compounds:

Olanzapine and in particular Symbyax®.
Clozapine
Pimozide (Orap®)
Quetiapine

These class effects are of particular concern in children as older antipsychotics are less likely to be approved and used in children and the toxicities identified may be especially clinically relevant in a population with forced compliance and that is otherwise at low risk for the type of cardiovascular toxicities expected, in addition due to less accumulated underlying cardiovascular disease it may take longer than in adults for adverse effects to become apparent or to be properly identified.

The elderly may also be at greater risk of long term toxicities (> 1 year) due to underlying physiologic changes. In general, the same age population that suffers from erectile dysfunction may also be at increased risk for cardiovascular toxicity.

2.3.2.2 Other Therapeutic Classes and Specific Therapeutic Agents

Many other drugs such as SSRIs, fluoroquinolones, steroids, avermectins, and food additives may also have similar effects but to various degrees. Information on an emerging public health issue on these and other compounds should be communicated in the next week with an Advisory Committee meeting scheduled as soon as possible.

2.3.3 Recommendations re: Criminal Investigations

Per instructions from OCP management (Dr. Mehta) any recommendations (or communications) regarding criminal investigations from this reviewer first obtain approval from the management chain of command. This constitutes a formal request to FDA management and recommends criminal investigation of individuals in various companies and organizations for failure to report deaths, attempting to mislead reviewers by various devices that are apparently intended to obfuscate and hide data required for review and that are needed to make safety assessments that would effect approval, and potentially sales and reimbursements. In fact the evidence suggests that there may have been an intentional design to harm, maim, and occasionally kill children so as to induce the need for purchasing other products from the sponsor or cosponsors.

[2] N.B. The term atypical antipsychotic has no clear definition and is typically used colloquially to denote more recently marketed drugs with differing effects at serotonergic receptors as compared to phenothiazines and less tardive dyskinesia as compared to the butyrophenone, haloperidol. Some of the older antipsychotics such as pimozide, molindone, and loxapine that are often included as 'typical' or 'classic' antipsychotics actually have much more in common with clozapine, and other 'atypical' antipsychotics.

Consequently this reviewer believes that the following section of federal law may have been potentially violated:

SEC. 301. [21 USC §331] Prohibited Acts.

> (ii) The falsification of a report of a serious adverse event submitted to a responsible person (as defined under section 760 or 761) or the falsification of a serious adverse event report (as defined under section 760 or 761) submitted to the Secretary, (see §3.5.1.2 and §3.5.1.6).

There are more than instance which will require more time to cite appropriately and will be communicated only to the appropriate criminal investigators.

This reviewer believes the following laws may have also been violated; these include possible violations of law by FDA personnel. (N.B. This list does not encompass all potential violations). Per instructions from Dr. Mehta this reviewer requests that these concerns be referred to the appropriate criminal investigators.

18 USC § 201
18 USC § 286
18 USC § 371
18 USC § 372
18 USC § 1001
18 USC § 1002.
18 USC § 1018.
18 USC § 1111
18 USC § 1112
18 USC § 1117
18 USC § 1343
18 USC § 1347
18 USC § 1349
18 USC § 1505.
18 USC § 1512
18 USC § 1518

2.4 Comments and Requests

2.4.1 Comments to the Sponsor

2.4.1.1 Comments to be Forwarded Regardless of Approvability

With respect to the pregnancy that resulted in a premature delivery and death within 5 minutes of birth, it was noted that there is a history of a number of other pregnancies in this mother with poor outcomes.

This confounds interpretation however the timing of 2 of the spontaneous abortions indicate the either that these fetuses may have been malformed or that there may have been a hormonal issue. In addition other pregnancies in this patient resulted in a spontaneous abortion occurring at 20 weeks, and a caesarian section occurring at 34 weeks due to fetal distress. These other outcomes in combination with the premature birth with death occurring at 5 minutes post birth in the clinical trail raises questions as to the underlying cause(s). Specifically could there have been pre-eclampsia or vasoconstriction of blood flow to the placenta or to fetal tissues due to serotonergic effects of drugs, or a combination of the two. A medication history, fuller histories of the previous pregnancies including the postnatal history of the surviving infant, and an autopsy in the present case would be informative and as much of this information as possible should be obtained.

2.4.1.2 Comments to be Forwarded Only if Asenapine is found Approvable

Structures of all compounds with stereoisomerism and all information on receptor binding and potential pharmacologic activities of any and all metabolites and degradation products are needed including nomenclature. This will likely necessitate new mass balance studies. Please note this request is not limited to 'major' metabolites as this may eliminate clinically important species.

In addition, complete drug substance and drug product information for any asenapine or asenapine derivative structure that has been used in any clinical or preclinical study is requested.

Complete data sets from any clinical study that has not been submitted so far is also needed. This includes data from the thorough QT study and includes pharmacokinetic, clinical laboratory, and AE data. As well as similar information that has not been submitted for early human studies or for any 'ongoing' studies should also be included. 'Ongoing' studies should be interpreted to include both studies that were ongoing at the time of the original NDA submission as well any subsequently conducted studies.

2.4.2 Comments to the Medical Division

The sponsor has published several *in vitro* and preclinical articles implying that asenapine might be useful for impaired cognition and negative symptoms[3],[4]. With respect to cognition, asenapine impaired both short and long term memory in humans and would be expected to make certain features of dementia worse. OCP recommends that any final labeling include language that would mitigate ill-advised off-label use.

Please see:

§ 2.4.3 Comments to Pharmacology / Toxicology Review Team
§ 2.4.4 Comments Regarding Pilot Review Project
§ 2.4.5 Comments Regarding New FDA Regulations, Policies etc

In addition to the information available from this submission that indicates that the risk of all cause mortality increases over time; recent publications indicate that the risk of suicide is lower than previously thought and decreases over time and that a subpopulation at greatest risk may be identifiable. This suggests that the risk benefit ratio of antipsychotic medications changes over time and the chronic use of antipsychotic medications in schizophrenics is a public health issue that needs to be reexamined.

2.4.3 Comments to Pharmacology / Toxicology Review Team

Please consider the following comments with regards to your suggested labeling:

1. In the mechanism of action and pharmacodynamics section please include other receptors that have been excluded that are expected to contribution to pharmacologic actions, e.g. 5HT2B, D4 etc., including subtypes

2. With regard to pharmacodynamics, indicating whether compound activity is agonistic or antagonistic, and including effects by parent drug, metabolites, and degradation products as well their potencies is recommended as a minimum. In addition information on the expected clinical implication of effects at various receptors would be welcome if it's expected to be clinically important.

[3] Psychopharmacology (Berl). 2008 Feb;196(3):417-29. Epub 2007 Oct 17
[4] *Neuropsychopharmacology* advance online publication 16 April 2008; doi: 10.1038/npp.2008.20 http://www nature.com/npp/journal/vaop/ncurrent/full/npp200820a html

3. Please consider adding information addressing differences in efficacy and toxicity by stereoisomers that may be observed especially when they are produced by degradants, contaminants, physical drug interactions, and *in vivo* metabolism.

4. Please reconsider the wording of the pregnancy section. Although asenapine wasn't 'teratogenic' it did have dose dependent embryo-fetal toxicity in all species and strains, and in some studies some effects were observed at all dose levels. Some of these effects were consistent with known, likely mechanism based AEs, seen in humans with similar drugs and asenapine is expected to result in the same toxicities. Specifically, pulmonary arterial hypertension in newborns especially when coadministered with antidepressants. Plus asenapine may possibly increase pre-eclampsia in women.

5. Even in pups not exposed *in utero* there was an increase in the postnatal loss of pups exposed to asenapine only through breast milk.

6. Effects on skeletal muscle formation, and remodeling, including poor ossification, was seen in all animal species and appears to be a class effect. Consequently asenapine is expected to effect bone and connective tissue especially during development, growth, and in the elderly or other populations at risk, e.g. renal failure patients.

2.4.4 Comments Regarding Pilot Review Project

Please refer to the following appendices:

§ 4.7 Appendix 7 – Quality of the Submission

§ 4.8 Appendix 8 – Evaluation of Pilot NDA Review Process

2.4.5 Comments Regarding New FDA Regulations, Policies etc

Please see:

§ 4.9 Appendix 9 – Lessons Learned and Feedback on FDA Policies, Procedures and Regulations

2.5 Signatures

Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D. **Date**

Senior Reviewer
Division of Clinical Pharmacology I

John Duan, Ph.D. **Date**

Acting Team Leader
Division of Clinical Pharmacology I

3 Review

3.1 Background

3.1.1 Introduction

Asenapine and structurally related drugs (e.g. olanzapine and clozapine) exhibit a constellation of side effects that suggest agonist effects at serotonin 5HT2B receptors and possibly related serotonin receptors.

5HT2B receptor stimulation has been implicated in the valvular heart disease and pulmonary arterial hypertension associated with phen-fen.

3.1.2 Signs and Symptoms Associated 5HT2B Agonism

The following is a list of symptoms from the National Heart Lung and Blood Institute at NIH that are associated with pulmonary arterial hypertension:

3.1.2.1 Pulmonary Arterial Hypertension

Difficulty breathing or shortness of breath (dyspnea) is the main symptom of pulmonary arterial hypertension (PAH). If you have PAH, you may feel that it is difficult to get enough air.

Other Common Signs and Symptoms

- Fatigue
- Dizziness
- Fainting spells (syncope)
- Swelling in the ankles or legs (edema)
- Bluish lips and skin (cyanosis)
- Chest pain
- Racing pulse
- Palpitations (a strong feeling of a fast heartbeat)

As the disease advances:

- The pumping action of your heart grows weaker.
- Your energy decreases.

In the more advanced stages, you:

- Are able to perform very little activity
- Have symptoms even when resting
- May become completely bedridden

It is clear from the list, that the symptoms are relatively nonspecific. Thus a high index of suspicion is needed for detection.

In addition to direct effects on the heart due to pharmacologic action at cardiac 5HT receptors, there may also be secondary effects due to the heart working against the resistance caused by pulmonary vasculature vasoconstriction that results in the increased pulmonary arterial pressure.

Acutely, this may include coughing up blood[5]. In addition there may be secondary effects on the heart that may show up either acutely or chronically depending upon the patient's underlying baseline physiology.

3.1.2.2 Cardiotoxicity

5HT2 agonsim may also result in a variety of cardiac arrhythmias both acutely and chronically. For example Right Bundle Branch Block may be induced by a number of different illnesses that may be secondary to a variety of effects that can be secondary 5HT2B agonism as shown in Table 1.

Table 1 Differential Diagnosis of RBBB

Table 3. Differential Diagnosis of Right Bundle Branch Block.	
Congenital	- Isolated, idiopathic, and of no functional significance.
	- Atrial Septal Defect.
	-Other congenital heart disease resulting in systolic overload of the right ventricle.
Acquired.	- Idiopathic.
	- Ischaemic Heart Disease (IHD).
	- Myocardial Infarction (AMI).
	- Degenerative or destructive diseases of the conducting system *(10)*.
	- Cor pulmonale.
	- Myocarditis *(11)*.
	- Acute right ventricular strain *(12).*
	- Surgical ventriculotomy.
	- Trauma

Source: http://aeromedical.org/Articles/XAVM_714-9.html

A good example of the variety of cardiovascular symptoms that are seen with stimulation of serotonin receptors (e.g. 5HT2B) can be found simply by examining the side effect profile for dihydroergotamine as described in Micromedex:

"DHE Micromedex

Symptoms of ERGOTISM from high doses of dihydroergotamine (or prolonged use) include circulatory disturbances manifested by COLDNESS OF THE SKIN, severe MUSCLE PAINS, and vascular stasis, which can result in dry peripheral GANGRENE; symptoms are related to intense VASOCONSTRICTION and thrombus formation (AMA, 1990; Reynolds, 1982); ANGINA-LIKE PRECORDIAL PAIN, transient sinus tachycardia, and bradycardia may occur, along with either HYPOTENSION or HYPERTENSION (AMA, 1990; Reynolds, 1982). The incidence of vasoconstriction and gangrene appears to be less with dihydroergotamine than with ergotamine (AMA Department of Drugs, 1983).

Migraine drugs, including ergotamine, DIHYDROERGOTAMINE, methysergide, sumatriptan, avitriptan, and zolmitriptan, were found to cause coronary vasoconstriction to a degree that would not be hazardous in healthy subjects but could be harmful in patients with cardiovascular impairment, based on testing in isolated coronary artery segments. Coronary vasoconstriction was also significantly more prolonged with

[5] http://www.pph-net.org/pph-symptoms-pph-diagnosis.htm

ergotamine and DIHYDROERGOTAMINE compared with sumatriptan and related 5-HT antimigraine agents (Maassen VanDenBrink et al, 1998a).”

3.1.2.3 Connective Tissue Disorders

Connective tissue disorders and alterations in skeletal formation may also be affected by drugs that stimulate certain serotonin receptors. Whether this is due to effects at alternative receptors that might also accept the drug, a common pathway, or both is not clear.

According to the Merck Manual Primary Pulmonary Hypertension (PPH) *“can be familial or sporadic; sporadic cases are about 10 times more common. Most familial cases have mutations in the gene for the bone morphogenetic protein receptor type 2 (BMPR2), part of the transforming growth factor (TGF)-β family of receptors. About 20% of sporadic cases also have BMPR2 mutations. Many people with PPH have increased levels of angiopoietin-1; angiopoietin-1 appears to down-regulate BMPR1A, a sister receptor to BMPR2, and may stimulate serotonin production and endothelial smooth muscle proliferation. Other possible contributing factors include abnormalities in serotonin transport and previous infection with human herpes virus*.””[6]

PPH is also associated with scleroderma and other connective tissue disorders. As mentioned previously BMPR2 may have common final pathways with certain serotonin receptors, thus drugs that effect serotonin receptors should also be evaluated for effects on skeletal bone formation as well as effects on fibrosis of certain organs such as the heart and liver, and weakening of other connective tissues such as tendons and other tissues as evidenced by increases in congenital hernias.

Effects on skeletal bone formation and remodeling would be expected to be a more chronic toxicity and would be expected to show up in fetal skeletal formation, during growth when there is extensive bone remodeling, and in the elderly and especially in slightly built women or other populations where osteoporosis is an issue.

3.1.2.4 Other Associated Toxicities

A number of other adverse effects are also seen with the same drugs or conditions that cause PAH and include:

- Renal Failure
- Cirrhosis of the Liver (May be related to fibrotic tissue formation due to effects at serotonin receptors)
- Seizures[7]
- Psychosis and Suicidality

3.1.2.5 Effects on Neonates

When pulmonary arterial hypertension occurs in a fetus, death shortly after birth due to suffocation is a common complication. In those neonates who survive, 50% experience deafness and other neurologic deficits.

In fact the association of primary PAH and serotonin in neonates has been noted by FDA for selective serotonin reuptake inhibitors when used alone[8].

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[6] http://www.merck.com/mmpe/sec05/ch058/ch058a.html accessed June 11, 2008
[7] Spencer DC, Hwang J, Morrell MJ. Fenfluramine-Phentermine (Fen-Phen) and Seizures: Evidence for an Association. Epilepsy Behav. 2000 Dec;1(6):448-452.
[8] http://www.foxnews.com/story/0,2933,184396,00.html

3.1.3 Time Course of Effect

With some patients with underlying pathophysiologic conditions that predispose them to serotonergic toxicities, cardiac effects such as asystole might be immediate, although as will be discussed later this can also vary with the specific agent involved, which serotonin receptors are affected, how they are effected and its potencies at various receptors as well as the effects of drug interactions.

With phen-fen, the prototypical 5HT2B clinical agonist, the effects may occur only after chronic use. This has been noted both by the FDA and others. [9,10]

For example studies that have looked for evidence of phen-fen induced valvulopathy by echocardiography have found a 30% incidence after 3 months of use.

Other sources have claimed: *"A significant association exists between the use of the fen phen diet drug and PAH/PPH. Fen phen was taken off the market in the US in 1997. Studies have shown that it can be several years after having stopped taking diet drugs that patients develop the disease. Medical experts have testified that there is a potential latency of ten or more years between the last date on which a patient is exposed to diet drugs and the date at which the patient develops the first symptoms of what is ultimately diagnosed as PAH/PPH."*

It should be noted that a high index of suspicion is required to see the signs of PAH with drugs, in fact the FDA website states: *"And even in symptomatic patients, the link between the symptoms and drug use may not be obvious because such a reaction is not common. These factors may explain why this problem was not discovered earlier."*

Regardless of the time of onset, the duration may be in years resulting in significant morbidity even with treatment, if not mortality, and even if the effects are reversible the process may take years. For additional information the following articles may be of use.

Fleming RM, Boyd LB. The longitudinal effects of fenfluramine-phentermine use. Angiology. 2007 Jun-Jul;58(3):353-9. Angiology. 2007 Dec-2008 Jan;58(6):772-3; author reply 774.

A number of other references regarding PAH and 5HT2B agonism are available and include the following:

Harrison W. Farber, M.D., and Joseph Loscalzo, M.D., Ph.D. Pulmonary Arterial Hypertension, NEJM October 14, 2004 Volume 351:(16) 1655-1665

Robert J. Levy Serotonin Transporter Mechanisms and Cardiac Disease (Editorial) Circulation 2006;113; 2-4 (http://circ.ahajournals.org/cgi/content/full/113/1/2)

Robert Naeije, M.D.a and Saadia Eddahibi, Ph.D. Serotonin in Pulmonary Arterial Hypertension (Editorial) American Journal of Respiratory and Critical Care Medicine Vol 170. pp. 209-210, (2004) (http://ajrccm.atsjournals.org/cgi/content/full/170/3/209)

3.1.4 Risk Factors

As shown by Fen-phen there is an even greater concern that a combination of a SSRI with an antipsychotic may increase risks substantially. Such a combination was approved in December 2003 for bipolar depression, (Fluoxetine/Olanzapine - Symbyax®; N21-250 - Lilly). The labeled indication is for "Depression associated with Bipolar Disorder". In addition, such combinations are being proposed for more rapid onset in depression and may potentially be used off-label for bipolar spectrum disorder.

[9] *http://www.fda.gov/cder/news/phen/fenphenqa2.htmDiet Drugs - Fen Phen*
[10] http://www.fda.gov/cder/news/mmwr.pdf

Risk factors for PAH include smoking as hypoxia may contributory, and AIDS.[11], although it's claimed that the effect of cigarette smoking on PAH is due to hypoxia, an alternative or synergistic mechanism may be due to stimulation of 5HT receptors by cigarette additives, for example pyrroles such as found in asenapine are among the most common additives to cigarette tobacco.

Age may also be a risk factor not only due to decreased elimination of toxic substances, increased risk of drug-drug interactions, but also physiological changes due to aging such as atherosclerosis, and the loss of vascular elasticity and associated increased systolic hypertension in addition to the osteoporosis mentioned earlier.

3.1.5 Alternative Mechanisms for PAH

In addition to effects on serotonin receptors there are several other mechanisms that have been implicated in primary PAH. Foremost among them are due to effects on arachadonic acid and prostaglandins. Since, the clinical effects of acute cardiotoxicity with COX inhibitors such as rofecoxib (Vioxx® - Merck) are so similar, yet there is differing effects on survival by drug, e.g. sulindac and rofecoxib both cause effects on renal vasculature (rofecoxib in rabbits and sulindac (Clinoral® – Merck) in humans) yet rofecoxib has a high incidence of cardiac toxicity whereas sulindac doesn't'. This may indicate species differences or unidentified COX-2 subtypes.

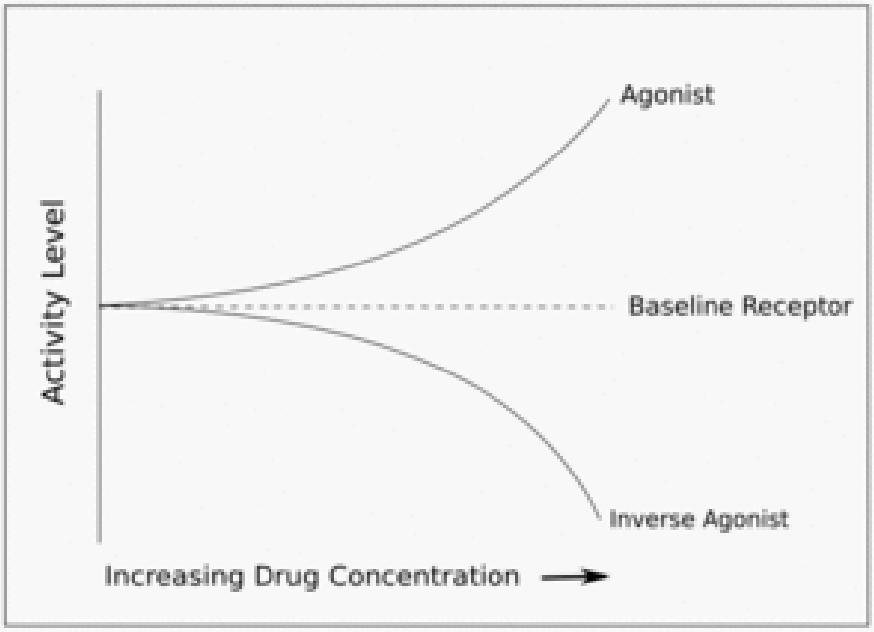
Some other mechanisms such as agonism of endothelin receptors may have similar final common pathways with stimulation of certain serotonin receptors.

[11] Ngo MV, Gottdiener JS, Fletcher RD, Fernicola DJ, Gersh BJ. Smoking and obesity are associated with the progression of aortic stenosis. Am J Geriatr Cardiol. 2001 Mar-Apr;10(2):86-90.

3.1.6 Serotonin Receptors

Except for 5HT3 all known 5HT receptors are G-coupled receptors with an inverse agonist effect. A receptor with an inverse agonist effect is essentially a 3 way switch. The baseline state without a ligand bound to the receptor produces no effect (i.e. it's neutral). Whereas some ligands when they bind cause an effect in one direction, for example up regulation of mitochondrial activity, and other ligands cause the opposite effect, for example down regulation of mitochondrial activity. Figure 1 is an example demonstrating the 3 possible responses seen with experiments that are typically performed with 5HT receptors.

Figure 1 Schematic of Potential Effects on Inverse Agonist Serotonin Receptors



Source: http://en.wikipedia.org/wiki/Inverse_agonist

Table 2 is a summary of various 5HT receptors and their agonist and antagonist activities. This table was taken form a public website that is not peer reviewed and so may be in error. Consequently, this table is only included for conceptual purposes. Although this reviewer uses the term 5HT2B for the effects of phen-fen the table indicates it's mediated via 5HT1B. It's possible that this reviewer is using older nomenclature that has since been changed. However, it's also possible that effects are mediated at both receptors. As phen-fen cardiac valve effects are listed as an effect on 5HT2B by the new NIMH Psychoactive Drug Screening Program.[12] Rather than spend time clarifying this issue this reviewer will simply ascribe the effects to 5HT2B with the understanding that this might be an erroneous or incomplete designation.

Regardless of the nomenclature used it's clear that pulmonary vasoconstriction is a major problem with phen-fen and also occurs with ergots. It's noteworthy that the cardiac side effect profile noted with dihydroergotamine earlier is virtually identical to the side effects seen with asenapine.

A good review of 5-HT receptors has been written by scientists from Novartis, however as the article is 7 years old it is likely dated.[13]

A likely more reliable , although abbreviated description of serotonin receptors and functions may be found in section 4.1 in the appendix, and is from the website of the Lundbeck Institute, which is associated with Lundbeck Pharmaceuticals.

It's clear from this that simply reporting affinities for serotonin receptors without providing such plots is useless.

[12] http://pdsp.med.unc.edu/ accessed June 2, 2008
[13] Daniel Hoyer, Jason P. Hannon, Graeme R. Martin; Molecular, pharmacological and functional diversity of 5-HT receptors Pharmacology, Biochemistry and Behavior 71 (2002) 533–554

Table 2 Summary of characterized 5-HT receptors, with selected high affinity agonist and antagonist ligands

Receptor	Gene	Actions	Agonists	Antagonists
5-HT_{1A}	*HTR1A*	CNS: neuronal inhibition, behavioural effects (sleep, feeding, thermoregulation, aggression, anxiety)	buspirone psilocin LSD 8-OH-DPAT	spiperone methiothepin ergotamine yohimbine
5-HT_{1B}	*HTR1B*	CNS: presynaptic inhibition, behavioural effects vascular: pulmonary vasoconstriction	ergotamine sumatriptan	methiothepin yohimbine metergoline Risperidone
5-HT_{1D}	*HTR1D*	CNS: locomotion, anxiety; vascular: cerebral vasoconstriction	5-(Nonyloxy)tryptamine,[4] sumatriptan	methiothepin yohimbine metergoline ergotamine
5-HT_{1E}	*HTR1E*			
5-HT_{1F}	*HTR1F*			
5-HT_{2A}	*HTR2A*	CNS: neuronal excitation, behavioural effects, learning, anxiety smooth muscle: contraction, vasoconstriction / vasodilatation platelets: aggregation	α-methyl-5-HT LSD psilocin DOI	Nefazodone trazodone mirtazapine ketanserin cyproheptadine pizotifen atypical antipsychotics
5-HT_{2B}	*HTR2B*	stomach: contraction	α-methyl-5-HT LSD DOI Fenfluramine	yohimbine
5-HT_{2C}	*HTR2C*	CNS: anxiety, choroid plexus: cerebrospinal fluid (CSF) secretion	α-methyl-5-HT agomelatine LSD psilocin DOI	mesulergine agomelatine fluoxetine methysergide[5]
5-HT_{3}	*HTR3A*, *HTR3B*	CNS, PNS: neuronal excitation, anxiety, emesis	2-methyl-5-HT	metoclopramide (high doses) renzapride ondansetron alosetron mirtazapine memantine
5-HT_{4}	*HTR4*	GIT: gastrointestinal motility CNS: neuronal excitation, learning, memory	5-methoxytryptamine metoclopramide renzapride tegaserod RS 67333	GR113808 Piboserod
5-HT_{5A}	*HTR5A*	CNS (cortex, hippocampus, cerebellum): unknown	5-carboxytryptamine LSD[3]	unknown
5-HT_{6}	*HTR6*	CNS: unknown	LSD	SB271046[6]
5-HT_{7}	*HTR7*	CNS, GIT, blood vessels: unknown	5-carboxytryptamine LSD	methiothepin risperidone

a Note that there is no 5-HT1C receptor since, after the receptor was cloned and further characterized, it was found to have more in common with the 5-HT2 family of receptors and was redesignated as the 5-HT2C receptor.

b Source: http://en.wikipedia.org/w ki/Serotonin_receptor Accessed June 2, 2008

A recent publication suggests that at least part of the efficacy of certain antipsychotics in schizophrenia may be mediated via antagonism of the 5-HT_6 receptor, which is a Galpha coupled receptor. Although antagonism by parents does not account for the effects of metabolites.[14]

In addition, it has been reported that agonism of the Endothelin-A receptor, Galpha subunit may induce cardiac hypertrophy.[15]

3.2 Receptor Activity

Table 3 shows the receptor affinities with asenapine and a number of other antipsychotics.

Every antipsychotic listed except for haloperidol and risperidone binds more potently to the 5HT2B receptor than the dopamine D2 receptors, however without information on whether there is agonist or antagonistic effects at the individual receptors predications of the potential clinical implications cannot be assessed.

Table 4 is from the original NDA and shows that in addition to asenapine various asenapine metabolites have similar or greater binding affinities to various serotonin receptors as compared to asenapine.

[14] Eur J Pharmacol. 2008 Jul 7;588(2-3):170-7. Epub 2008 Apr 20. http://www.ncbi.nlm.nih.gov/pubmed/18511034?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum Accessed June 17, 2008

[15] J Recept Signal Transduct Res. 2004;24(4):297-317. http://www.ncbi.nlm.nih.gov/pubmed/15648448 Accessed June 17, 2008

Table 3 Comparative Receptor Binding Affinities for Various Antipsychotics Expressed as IC50s (Moles/L)

	Function	Receptor	asenapine	aripiprazole	ziprasidone	quetiapine	olanzapine	risperidone	clozapine	haloperidol
G protein Coupled		5-HT1A	2.51E-09	2.69E-09	9.77E-10	1.66E-07	1.51E-06	1.78E-07	8.71E-08	5.13E-07
		5-HT1B	3.98E-09	2.82E-09	8.91E-10		2.51E-07	5.13E-08	2.69E-07	
		5-HT2A	7.08E-11	9.55E-09	3.09E-10	1.55E-07	1.32E-09	2.04E-10	4.07E-09	5.25E-08
		5-HT2B	1.78E-10	2.57E-10	8.32E-10	4.68E-08	3.89E-09	1.02E-08	1.62E-09	3.31E-07
		5-HT2C	3.47E-11	2.82E-08	9.77E-10	1.05E-06	3.89E-09	6.76E-09	2.75E-09	1.62E-06
Ligand gated cation channel		5HT3								
G protein Coupled	Fxn Unk	5-HT5A	1.45E-09	8.91E-07	1.12E-06	2.00E-06	1.00E-07	5.89E-08	2.51E-08	7.94E-07
	"	5-HT6	2.51E-10	2.29E-07	1.66E-07	2.29E-06	3.24E-09	2.19E-06	8.91E-09	3.63E-06
	"	5-HT7	1.15E-10	3.47E-08	2.51E-09	5.62E-08	3.72E-08	7.41E-10	6.46E-09	8.91E-08
	Excitatory	D1	1.41E-09		3.55E-09		1.17E-08	2.09E-08	2.29E-08	6.31E-09
G protein Coupled	Inhibitory presynaptic	D2A	1.26E-09	1.15E-09	8.13E-09	4.17E-07	2.14E-08	6.17E-09	1.35E-07	1.45E-09
		D2B	1.45E-09	1.23E-09	1.02E-08	4.79E-07	2.63E-08	8.51E-09	1.55E-07	1.74E-09
	postsynaptic	D3	4.17E-10	1.41E-09	4.47E-09	3.89E-07	3.47E-08	6.92E-09	2.19E-07	2.75E-09
4.7 assoc with ADHD		D4	1.12E-09	1.29E-07	4.68E-08	1.41E-06	1.78E-08	6.17E-09	4.68E-08	1.48E-09
		α1A	1.17E-09	3.24E-07	1.55E-08	6.46E-08	2.24E-08	5.13E-09	1.26E-08	2.51E-08
		α2A	1.15E-09	6.92E-08	2.57E-07	5.62E-07	1.48E-07	8.13E-09	2.88E-08	8.71E-07
G coupled	Ag dec BP	α2B	3.24E-10	1.91E-07	2.40E-07	8.32E-08	3.31E-07	9.55E-09	2.82E-08	5.62E-07
	Ag inc BP	α2C	1.23E-09	1.17E-08	4.17E-08	3.80E-08	4.07E-08	1.82E-09	1.58E-09	1.32E-07
	CNS integrative	H1	1.00E-09	2.04E-08		1.10E-08	3.39E-09	8.13E-08	1.74E-09	
		H2	6.17E-09							
		M1	8.13E-06	3.89E-06		2.82E-07	1.20E-08	2.69E-05	5.13E-09	5.62E-06
		M2	3.16E-05	1.20E-05		6.03E-07	3.98E-08	3.89E-05	7.08E-08	8.91E-06
		M3	2.14E-05	7.76E-06		5.13E-07	3.39E-08	2.51E-05	2.45E-08	1.35E-05
		M4	9.12E-06	5.89E-06		2.45E-07	2.24E-08	1.07E-05	2.09E-08	5.62E-06
		5HT2B/D2A Ratio	7.08	4.47	9.77	8.91	5.50	0.60	83.18	0.00

Table 4 Estimated IC_{50}s (nMol/L) for Human Receptor Binding and Transporters Based on Reported pK_is

	R&DRR INT00002643					Study 00003223				
Receptor	Asenapine	(-)asenapine	(+)asenapine	N-desmethyl	N-oxide	Org 191634-0 N-sulfated- N-Desmethyl	Org 213772-0 11-OH	Org 214025-0 11-O-sulfate	Org 216761-0 N-Gluc	Org 220473-0 7-OH
5-HT1A	2.5	9.1	2.7	6.2	1,071.5	10.0	4.0	31.6		25.1
5-HT1B	4.0	1.7	2.5	199.5	35.5					
5-HT2A	0.1	0.1	0.0	2.4	6.0	25.1	0.10	0.13		0.13
5-HT2B	0.2	0.4	0.9	2.5	38.0	10.0	0.10	0.40		0.32
5-HT2C	0.03	0.1	0.0	1.9	6.0	20.0	0.13	0.40		0.13
5-HT5A	1.4									
5-HT6	0.3	0.3	0.1	13.8	85.1	20.0	0.1	0.2		0.8
5-HT7	0.1	0.1	0.2	10.5	57.5	31.6	0.2	0.3		1.6
D1	1.4									
D2L	1.3	2.0	1.9	55.0	631.0					
D2S	1.4	1.4	1.1	47.9	478.6	100.0	4.0	15.8		4.0
D3	0.4	0.4	0.5	19.1	204.2	39.8	4.0	7.9		0.8
D4	1.1	1.0	2.5	97.7	446.7					
D4.7										
α1A	1.2	1.4	1.0	27.5	316.2	15.8	1.0	5.0		4.0
α2A	1.1	0.9	2.4	17.4	549.5	79.4	6.3	20.0		6.3
α2B	0.3	0.2	0.4	2.3	128.8					
α2C	1.2	1.1	4.9	37.2	616.6	63.1	10.0	15.8		10.0
H1	1.0					20.0	1.3	1.6		0.1
H2	6.17									
M1	8,128	7,244	10,233	8,318	60,256					
M2	31,623	38,905	33,113	36,308	64,565					
M3	21,380	15,488	21,878	25,704	67,608					
M4	9,120	7,244	6,166	9,333	37,154					
M5	2.5	9.1	2.7	6.2	1,071.5	10.0	4.0	31.6		25.1
SERT	4.0	1.7	2.5	199.5	35.5					
NET	0.1	0.1	0.0	2.4	6.0	25.1	0.10	0.13		0.13
DAT	0.2	0.4	0.9	2.5	38.0	10.0	0.10	0.40		0.32

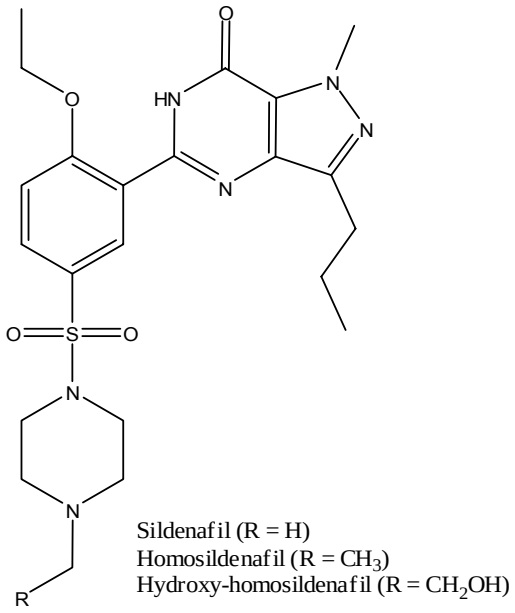
3.3 Potential Effect of Metabolism on Receptor Activity

Although it has been claimed by the sponsor in summary documents as well as in publications that asenapine itself is a 5HT2B antagonist this does not mean that metabolites are also antagonistic.

3.3.1 Evidence from Other Pharmacologically Active Agents

A recent and relevant example of this possibility is the May 27, 2008 FDA announcement that Xiadafil™ contains hydroxy-homosildenafil a structural analog of sildenafil (Viagra® - Pfizeer) that may be "*potentially harmful*" and "*can interact in dangerous ways with drugs that a consumer is already taking*".[16,17] The structures of sildenafil, homo-, and hydroxy-homo-sildenafil are shown in Figure 2.

Figure 2 Structures of Sildenafil and Selected Sildenafil Analogs



Sildenafil in addition to being used for erectile dysfunction, (Viagra® - Pfizer), is also approved to treat pulmonary arterial hypertension, (Ravatio® - Pfizer), which is one of the toxicities that Phen-fen was eventually recalled from the market for producing.

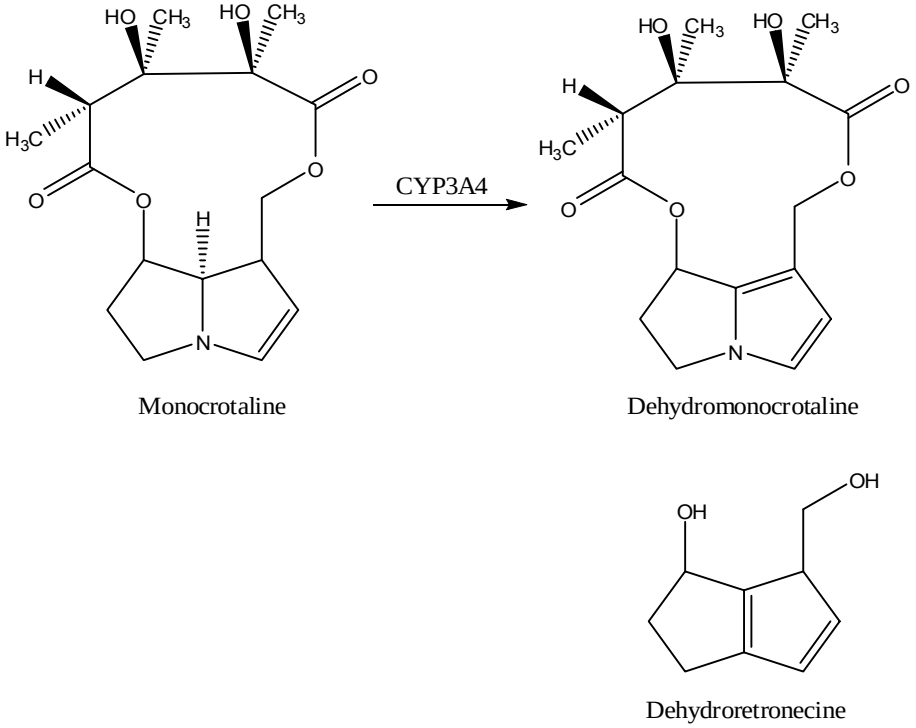
With regards to 'herbal Viagra', Dr. Todd Nippoldt of the Mayo Clinic has made a very interesting comment: "*Many herbal products marketed as sexual stimulants claim to be 'natural versions' of Viagra — but they aren't the same as the prescription drug. Some contain substances (vasodilators) that improve blood flow by relaxing the walls of blood vessels. But no herbal products are as specific for blood vessels to the penis as Viagra and other similar prescription drugs are. As a result, these herbal remedies may cause generalized low blood pressure and restrict blood flow to vital organs.*"[18]

This raises questions as to which vital organs are blood flow diminished, and if a minor change in structure on the opposite end of the sildenafil molecule, which is the part that is similar to serotonin, alters the type of pharmacologic activity at certain serotonin receptor subtypes, then why wouldn't metabolism of asenapine result in similar effects with respect to change a critical pharmacologic function.

[16] http://www.fda.gov/medwAtch/safety/2008/safety08.htm#Xiadafil accessed June 2, 2008
[17] http://www.fda.gov/bbs/topics/NEWS/2008/NEW01840.html accessed June 2, 2008
[18] http://www.mayoclinic.com/health/herbal-viagra/AN00702 Accessed June 2, 2008

Even more noteworthy is the fact that the pulmonary arterial hypertension secondary to monocrotaline[19], is mediated by its active metabolite monocrotaline pyrrole, (See Figure 3).

Figure 3 Structure and Metabolism of Monocrotaline



Monocrotaline

Dehydromonocrotaline

Dehydroretronecine

Ref: Nucleic Acids Research Volume 26, Number 23 Pp. 5441-5447
http://nar.oxfordjournals.org/cgi/content/full/26/23/5441 accessed June 4, 2008

[19] Monocrotaline is a plant pyrrolizidine alkaloid that has been used for decades to study mechanisms of pulmonary arterial hypertension.

3.4 Cardiopulmonary Safety Signals Observed with Asenapine

Near the end of the PDUFA review cycle this reviewer noticed a high incidence of cardiopulmonary SAEs and liver injury in healthy volunteers. In addition, there was a high rate of AEs when asenapine was given in a single low dose in combination with paroxetine or carbamazepine to healthy volunteers, thereby indicating serious pharmacodynamic and/or pharmacokinetic interactions.

While checking to see if any significant SAEs had been reported in the NDA that might be attributable to drug-drug interactions this reviewer found a death that appeared to be secondary to a developing aplastic anemia. Based upon known structure activity relationships, although 'unexpected' this was not totally surprising. Further analysis revealed that while all blood cell lines were decreasing, neutropenia and agranulocytosis and their complications would have likely ensued prior to full aplastic anemia developing, (see Figure 4 and Figure 5 in section 3.5.1.8). Therefore while death due to agranulocytosis is presumed by this reviewer and cannot be ruled out, presently due to the limited laboratory values available from prior to death only a moderate leucopenia can be presently documented and death would have likely ensued prior to full blown aplastic anemia developing. However, this reviewer believes that if the labeled actions indicated for similar events with the structurally and pharmacologically similar clozapine had been undertaken by the sponsor, the subject might still be alive. Instead documents in the IND and NDA indicate that the sponsor(s) were aware of what was occurring and simply did not take reasonable actions that might have prevented the patient's death. In addition, it's clear that this event was not reported to the IND as required, although it may have prompted the sponsor to institute a request to the IND for a drug safety monitoring board in order to break the study blind so as to fulfill reporting requirements for SAEs in Europe where the study was taking place.

This death and a second case of decreasing WBCs associated with death appear to be time dependent and due to a cumulative toxicity as they were associated with long term treatment, i.e. > 1 year. Examination of alternative mechanisms to explain other deaths that could not be attributed to the N-oxide revealed the potential for phen-fen type toxicities with asenapine or metabolites. This and requests for further clarification of subject identification by Dr. Temple along with serendipitous findings revealed numerous other cases of potentially life threatening toxicities. Some of which were known from the initial 30 day IND submission, (see §4.2 Appendix 2 – Safety Signal from Original IND Submission).

It should be noted that the signs and symptoms can appear contradictory as seen with dihydroergotamine. This variability in observed toxicities effect appears to be due to variability in effects at structurally related receptors, the complexity of opposing effects of parent drug as well as metabolites, and the variability in exposures and interindividual response potentially due to individual pharmacogenomic phenotypes, drug interactions, and underlying illnesses,. Thus potentially contradictory signs and symptoms should not be separated in assessing risk; rather they should be assessed cumulatively.

3.5 Listings of Adverse Events Potentially Related to Proposed Mechanism(s)

The following subsections include modifications of lists of potential cases previously provided to Dr. Temple on Tuesday, May 27, 2008.

Due to time constraints to provide this information, this reviewer has simply modified some tables provided by the sponsor. This is why the various tables are not 'pure'. For example suicide is included in the list of deaths in the phase II/III studies. This is clearly not a cardiopulmonary related death, although based on the acute bipolar studies and the known effects of certain serotonin receptor subtypes in the brain, suicide and suicidality should be considered a drug induced toxicity especially in patients with bipolar disorder.

In addition, cardiopulmonary effects, vasoconstriction and effects of serotonin and serotonergic receptors on platelet aggregation may also explain the increased risk of venous thromboembolism with antipsychotics.

This reviewer realizes that not all cardiac observations listed may be either due to asenapine or even similarly ascribed to asenapine by all people, however when the totality of the evidence including potential mechanisms are examined the data evinces to this reviewer that the toxicities and risks are likely associated with asenapine and cannot be easily dismissed as being unrelated.

Lastly this is only a limited listing of potential SAEs related to these underlying mechanisms, when going back to identify subject numbers for deaths per Dr. Temple's request this reviewer found numerous additional SAEs for cardiac arrhythmias in a single study. Since, SAEs in studies and in particular in chronic long term studies where they are most likely to occur due to cumulative toxicities were not examined, there is likely many more SAEs that are included the safety information that is available but that has not been identified as yet. Therefore the true risk of SAEs is likely under estimated even for the presently available data.

Many but not all potential SAEs of particular interest are highlighted in various ways. Highlighting was curtailed with §3.5.1.8 (Other SAEs Reported in Original OCP Review), due to a lack of time.

3.5.1.1 Subjects who Died in Primary Efficacy and Safety Phase 2/3 Studies

Table 61 Listing of subjects who died (combined Phase 2/3 studies, cohort E)
(N.B. additional subjects added found while examining details of deaths from Study P25517)[a]

Study	Subject ID	Treatment	Preferred Term	Age/ Sex/ Race	AE Start / Stop Day	Action Taken	Related According to Sponsor	Intensity according to Sponsor
041013	28	asenapine 1.6 mg BID	epiglottis laryngitis tinea pedis dystonia insomnia psychotic disorder dyspnea hematoma	49/Male/ Caucasian	5/5 5/5 4/5 5/5 4/5 3/5 5/5 3/5	NA NA None NA None Stopped NA None	No No No No No No No No	Severe Severe Mild Severe Severe Severe Moderate Moderate
			Pathologic examination showed erythema and severe edema of epiglottis and laryngo-pharynx and tracheitis consistent with acute laryngitis; stenosis of left anterior descending and first lateral branch of the left circumflex artery, mild stenosis of the right coronary artery and nephrosclerosis consistent with hypertensive atherosclerotic cardiovascular disease. The examiner's report also noted injuries to the left side of upper chest (CPR related), abrasions to the right elbow and confluent contusions of the lower extremities.					
041013	48	asenapine 1.6 mg BID	hyperthermia pulmonary embolism	57/Male/ Caucasian	47/47 47/47	None NA	No No	Severe Severe
			At screening, ECG showed right atrial enlargement purportedly due to the subject's history of COPD. The autopsy report indicated that the cause of death was pulmonary thromboembolism in the right pulmonary artery. Anorexia beginning 6 days after starting drug.					
25517	115024	asenapine 5-10 mg BID	completed suicide schizophrenia	25/Male/ Caucasian	18/18 18/18	None None	No No	Severe Severe
25517	127004	asenapine 5-10 mg BID	completed suicide	32/Male/ Caucasian	152/152	None	No	Severe
25517	130013	asenapine 5-10 mg BID	completed suicide	31/Male/ Caucasian	257/257	None	Unlikely	Severe
25517	131010	asenapine 5-10 mg BID	completed suicide	25/Male/ Caucasian	33/33	None	Unlikely	Severe
25517	186007	asenapine 5-10 mg BID	lobar pneumonia pneumonia	52/Male/	42/46 40/46	None None	Unlikely No	Moderate Severe
			On 4 August 2004 subject experienced productive cough. He was found to be pyrexic and had some shortness of breath on 6 August 2004. Subject was transferred to the casualty department and was diagnosed with pneumonia of left lower lobe **(Lobar pneumonia)**. He was treated with ampicillin intravenously (and oxygen as needed) and improved. On 8 August 2004 subject returned to psychiatric hospital. There, subject collapsed; he coughed up brown sputum and then stopped breathing. Subject died on 10 August 2004, 7:45 AM. The reported cause of death was bronchopneumonia, no other medical problems or clinical signs could have played a role in subject's death, according to the investigator. No autopsy was performed. Cardiologist's report locally at screening said borderline left ventricular					

			hypertrophy but no evidence of left ventricular strain. Could be normal variant. In light of absence of any other cardiac features (signs or symptoms) taken to be normal variant. No cardiac or cardiovascular problems in the past or prior to the SAE					
25517	242020	asenapine 5-10 mg BID	coronary artery insufficiency	50/Male/ Caucasian	6/6	None	Unlikely	Severe
			he was found dead lying near his bed at 03:10. The nurse had seen him sleeping in his bed at 02:00. Autopsy was performed on 29 November 2004. The preliminary report indicates acute coronary failure in the present of non-significant coronary sclerosis. The performed autopsy and microscopy have revealed the following abnormalities: 1. Signs of severe hypoxia or anoxia in the cortex of the cerebral hemispheres evidenced by nerve cell changes following the so-called "ischaemic type". No such changes are observed in the rachidian bulb. 2. Small (40-100 um in diameter) fresh haemorrhages (most likely of diapedetic origin from micro vessels) in the cortex of the cerebral hemispheres. No haemorrhages are observed in the rachidian bulb. 3. Initial signs of artherosclerosis in the aorta and coronary artery. 4. Emphysema in the uppermost part of both lungs 5. Colloid nodular goiter None of the above factors can explain the sudden death. It is most likely that due to some factors which cannot be detected at autopsy there was cerebral claudation of the cerebral hemispheres that caused severe hypoxia or anoxia of the cortex of the cerebral hemispheres. The hypoxia or anoxia, in its turn, resulted in disturbance of microvascular wall permeability in microvessels which led to small, microscopic haemorrhages in the cortex of the cerebral hemispheres. Further we can suppose that, as a result of some functional shifts, the changes in the cortex of the cerebral hemispheres caused acute reflex cardiac arrest **(Cardiac failure acute)** that was a direct cause of the sudden death. No relevant medical history. No relevant concomitant diseases were reported. No cardiac signs or symptoms present QTc 471					
P25517	188002	Olanzapine 10 – 20 mg qd	On drug 364 days. Meds D/Ced 18Nov2004. On day of med d/c peripheral edema and joint stiffness reported.					
25517	248014	asenapine 5-10 mg BID	completed suicide schizophrenia, paranoid type	21/Male/ Caucasian	8/8 8/8	None None	Unlikely Unlikely	Severe Severe
A7501004/ A7501006		asenapine 5-10 mg BID	accidental overdose	32/Male/ Caucasian	53/53	NA	None	Missing
A7501004	40111002	asenapine 5-10 mg BID	completed suicide	49/Male/ Caucasian	12/12	NA	Possible	Severe
041021	125010	olanzapine 15 mg QD	overdose	33/Male/ Other	37/37	Stopped	Unlikely	Severe
25517	204011	olanzapine 10-20 mg QD	completed suicide	41/Male/ Caucasian	376/376	None	Unlikely	Severe
A7501004	41331009	olanzapine 5-20 mg QD	completed suicide	40/Female/ Asian	13/13	Missing	Unlikely	Missing
041023	363015	placebo	thymoma malignant	42/Male/ Caucasian	7/24	Stopped	No	Severe
P25517	192001	Asenapine 5 – 10 mg bid on meds 365	A 38 year old male subject, with a history of chest pain, started study medication on 20 November 2003. From 8 December 2003 to 10 December 2003 he experienced atypical chest pain. He was treated with paracetamol, acetylsalicylic					

		days.	acid and caffeine. An ECG done at week 3 visit was reported to be abnormal. Cardiology was consulted and a Troponin T test was found to be positive. Subject was hospitalized on 11 December 2003 for further investigation. Study medication was interrupted the same day. An angiogram was performed on 12 December 2003 for final diagnosis. Myocardial infarction **(Myocardial infarction)** (occlusion of right posterior inferior coronary artery) was confirmed. Study medication was continued and he was treated with isosorbide. He recovered with sequelae and was discharged on 12 December 2003. Also Sinus rhythm 96 bpm. Mild left ventricle hypertrophy No murmur T wave inversion in AVF,I and II. No ST depression or pain on stress ECG.
P25517	194001	Asenapine 5 – 10 mg BID	19 yo BM Subject started taking study medication on 25 October 2003. On 1 October 2004 subject was hospitalized for observation and for monitoring of his eating habits. He had experienced weight loss **(Weight decreased)**, as he had no money to buy food. On 26 October 2004 study medication was discontinued according to protocol (not due to the adverse event). Subject recovered and was discharged on 25 November 2004.
P25517	194003	Asenapine 5 – 10 mg BID	19 yo BM On drug 310 days "Non-specific ST segment changes with ST elevation in the antero-septal leads as well as the infero-lateral leads. This is a normal early repolarization variant. Corrected QT interval is prolonged at 0.5. 22-DEC-04 Stress ECG subject only managed 5 minutes 14 seconds on a Bruce protocol achieving a maximum heart rate of 125/min with no evidence of arrhythmia or ischaemia."
P25517	22003	Asenapine 5 – 10 mg BID	50 yo WM on drug 281 days A subject using study medication was admitted to the hospital on 3 August 2004 due to breathlessness and thoracic compressing pain (5 hour duration). Subject was diagnosed with heart failure exacerbation **(Cardiac failure)**. Study medication was continued and subject did not drop out of the trial. He was treated with metoprolol, polfilin, nitroglycerin, clexane, furosemide, enarenal and acetyl salicyclic acid. Subject recovered and was discharged on 12 August 2004.
P25517	221001	Asenapine 5-10 mg bid	36 yo WM 63 days on drug. Also took ciprofloxacin and pefloxacin due to 2nd degree burns Dec 7 – Dec 23 had Headaches.
P25517	221005	Asenapine 5-10 mg bid	47 yo WF on drug 367 days. lowering of her hemoglobin level and hematocrit was noticed. She was hospitalized on 16 March 2004 and diagnosed with anaemia **(Anemia)**. Study medication was continued. Subject was discharged on 24 March 2004. Anaemia had resolved on 20 April 2004.
P25517	174001	Asenapine 5 – 10 mg BID	ECG changes 19FEB2004 Moderate None Still present Probable
P25517	221010	Olanzapine 10-20 mg qd	On olanzapine 22 days. diagnosed with an abnormal ECG: T wave abnormality, considered inferolateral ischemia, ST abnormality (decreased) (**Myocardial ischaemia**). Study medication was discontinued due to this adverse event. At the time of report subject had not recovered.

a Additional subjects were found by serendipitously while looked for information requested by Dr. Temple. A search of the case report forms for study P25517 was then performed using the search term ECG. Additional suspicious AEs are likely to have been found if additional search terms based on expected toxicities were to be performed and expecially if all studies are examined.

Some of the deaths are particularly troubling as they could be due to an exacerbation of underlying conditions by asenapine including at doses that are considered to be subtherapeutic doses. If this is the case with a population that has been presumably carefully screened under conditions where the sponsor appears to have been aware of the risks *a priori* then it raises serious questions regarding the safety of asenapine in the studied population, which would be expected to be at lower risk than the population that would actually use the drug.

Another troubling aspect of this and other tables are the relative number of SAEs reported with asenapine as compared to active comparators which would be expected to have similar toxicities

Another concern is that subjects in these studies may have already been on similar drugs. Thus the degree of risk in treatment naïve patients is likely unknown as subjects who are likely to experience toxicities with asenapine acutely have already been screened out. This is likely to be less of a concern initially, however over time as older drugs come off patent and treatment naïve patients are more likely to be placed on asenapine first, the incidence of toxicities when patients are beginning treatment with asenapine is likely to rise as patients who may be genetically predisposed will not have been screened out as was the treatment population in the clinical trials.

3.5.1.2 Listings of Subjects who Died in Ongoing Studies

Table 5 Subjects Who Died in Ongoing Studies

Study	Subject ID	Treatment	Preferred Term	Age/Sex/ Race	AE Start / Stop Day	Action Taken	Related According to Sponsor	Intensity According to Sponsor
041513/	315504	double-blind	respiratory failure	37/Male/ Caucasian	204/204	NA	Unlikely	Severe
041513/	368509	double-blind	sudden death completed suicide	23/Male/ Caucasian	96/96 96/96	NA Stopped	Unlikely Unlikely	Severe Severe
25543/	125005	double-blind	completed suicide not coded (suicide)	64/Male/ Caucasian	31/31 30/30	NA Stopped	Possible None	Severe Severe
25543/	125006	double-blind	completed suicide schizophrenia, paranoid type	51/Male/ Caucasian	191/191	NA	Possible	Severe
A7501007/	50281012	double-blind	bipolar I disorder completed suicide	24/Male/ Caucasian	178/178 178/178	NA NA	Unlikely Unlikely	Severe Severe
A7501007/	51241008	double-blind	death neonatal drug exposure during pregnancy India died 5 min after birth	37/Female/ Asian	385/385 385/385	NA NA	Possible Possible	Severe
P25520/	132017	double-blind	death	44/Female/ Caucasian	491/521	None	None	Severe
P25520/	241041	double-blind	pulmonary embolism arteriosclerosis	57/Female/ Caucasian	470/474 470/474	Stopped Stopped	Unlikely Unlikely	Severe
P25520/	246021	double-blind	cardiac failure	57/Male/ Caucasian	430/430	None	None	Severe

3.5.1.3 Neonatal Risks

3.5.1.3.1 Human Data

The death of the neonate in the previous section is noteworthy as mechanistically it's expected that exposure to asenapine late in pregnancy might cause pulmonary arterial hypertension, (PAH). PAH in neonates frequently causes death within a few days of birth and of the infants who survive 50% experience deafness or other neurologic deficits.

Table 6 on the following page is a summary of the pregnancies reported in the NDA.

The studies are divided into completed and ongoing studies, which are essentially acute and chronic treatment studies. Since subjects are screened for pregnancies prior to enrollment and before starting drug any exposures in completed (acute) studies would occur early in pregnancy and would not be expected to show pulmonary arterial hypertension even if the pregnancy was allowed to proceed to birth. In addition, since exposure would be so early, if there were fetal damage and the the pregnancy were allowed to continue the most likely outcome would be a spontaneous abortion at around the end of the first trimester. Thus it is not surprising that the one pregnancy that proceeded to completion resulted in a healthy birth. This is not to say that there might not be more subtle effects but these 4 cases would not be expected to be informative unless there were a number of spontaneous abortions.

The ongoing studies (chronic) studies are potentially more informative. Table 6 was a first attempt by this reviewer to glean information, but work on this table was stopped at the end of the workday and the following day it was realized that a different approach was needed. This resulted in Table 7, which is a more detailed table for the pregnancies in the chronic studies and which was constructed that following day.

Treatments are still 'blinded' in the ongoing studies and although it would be possible to unblind them and even though study 25520 has already been unblinded even knowing the treatments would not be informative, as 3 of the pregnancies were terminated early and another appears to be a mistaken report.

With respect to the other 2 pregnancies treatments were stopped at around the end of the second trimester and since pulmonary arterial hypertension would only occur if exposure is later in pregnancy the healthy birth that is from this subset does not address this particular risk.

The last pregnancy is the case of the premature delivery and death. This is the same case which the sponsor listed as a possible death due to asenapine. The fact that the sponsor listed this death as potentially due to asenapine was the original flag that raised the concern of drug induced neonatal PAH to this reviewer.

This particular woman had a history of a number of other pregnancies with poor outcomes. This confounds interpretation, however the timing of 2 of the spontaneous abortions indicate either that these fetuses were malformed or that there may have been a hormonal issue. The third spontaneous abortion at 20 weeks, the caesarian section at 34 weeks due to fetal distress, and the premature birth in the present case, with death occurring at 5 minutes postnatal raise questions as to the causes. One wonders if there could there have been pre-eclampsia or vasoconstriction of blood flow to the placenta or to fetal tissues due to the patient's genetics or the serotonergic effects of antipsychotic drugs, or a combination of the two. A medication history, fuller histories of the previous pregnancies including the postnatal history of the surviving infant, and an autopsy in the present case would be informative and as much of this information as possible should be obtained and submitted to the NDA.

Table 6 Summary of Pregnancies Reported in Summary of Clinical Safety

Total Pregnancies Reported in NDA				9						
Completed Studies	# Pregnancies in Completed Studies			4						
	Treatments Associated with Pregnancies in Completed Studies	Asenapine		1						
		Olanzapine		3						
	Outcomes				**Study**	**Subject**	**Country**	**Gestational Age at Exposure**	**Duration of Exposure**	**Comments**
		Asenapine	Pregnancy Ongoing							Since completed studies included mainly short term studies and a few continuation studies of up to 6 months and since subjects were screened at enrollment for pregnancy, exposures were unlikely to have been in the last part of pregnancy where exposure of drugs that induce PAH is critical.
			Healthy Births							
			Birth Defects							
			Neonatal Deaths							
			Therapeutic Abortions	1	A7501006	50341004	US	Not reported	4 weeks	
			Lost to FU							
		Olanzapine	Pregnancy Ongoing							
			Healthy Births	1	A7501004	41211007	US	Not reported	10 days	
			Birth Defects	0						
			Neonatal Deaths							
			Therapeutic Abortions	1	41021a	125023	US	Not reported	9 days	
			Lost to FU	1	41021a	206003	US	Not reported	8 days	
Ongoing Studies	# Pregnancies in Ongoing Studies			5						
	Treatments Associated with Pregnancies in Ongoing Studies	Blinded		5						
	Outcomes	Blinded Treatments	Pregnancy Ongoing	0						
			Healthy Births	0						
			Birth Defects	1	A7501007	51231013		7 - 25 weeks?	24.5 weeks?	D/C 'ed drug at week 25 Allowed to go forward time of lowest risk. Likely would have spontaneously aborted or risk of early developmental low.
			Neonatal Deaths	1	A7501007	51241008	India	Not Reported	26 weeks	Preterm delivery Hxs of other perm prob Stop 3 weeks short of ? delivery at home. No information on Gestational Age
			Therapeutic Abortions	3	41513	376503	US	Not Reported	8 weeks	
					41513	361500	US	Not Reported	2 weeks	
					25520	242008	RU	Not Reported	?	
			Lost to FU	0						

Study A7501006 9 week Extension Bipolar Maint Study Multinational PBO, Asenapine 5 – 10 mg BID, Olanzapine 5 – 20 mg Completed June 2006
Study A7501004 3 week Acute Bipolar Study Multinational PBO, Asenapine 5 -1 0 mg BID vs. Olanzapine 5 – 20 mg Completed April 2006
Study 41021 6 week Acute schizophrenia Study Multinational PBO, Asenapine 5 mg , Asenapine 10 mg, Olanzapine 15 mg QD, Completed May 2006
Study A7501007 (Ext of A7501006) 40 week Extension Bipolar Maint Study Multinational, PBO, As 5 – 10 BID, Olanzapine 5 – 20 mg (Cut off for clinical database Jan 15, 2007) Study End May 2007 Planned
Study 41513 (ext of 41023) 52 week total duration Extension Schizophrenia; PBO, As 5 mg, As 10 mg, Haldol 2 – 8 mg BID, Ongoing (Cut off for clinical database Jan 15, 2007) Study End Nov 2007 Planned
Study 25520 52 week efficacy in Schizophrenia / Schizoaffective Disorder; PBO As 5 – 10 BID, Olanzapine 10 – 20 mg QD B Study End Sept 2006 (Terminated)

Table 7 Detailed Information on Pregnancies in Ongoing Studies

Study	Subject	Country	Drug Start Date	Drug Stop Date	Duration on Drug (weeks)	Date of Conception	Detection of Pregnancy	Duration of Exposure to Fetus	Outcome	Gestational Age at Pregnancy Termination (weeks)	Comments
41513	376503	Romania	7-Jan-2006	11-Jun-2006	22.1	9-Apr-2006	9-Jun-2006	8 weeks	Pregnancy Terminated June 22, 2006	10	
41513	315507	US	19-Jan-2006	12-Jul-2006	24.9	April-06	15-Jul-2006	3 months	Not Applicable	NA	Nov 8, 2006 Reported that Pregnancy Test was false + - needs clarification
41513	361500	Russia	10-Nov-2005	26-Dec-2005	6.6	10-Dec-2005	24-Dec-2006 (est)	16 days	Pregnancy Terminated Jan 26, 2006	6	
25520	242008	Russia	14-Sept-2004	24-Jul-2006		~ Jul 1, 2006	14-Jul-2006 (est)	3 weeks	Pregnancy Terminated Jul 21, 2006	3	It was claimed that subject did not inform investigator of pregnancy
A7501007	51241008	India	30-Jul-2005	27-Jul-2007	103.9	1-Jan-2006	27-Jul-2007	26 weeks	Preterm Delivery Aug 18, 2006	29 - 31.5	Positive pregnancy test when tested at end of trial. The mother has a history of four pregnancies. One live birth per Caesarean section, due to fetal distress, performed at the gestational age of 34 weeks and three spontaneous abortions: the first at the gestational age of 14 weeks, the second at the gestational age of 12 weeks and the third at the gestational age of 20 weeks.
A7501007	51231013	India	5-May-2006	14-Dec-2006	32	25-Jun-2006	13-Dec-2006	24.5 weeks	Healthy Baby - Estimated Delivery Date March 31, 2007		

3.5.1.3.2 Animal Data

The pharmacology / toxicology review was referred to in order to see if preclinical data might shed light on the risk of pulmonary arterial hypertension with asenapine.

Table 8 shows a summary of fertility and early embryonic development studies from the April 30, 2008 Pharm/Tox Review. It is divided into 4 sections:

- Pilot Mating and Fertility Studies
- Mating, Fertility, and Teratogenicity Studies
- Embryo-fetal Development and Teratogenicity Studies
- Pre- and Post-Natal Development Studies

The table is largely self-explanatory. Comments include comments taken directly from the pharmacology and toxicology review and are shown in italics. Those comments that this reviewer believes are interest are highlighted in red or blue text. Where additional data or information elucidate the results they are also referred to in the comments section, and these tables immediately follow Table 8.

Pilot Mating and Fertility Studies

There was little effect of asenapine.

Mating, Fertility, and Teratogenicity (Early Embryonic Development) Studies

This study was considered inadequate however it's noteworthy that there's a congenital heart defect in one rat. It's noteworthy that there's a dose dependent post-natal mortality that occurs primarily in the first few days post partum and there's a high degree of cannibalism in the high dose group. This indicates potential issues with both late stage fetal development and possibly with breast feeding. These results are consistent with the suspected toxicities. It should be noted that in this study Wistar Rats were used, however with monocrotaline the risk of PAH is greatest with Sprague-Dawley Rats and might be due to differences in metabolic activation due to metabolism.

Embryo-fetal Development and Teratogenicity

There were 6 embryo-fetal development and teratogenicity studies where rats or rabbits were exposed to asenapine during the period of fetal development that corresponds to implantation to closure of the hard palette in rats or the period or organogenesis in rabbits.

What's striking is that in every one of these six studies there are indications of effects on bone formation and in some there are also indications of effects on connective tissue. Specifically there are dose dependent effects on bone ossification, including increases in poorly ossified and nonossified bone.

As has been seen with other drugs when a particular litter is effected the data is excluded from the analysis, even that this may indicate that is a borderline dose for the toxic effect and there may be increased exposure to parent drug or metabolite in that particular dam.

These studies were initially conducted in Sprague-Dawley and Wistar/HAN rats with PO administration and later in 2005 in Sprague-Dawley Rats with IV administration. In addition 3 different rabbit strains were used. The fact that effects were seen in two different species and all strains, were dose dependent and were even seen when conditions would be expected to minimize finding effects, significantly raises the level of concern that these effects are based on a mechanism that is common across a variety of species and will be seen in humans. In addition the suspected mechanism indicates that connective tissue effects will be seen not only in neonates but also in older individuals where bone remodeling is ongoing, such as growing children whose skeletons are constantly reforming as they grow.

A high incidence of bone malformations were seen in rabbits at doses of 30 mg/kg/day (see Table 8 and Section 0 (
Appendix 3 – Skeletal Exams in Chinchilla Rabbits - Study SDG RR 2914) however even at low doses likely to produce exposures only a few fold higher than in humans effects on bone ossification were seen.

Other findings include brain malformation and an umbilical hernia and repeated findings include effects on the eye, and hydronephrotic kidneys in both rabbits and rats. Particularly worrisome is the evidence of pulmonary effects in rabbits and that for several experiments the examinations appear designed to avoid detecting certain problems, i.e. visceral and soft tissue findings, in spite of the fact that the sponsor appears to be looking specifically for skeletal problems.

Based on these studies there is no margin of safety relative to the human dose in Sprague-Dawley Rats. Plus in Chinchilla and New Zealand White Rabbits there is a 2 – 3 fold increased risk for major visceral malformations at asenapine exposures only double those in humans.

Pre- and Post-Natal Development Studies

There were 5 pre- and post-natal development studies in Sprague-Dawley Rats.

Two of these, including one conducted in 1992, were fostering studies where pups either exposed or not exposed in utero were fostered by dams either exposed or not exposed to asenapine. This is highly unusual unless the sponsor is looking for a specific effect such as toxicity due to breast feeding. Also troubling is that all but one of these studies utilized IV dosing which would minimize the formation of any toxic metabolites. The IV pilot studies that appear to be primarily for dose selection purposes for the second fostering study clearly show that there is an increase in mortality due to exposure in utero late in pregnancy, as would be expected with a drug causing PAH. Having both an IV and PO fostering allow comparisons and although the IV dose was 1/10 the PO dose the pup mortality was still increased in the first 4 days post-partum, (20% - 25%), as compared to 3% in the control group, but what is amazing is that this increased mortality was seen even when the pups were only exposed by breast feeding.

Although 2 of these studies noted that pups were bluish and this was explained as hypothermia, the fact that this also occurred on the heads and snouts and is consistent with the mechanism suggests that it may actually be due to cyanosis.

Table 8 Summary of Fertility and Early Embryonic Development Studies from the April 30, 2008 Pharm/Tox Review

Type of Study	Study No	Date	GLP	Species / Strain	Route	D & A	Timing of Exposure	Comments (*Comments in Italics from Pharm/Tox Review*)
Pilot Mating and Fertility	SDG 2315	1981	NO	Rat Sprague-Dawley	PO	30 mg/kg/day		Males: No Effect of asenapine Females: Decrease in Pregnancy Rate
Mating, Fertility, and Teratogenicity (Early Embryonic Development)	SDG RR 3115	1990	YES	Rat Wistar	PO	0, 0.5, 2.5,15 mg/kg bid	Up to day 21 (i.e. parturition) or 21 days post partum	*"There were no teratogenic effects observed in this study. However, it is unclear whether the external and visceral malformations were properly examined. Visceral examination demonstrated one MD fetus with a heart defect. Two abnormal fetuses were reported at the LD upon external examination. Therefore, only 3 malformed fetuses were reported upon external or visceral examinations. It appears extremely unlikely that no spontaneous external or visceral findings were detected in any fetus in all other groups. Therefore, evaluation of teratogenic effects in this study is considered inadequate."* See Table 9. There was a dose response in both fecundity and with post-natal survival. Most of the postnatal deaths occurred by day 4. *"The incidence of cannibalism in Group 4* (the high dose group) *was high."*
Embryo-fetal Development and Teratogenicity	SDG RR 2316	1988	NO	Rat Sprague-Dawley	PO	30 mg/kg/day	Days 6 to 17	*"The abnormal litter ratio was 13.3% and 40.0% in the control and asenapine treated group, respectively. Malformations were detected in 2/213 control fetuses in 2 litters and 4/107 treated fetuses in 4 litters (hydronephrotic kidney in 2 control and 2 asenapine-treated fetuses, and bilateral anophthalmia in 2 additional asenapine-treated fetuses). The degree of ossification of various skeletal elements (e.g. sternebrae 5, 5th proximal phalange) was slightly less in fetuses of asenapine treated group."*
	SDG RR 2961	1990	YES	Rat Wistar/HAN	PO	0, 0.5, 2.5,15 mg/kg bid	Days 7 - 17	*"Asenapine was not teratogenic in this study. The NOAEL for maternal toxicity was considered to be below the LD. The NOAEL for the reproduction and F1 parameters was the MD. However, it is unclear whether the external and visceral malformations were properly examined. Only one malformed fetus was reported upon external or visceral examinations in the LD group. It appears extremely unlikely that no spontaneous external or visceral findings were detected in any fetus in all other groups. Therefore, evaluation of the external and visceral teratogenic effects in this study is considered inadequate."* *"This study was also reviewed by Dr. Lois Freed under the IND 51,641. She concluded that "the lack of specific findings suggests reduced sensitivity to detect soft tissue abnormalities, variants, etc. Unless data can be provided that adequately document the sensitivity of the methods used to assess fetal effects, the studies may need to be repeated".* *"On visceral examinations, no abnormal findings" was reported for all groups, including control. Drug-related effects on skeletal parameters were noted, including both increases and decreases in ossification. The incidence of incomplete ossification and non-ossified skeletal elements (sternebra, vertebra, and limbs) was slightly increased in the asenapine-treated groups. These findings were generally not statistically significant, except non-ossified metatarsalia 1 (hind limb) at the HD and decreases in non-ossified digit 5 distal phalanx (forelimb) at all doses."* *"Wavy ribs were observed in the control, LD and MD, but not in the HD fetuses. There were no increases in skeletal malformations in dosed groups."*
	INT00002826	2005	YES	Rat Sprague-Dawley	IV	0, 0.3, 0.9, 1.5 mg/kg body weight/day Rate not specified	Days 6 to 17 from implantation to closure of the hard palate	*"within short time after application animals show short-lasting ataxia and then persist in a motionless condition. Muscle tone was in increased. Animals remain conscious, but high-grade reduced in motoric activity."* *"There were no external or visceral findings related to the test article. Skeletal abnormal findings (malformations and variations) were noted in 4 fetuses in 3 litters (14% of all litters) of the control group, 3*

Type of Study	Study No	Date	GLP	Species / Strain	Route	D & A	Timing of Exposure	Comments (*Comments in Italics from Pharm/Tox Review*)
								fetuses in 3 litters (14% of all litters) at the LD, 4 fetuses in 3 litters (14% of all litters) at the MD, and 10 fetuses in 5 litters (24% of all litters) at the HD. The percentage of all fetuses affected was 2.6% (4/152), 1.9% (3/154), 2.7% (4/148), and 6.6% (10/151). Abnormal findings at the HD included zygomatic arch fusion, rudimentary cervical rib, misshapen scapula, fused thoracic vertebral arch, dumbbell-shapen or bipartite lumbar or thoracic vertebral body, misshapen cervical vertebral arch, and fused rib. These findings were of low incidence and restricted to one to three litters. The majority of findings occurred in several fetuses of one single litter delivered by dam no. 85). Dam no. 85 was more sensitive than other animals since its body weight development was lower than that of all other animals in this group on days 6-10 of pregnancy. Macroscopic observations indicated a mass in the chest wall region (d=20 mm) of dam no. 85, which was considered an incidental occurrence by the Sponsor. Excluding the litter delivered by the dam no. 85, malformations were observed in 6 fetuses in 4 litters (20% of all litters; 3.9% of all fetuses) at the HD." *"There were no test article-related external or visceral findings in fetuses at any dose level. Skeletal examinations demonstrated minimally increased incidence of a variety of abnormal findings in 5 HD litters. However, the majority of the findings occurred in one individual litter from the HD dam no. 85. Macroscopic observations indicated a mass in the chest wall region of this dam, which was considered an incidental occurrence. Therefore, findings in the litter from the dam no. 85 can be excluded from the assessment of teratogenic effects. In conclusion, findings at the HD are not considered drug-related. The NOAEL for maternal toxicity and for fetal and skeletal abnormalities is the HD of 1.5 mg/kg/day AE (2.11 mg/kg/day expressed as the maleate). This dose is equal the MRHD of 10 mg b.i.d. on mg/m2 basis."*
	SDG RR 2328	1982	NO	Rabbit Dutch	PO	30 mg/kg/day	Day 6 to 18 of Pregnancy Period of organogenesis	*"Fetal examinations included external malformations, sectioning for brain and eye defects, and trunks examined only for skeletal malformations (alizarin red stain) (Individual animal data for malformations were not submitted). One control and two drug treated females were not pregnant, resulting in a slight decrease in pregnancy rate (91.7% and 83.3%, respectively). There were no other drug-related effects on any other parameters, except* ***malformed brain*** *in one fetus in group administered asenapine."* N.B. the trunks were not examined for visceral malformations.
	SDG RR 2914	1990	YES	Rabbit/Chinchilla	PO	0.5, 2.5, and 15.0 mg/kg b.i.d at an interval of 5 hours	Day 6 to 18 of Pregnancy	Mortality (dams): Two HD females (No. 62 and No. 52) died about 5 minutes after the second daily administration: No. 62 (day 10 of gestation, day 5 of dosing) and No. 52 (day 15 of gestation, day 10 of dosing). In female No. 62 dyspnea and ventral recumbency were observed prior to death. These symptoms started about 20 minutes after the first daily administration in the morning. No clinical signs were observed in female No. 52. At necropsy, reddened and incompletely collapsed lungs were noted in female No. 52. The Sponsor considered both deaths to be drug related. Clinical signs (dams): Animals were observed twice daily. Dyspnea and ventral recumbency were observed in HD female No. 54 on days 18 and 19 of pregnancy. These signs were similar to the observations in HD female No. 62 that died as described above. *"There were dose-related (all doses) increases in non-ossification or incomplete ossification of the number of skeletal elements when expressed as affected fetuses. When expressed as the number of affected litters, drug-related increases were noted primarily at the HD. These developmental delay effects may be related to the decreased maternal body weight and food consumption at the HD. There were certain skeletal elements in which the incidence of non- or delayed ossification was reduced in dosed groups when data are expressed as number of affected fetuses, e.g., non-ossified rib 13 (left, right), decreases in incomplete ossification of digit 5 medial phalanx (right forelimb), toe 4 medial phalanx (left and right) were associated with increases*

Type of Study	Study No	Date	GLP	Species / Strain	Route	D & A	Timing of Exposure	Comments (*Comments in Italics from Pharm/Tox Review*)
								in the incidence of nonossification of these same sites. There was also an increase in shortened rib and flying rib at the HD." *(*See §0 Appendix 3 – Skeletal Exams in Chinchilla Rabbits - Study SDG RR 2914)
	SDG RR 4428	1995	YES	Rabbit NZ White	PO	0.025 0.125 0.625 mg/kg/day	Day 6 to 18 of Pregnancy with Toxicokinetics AUC 2 x Hum Exam for visceral AUC 179 Pulm red Foci	*"Mortality (dams): There were 7 unscheduled deaths. According to the Sponsor, 5 animals were sacrificed after being accidentally paralyzed; these animals were replaced. One MD female died on day 24 of gestation. Subcutaneous hematoma on the abdominal wall was noted in this animal at necropsy. One HD female died on day 9 of gestation. Polypnea and ptosis were observed between 5 min and 2 h after dosing in this animal. At necropsy, many red foci on the surface of all lobes of the lungs were noted. The reason of death was not further explained by the Sponsor* *Clinical signs (dams): Animals were observed daily for clinical signs. Polypnea (all animals), occasional motor incoordination (18/26 animals), occasional ptosis (all animals), and occasional hyperactivity (8/26 animals) were observed at HD usually from 5 to 30 minutes after dosing and lasted up to 2 hours after dosing* *Toxicokinetics: The exposure achieved at the HD in this study (AUC0-24: 179.02 ng·h/mL) was 2-fold higher than that achieved at steady state following sublingual administration of asenapine at the MRHD of 10 mg b.i.d. (AUC0-24: 86.8 ng·h/mL).* (See Table 10) *Offspring (malformations, variations, etc.): Visceral malformations (major defects) were observed in 1/177, 2/111, 1/97, and 4/164 control, LD, MD, and HD females, respectively. In the HD group, 1 fetus had 2 major defects; the other fetuses had each one malformation. The abnormal litter ratio was 0.5%, 1.4%, 1.0% and 3.9% in the control, LD, MD, and HD females, respectively. Malformations noted only in the HD fetuses consisted of the following: exencephaly (1), misformed pons cerebelli (1), and umbilical hernia (1). Hydronephrotic kidney was detected in 1 control, 1 LD, and 2 HD fetuses. Major skeletal malformation (flexure of the forelimb) was observed only in one fetus in the MD group. Minor skeletal and visceral anomalies were also observed. However, the LD and MD groups were not examined.* There is a 2 – 3 fold increased risk for major visceral malformations at asenapine exposures double those in humans (See Table 11) *This study was also reviewed by Dr. Lois Freed under the IND 51,641. She concluded in her review of January 9, 1998 that "Due to technical problems, data from a number fetuses could not be used (11 C, 5 LD, 6 MD, 13 HD fetuses). Unfortunately, individual line listings were provided only for those fetuses that could not be used. Due to the lack of adequate fetal examination, the data from this study cannot be considered to have adequately assessed the teratogenic potential of Org 5222". Therefore, the individual line listings for all fetuses included in the final analysis, with each fetus identified by number and litter, were requested from the Sponsor at that time. The requested data were submitted to the NDA 22-117. Although 6.2% and 7.9% of the total number of fetuses were not available for skeletal examinations in this study, the overall number of fetuses examined is sufficient for an adequate study"*
Pre- and Post-Natal Development	SDG RR 4299	1992	YES	Rat Sprague-Dawley	PO	0, 15 mg/kg bid at an interval of 5 hours	Days 17 – 21	During lactation, when dosing stopped, the decrease in body weight gain in parental animals was not observed anymore. In the group administered 3 mg/kg/day one female delivered dead fetuses only, one female had no live fetuses left on day 1 of lactation and one female had no live fetuses left on day 4 of lactation.

Type of Study	Study No	Date	GLP	Species / Strain	Route	D & A	Timing of Exposure	Comments (*Comments in Italics from Pharm/Tox Review*)
								"asenapine caused severe clinical signs of lethargy in the parent animals leading to adverse effects on nursing behavior. No signs of fetal mortality were observed in asenapine-treated animals terminated on day 21 of pregnancy. Body weight of pups delivered by asenapine-treated animals was transiently lower than that of the controls. Neonatal mortality was high (up to 85.7%) in all asenapine-treated groups at 24 hours after delivery. The neonatal mortality in the group of non cross-fostered animals was higher than the neonatal mortality in the group of cross-fostered animals. (see Table 12) *These data indicated that the increased neonatal mortality was most likely caused not only by changes in nursing/lactation process due to lethargy of parental animals or effect on lactation but also by the effects of asenapine on offspring development during pregnancy. The results of this study in comparison with the data indicating neonatal mortality in the Segment I rat study (No. SDG RR 3115) with treatment extended to the lactation period and no increase in neonatal mortality in the Segment II rat studies (No. SDG RR 2961) with treatment up to day 17 of pregnancy demonstrated that the neonatal mortality is caused by disturbances induced during the last part of pregnancy. In addition, this study demonstrated that the selected HD (15 mg/kg b.i.d.) exceeded the MTD for segment III oral study in rats."*
	NL0012545	1998	NO	Rat Sprague-Dawley	IV	0, 0.3, 3 mg/kg/day	Day 6 to Day of Delivery (Day 21)	*"The Sponsor concluded that the dosage of 3 mg/kg/day can be regarded as too high in the subsequent pivotal study because clinical signs observed at this dose are not desirable in the period of nursing. This conclusion appears to be reasonable based on the data obtained in this study."* (See Table 13)
	NL0048584	2003	NO	Rat Sprague-Dawley	IV	0.5, 1, 2 mg/kg/day	Day 6 to Day of Delivery (Day 21)	*"At the first check after parturition, 6 pups in each MD and HD groups and 1 pup in the control group were found dead with or without milk in their stomach, partly cannibalized or missing, and with bluish discolorations of the skin indicating hypothermia. Based on these findings, the HD was considered too high for the subsequent pivotal study NL0052638."* (See Table 14)
	NL0052638	2003	YES	Rat Sprague-Dawley	IV	0, 0.3, 0.9, 1.5 mg/kg/day	Day 6 to Day 20 post partum (weaning)	*"Dams were terminated and necropsy was conducted on day 21 post partum. Developmental and behavioral parameters of F1 generation (randomly selected 4 males and 4 females per litter) were assessed on days 4 and 21 post partum. Water maze test was conducted on day 35 post partum. Selected F1 animals (1 male/1 female per litter) were paired on day 70 post partum. C-section on these animals was performed on day 14 of pregnancy.* *F0 in-life: There were no test article-related deaths. After having lost all pups in their litters, 1 MD female and 4 HD females were sacrificed for humane reasons.* *The duration of pregnancy was extended by one day in some animals administered asenapine. The number of animals affected was 1, 4, 7 and 3 in control, LD, MD and HD females, respectively. Post implantation loss (i.e. number of implantation sites relative to the number of pups counted at the first litter check) was significantly increased in all groups administered asenapine (9.9, 15.5, and 10.9% at LD, MD and HD, respectively, compared to 2.1% in the control group). However, a more detailed analysis demonstrated evidence of undetected postnatal loss between parturition and performance of the first litter check. These findings indicate that post implantation loss values reflect to a great part postnatal pup loss. Postnatal loss was significantly increased from day 0 to day 4 post partum in the MD group (24 cases; 9% of pups in 10 litters) and in the HD group (72 cases; 25% of pups in 16 litters). Total litter loss occurred in 1 MD female*

Type of Study	Study No	Date	GLP	Species / Strain	Route	D & A	Timing of Exposure	Comments (*Comments in Italics from Pharm/Tox Review*)
								and 4 HD females. *According to the additional analysis conducted by the Sponsor, post implantation loss likely reflected undetected loss of pups during or after parturition i.e. before the first check could have been performed. Although the mean pup weights were initially similar for all groups, body weight gain was minimally to slightly decreased during lactation period in dosed animals compared to controls."* (See Table 15)
	INT00000051	2005	Yes	Rat Sprague-Dawley Fostering Study	IV	0, 1.5 mg/kg/day	Day 6 to Day 10 post partum	*"This study was designed to assess effects of asenapine on the pregnant and lactating female and on the development of the conceptuses and the offspring until day 10 of lactation. Female rats were treated intravenously with vehicle (group 1) or asenapine (group 2) from implantation (day 6 of pregnancy) through to day 10 of lactation. Cross-fostering (10 litters/group) was performed after littering (at first litter check) as indicated in the table below* (see Table 16). *At day 11 of lactation, the necropsy of dams and pups was conducted.* (See Table 16) *Post implantation loss (i.e. number of implantation sites minus number of pups counted at the first litter check) was slightly increased in animals administered asenapine (group 2; 17%; 79 out of 24 litters) compared to the control group 1 (9%; 45 out of 22 litters).* *F_1 physical development: At first litter check after parturition, 23 dead pups were noted in the group 2 administered asenapine compared to one dead pup in the control group 1. An increased incidence of missing pups (considered to be cannibalized by the dam or nursing female) was noted in group V/HD (23 pups from 7 litters), HD/HD (10 pups from 5 litters) and in HD Control (11 pups from 4 litters). There was no increase in other groups. 3 pups in 3 litters of asenapine treated females had no milk in the stomach and two pups were bluish discolored in the head or snout area. Postnatal pup loss was increased up to 19%-26% in the cross-foster group V/HD group, HD/HD group and HD Control group up to day 4 of lactation."* (See Table 17) During lactation days 1 to 10, suckling of individual pups had not occurred at all (or was low) in the HD/HD and HD Control groups as shown below: (See Table 18)

Table 9 Results of Fertility and Early Embryonic Development in Wistar Rats - Study SDG RR 3115

Group		Control	Low Dose	Mid Dose	High Dose
Dose mg/kg bid (Maleate salt)		0	0.5	2.5	15
Number of Births		122	106	65	32
# Pups found dead at first litter check		0	0	2	1
# Pups found alive at first litter check (Survival)		122	106	63	31
# Pups Alive at Day 4		122	102	58	24
# Pups Alive at Day 21		120	102	56	23
% Survival at:	First Litter Check Day 1 Post Partum	100%	100%	96.9%	96.9%
	Day 4 Post Partum	100%	96.2%	89.2%	75.0%
	Day 21 Post Partum	98.4%	96.2%	86.2%	71.8%

Table 10 Asenapine Toxicokinetics in New Zealand White Rabbits – Study SDG RR 4428

Dose (mg/kg/day)	t½ (min)	AUC (0-24) (ng.h/ml)	Normalized AUC (0-24) (ng.h/ml)/(mg/kg)	CL (ml/min/kg)	V.central (l/kg)
0.025	46.60	4.88*	192.56*	115.05	2.73
0.125	52.35	41.53	327.51	51.07	1.93
0.625	58.90	179.02	285.43	59.02	2.25

n = 5 rabbits per dosing group.
* As the AUC could not be calculated up to 24 h for the 0.025 mg/kg/day group, it was calculated up to and including the last measurable concentration (AUC 0-t).

Table 11 Rate of Major Visceral Defects with Asenapine in New Zealand White Rabbits – Study SDG RR 4428

Dose mg/kg/day	0.0	0.025	0.125	0.625
N	177	111	97	164
Visceral Major Defects	1	2	1	4
%	0.6	1.8	1.0	2.4

N.B. There's approximately a 2 – 3 fold increased risk at exposures twice human exposures.

Table 12 Design and Results of PO Asenapine Fostering in Sprague-Dawley Rats - Study SDG RR 4299

		Group		
		1	2	3
Dose mg/kg BID PO	Dose Prenatal	0	0	15
	Dose Postnatal	0	15	15
Fostered Post-natally		No	Yes	No
Comments			Delivered by C-section	
Survival 1st 24 hrs (%)[a]		100.0%	70.7%	14.3%
Survival on Day 7 (%)		92.7%	28.3%	7.15%
% Change in Survival from end of Day 1 to Day 7		7.3%	42.4%	50%

a Largely died by cann balization within 4 hours of birth

Table 13 Design and Results of Pilot Lactation Study in Sprague-Dawley Rats - Study NL0012545

		Group		
Dose mg/kg/day IV	Dose Prenatal	0	0.3	3
	Dose Postnatal	0	0	0
Survival 1st 24 hrs (%)		99.2%	96.7	57.3%
Survival at End of Lactation (%)		98.3%	94.6%	37.2%

Table 14 Design and Results of Pilot Lactation Study in Sprague-Dawley Rats - Study NL0048584

Dosage Group	LD	MD	HD
Dose mg/kg/day IV	0.5	1	2
Live Births	100%	100%	100%
Survival at Day 4	98%	88%	71%%
Survival at End of Lactation (%)	98.3%	94.6%	37.2%

Table 15 Survival in Pre-and Postnatal in Sprague-Dawley Rats - Study NL0052638

Group		Control	LD	MD	HD
Dose mg/kg /day IV		0	0.3	0.9	1.5
Implantations (Births)		292	293	310	321
Post Implantation Losses		6	29	48	35
Total Number Pups at First Litter Check		286	264	262	286
# Dead Pups at First Litter Check		0	0	1	1
# Living Pups	First Litter Check	286	264	262	285
	Day 1 Post Partum	286	259	254	271
	Day 2 Post Partum	276	254	240	225
	Day 3 Post Partum	275	253	239	219
	Day 4 Post Partum			238	215
	Day 5 Post Partum				216
	Day 6 Post Partum	274			217
	Day 7 Post Partum		251		
	Day 13 Post Partum			237	
	Day 26 Post Partum	273			
% Loss Birth to First Litter Check		2.1%	9.9%	15.8%	11.2%
% Survival	Birth to First Litter Check	97.9%	90.1%	84.5%	88.8%
	Day 1 Post Partum	97.9%	88.4%	81.9%	84.4%
	Day 2 Post Partum	94.5%	86.7%	77.4%	70.1%
	Day 3 Post Partum	94.2%	86.3%	77.1%	68.2%
	Day 4 Post Partum			76.8%	67.0%
	Day 5 Post Partum				67.3%
	Day 6 Post Partum	93.8%			67.6%
	Day 7 Post Partum		85.7%		
	Day 13 Post Partum			76.5%	
	Day 26 Post Partum	93.5%			

Table 16 Study Design in IV Asenapine Sprague-Dawley Rat Fostering Study – Study INT00000051

Cross foster groups	Exchange of litters (dam/litter)	Dam from	Litter from
Vehicle/vehicle	V/V (exchange of litter from vehicle treated dams)	Group 1	Group 1
Vehicle/high dose	V/HD (vehicle treated dam with litter from test-item-treated dam)	Group 1	Group 2
High dose/vehicle	HD/V (test item-treated dam with litter from vehicle-treated dam)	Group 2	Group 1
High dose/high dose	HD/HD (exchange of litters from vehicle-treated dam)	Group 2	Group 2
Control groups	**No exchange of litters**		
Vehicle control	V Control		
High dose control	HD Control		

Table 17 Postnatal Mortality in IV Asenapine Sprague-Dawley Rat Fostering Study – Study INT00000051

Period Post Partum	Statistics	V/V	V/HD	HD/V	HD/HD	V Control	HD Control
Days 1-4	Pup loss (%)	2.8	19.4	3.3	25.8	0.7	20.2
	No. of litters affected	3	7	2	9	1	6
Day 5-10	Pup loss (%)	0	0	2.8	0.9	2.1	6.0
	No. of litters affected	0	0	3	1	3	1

Table 18 Lack of Postnatal Suckling in IV Asenapine Sprague-Dawley Rat Fostering Study – Study INT00000051

No Milk in Stomach	V/V	V/HD	HD/V	HD/HD	V Control	HD Control
No. of pups affected	0	2	0	28	1	34
No. of litters affected	0	1	0	5	1	8

3.5.1.3.3 Neonatal Effects of Cis-Asenapine

Even more problematic is the Pharm/Tox review conclusions regarding a single oral dose embryo-fetal development study of Org 5033, (cis-asenapine).

"Moreover, a 9-fold increase in the incidence of malformations, and signs of embryotoxicity demonstrated as a 2-fold increase in post-implantation loss, were observed in fetuses of female rabbits dosed with Org 5033 at 80 mg/kg/day during the period of organogenesis in this non-GLP pilot study."

It should be noted that although cis-asenapine is dosed at 80 mg/kg/day in these animal toxicology studies which is likely much greater than any human doses it is possible that this study could be used as a surrogate toxicology study for other species with higher exposures in humans. Table 19 shows an example of how it could hypothetically be done, so that this data could be used to more fully inform us of the human toxicity of other circulating species. However, presently this can not be done without the receptor binding and metabolism information requested.

Table 19 Example of How Requested Mass Balance, Receptor Binding and Toxicology Data could Hypothetically be used to Evaluate Potential Safety Issues with Asenapine

Chemical Species of Interest	Relative 5HT2B Binding		Agonist or Antagonist	Dosage (mg/kg/day)		Relative Toxicologic Exposures	
	Humans	Rabbits		Humans	Rabbits	Humans	Rabbits
Cis-Asenapine	1	0.01	Agonist	0.0004	80	0.0004	0.8
Hypothetical Toxic Asenapine Metabolite	0.8		Agonist	1		0.8	

3.5.1.3.4 Conclusions Regarding Neonatal Effects

What's troublesome with asenapine is that a neonatal death was seen in the present NDA, and in animal reproductive studies a number of pups died within 1 – 4 days of birth. In this one neonatal death the mother had potentially confounding factors that makes interpretation problematic every other pregnancy I've found during the clinical trials resulted in a therapeutic abortion whereas in another NDA I've reviewed for a drug with clear teratogenic effects in animal studies therapeutic abortions were limited to 25% of pregnancies

Although the extrapolation of dose response from animals to humans is especially with regards to breast feeding, the fact that human infants, but generally not adults, produce CYP3A7 that may also increase exposures to toxic metabolites raises additional reasons for caution for toxicity to breast feeding infants in humans.

The totality of the data suggests that asenapine causes pulmonary arterial hypertension and death when there's exposure in utero and even potentially when exposure is only via breast feeding.

In addition to asenapine, mechanistically the observed toxicities are also expected with certain other atypical antipsychotics and certain toxicities such as PAH may have a more than additive risk in the presence of a concurrently administered selective serotonin reuptake inhibitor.

3.5.1.4 Potential Developmental Risks

Since the pharmacology / toxicology developmental studies indicate a risk of problems with bone remodeling during childhood and since the pharm/tox review of the juvenile development study immediately followed the pregnancy and lactation studies, I have included a summary here for convenience, (see Table 20).

In addition to Table 20, the following is from the pharm/tox review:

"Neurobehavioral assessment: Motor activity was significantly increased in all treated groups (up to 2.2-fold and 1.8-fold in males and females at the HD, respectively) when tested within a week of the end of treatment. Increased activity was also observed in males a week later and again at 30 days after the end of treatment. However, a recovery was noted in males. No recovery was noted in females following the completion of treatment as late as on day 30 (last testing)."

Two things are noteworthy, one is that only organ weights are reported and more detailed examinations were not performed that could point to connective tissue, bone, or other chronic toxicities, and second the fact that there is an increase in motor activity, which was also reported in adult animals. For a drug that may be used to treat bipolar or off-label' for bipolar spectrum disorder in children increased motor activity could be mistaken for a symptom of the illness and not drug toxicity and could induce prescribers to inappropriately increase the dose.

Note see footnote b, as the vehicle pH can effect solubility, bioavailability, and the degree of toxicity observed.

Table 20 Summary of Juvenile Development Studies from April 30, 2008 Pharm/Tox Review

Study No	Date	GLP	Species / Strain	Route	D & A	Timing of Exposure	Comments
INT00033485	2004	Yes[a]	Rats SD	SQ	0, 0.4, 1.2, 3.2 mg/kg/day[b]	Days 14 – 60 post partum	*"A group of sibling rats (22/sex) administered the vehicle served as a control group. An additional set of animals (18/sex/group) served as a satellite group for the assessment of toxicokinetic parameters on the first day of treatment. Three dosing sites were used: the central scapular region and the flanks by the left and right hind limbs.* *Motor activity was reassessed at 2 and 4 weeks after the end of treatment. The animals were paired at 14 weeks of age for the assessment of their reproductive performance (sexual maturation, estrus cycle, fertility and precoital interval), with the females killed and examined on day 14 after mating. At necropsy, a full macroscopic examination of the tissues was performed. Brain, pituitary, and reproductive organs were weighed. Brains of selected animals from the control and HD groups (N=10) were examined microscopically.* *Mortality: One HD male was killed for humane reasons on day 15 of age after showing clinical signs of under reactivity, irregular respiration, and reduced body temperature. This death may be drug-related. This animal was replaced.* *Minimal, dose-related reduction in activity and ptosis were noted at all dose levels until weaning on day 21 of age (mainly on days 1 and 2 of dosing). Towards the end of the treatment period, these effects were more obvious and were observed within 15 minutes of dosing and lasted for over 4 hours.* *A slight decrease in food consumption was observed in males in all treated groups from day 35 of age until the end of treatment. In females, food consumption was minimally higher from day 42 of age and remained higher in the MD and HD groups until the end of the study."* *Microscopic evaluation of the brain: There were no toxicologically significant differences in brains from the control and HD group animals at the end of the recovery period."*

a Except for toxicokinetics
b vehicle: solution of sodium citrate · $2H_2O$ (9.414 mg/mL) + Na_2HPO_4 (14.48 mg/mL) + NaCl (0.5 mg/mL) + NaOH to pH 5. N.B. pH can effect stability and potentially binding affinities of asenapine and could effect study results

3.5.1.5 Comments on Other Preclinical Data

Although not reviewed here, as this reviewer cannot remember if the following was pointed out in the original OCP review, the following is included so as not to inadvertently have this overlooked.

It was noticed that a few months ago the sponsor published a study in animals suggesting that asenapine might be useful in dementia. However human phase I studies showed that asenapine actually impaired both short and potentially long term memory. This should be included in any labeling as off-label use in the elderly is likely to result in a substantial increase in cardiovascular deaths.

3.5.1.6 Deaths in Clinical Pharmacology Trials

The following is from the sponsor's summary of clinical safety and from the Clinical Study Report for Study A7501018.

"There were no deaths that occurred within 30 days of the last dose or that were related to treatment in the clinical pharmacology trials. There was one subject (55 year old Caucasian male) in study A7501018 (Phase 1 study in subjects with hepatic impairment) who developed complications following surgery for an umbilical hernia and died from the complications. The surgery was performed 10 days after the subject completed the study (received 1 dose of asenapine 5 mg) and the death occurred two months later (more than 30 days after the last dose) and is not counted in the integrated database analysis."

"*Subject 10021006 (severe impairment, Child-Pugh C) died on Day 57 (46 days after completing the study) due to a severe umbilical hernia that was not considered related to study treatment. There were no other deaths and no withdrawals due to AEs. Two additional subjects had serious, non-fatal AEs (severe syncope and severe hepatic cirrhosis); both subjects recovered. Two AEs were considered severe, 23 were mild, and 58 were moderate. No AEs were reported for subjects receiving SL placebo tablets on Day -1. The most frequent AEs were somnolence, dizziness, dysgeusia, and oral hypoaesthesia; all but 1 occurrence of somnolence were considered treatment related. Additional AEs related to the mouth occurred in 1 subject each, including dry mouth, dysphagia, glossodynia, lip hemorrhage, and oral discomfort. There was no clear pattern in the incidence of AEs across treatment groups.*

Changes in clinical laboratory values in subjects with hepatic impairment were consistent with their diagnosis. Other laboratory deviations were sporadic and not considered clinically significant. Five subjects had decreases of >20 mm Hg in systolic blood pressure and/or >10 mm Hg in diastolic blood pressure. Three were associated with AEs (2 dizziness and the severe syncopal episode). Heart rates generally remained within normal limits, with the exception of the severe syncope. None of the findings from physical examinations or ECGs was considered clinically significant.

Conclusion(s): *These results indicate that:*

• Subjects with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment had similar total and unbound asenapine exposure to that of healthy subjects. The asenapine total and unbound exposure was increased 5- and 7-fold, respectively, in subjects with severe (Child-Pugh C) hepatic impairment.

• Desmethyl-asenapine exposure was reduced 33% in subjects with mild or moderate hepatic impairment and 70% in patients with severe hepatic impairment.

• Subjects with mild or moderate hepatic impairment had similar asenapine-glucuroinde exposure to that of healthy subjects. Asenapine-glucuronide exposure was increased 1.9-fold in subjects with severe hepatic impairment.

• Single, 5-mg doses of asenapine are generally safe and well tolerated when administered SL to healthy subjects and subjects with varying degrees of hepatic impairment."

This reviewer did not previously highlight the hernia or death that occurred, however the timing and to report it in the section of SAEs is suspicious. 5HT, BMRP2 and Smad may be involved in fibrosis of the liver and in weakening of connective tissue. In addition, there were several cases of umbilical issues in animal teratogenicity studies. Although this was only single dose study, adding an additional insult that might be expected to aggravate a chronic underlying process, when there may be prolonged exposures to asenapine and metabolites raises concerns with chronic use in both patients with cirrhosis, those who may tend to drink, e.g. patients with PTSD if it's used in them, or even otherwise healthy individuals who may take the drug chronically.

In addition, the sponsor's conclusions and sponsor's labeling proposals appear to be intentionally misleading especially with respect to subjects with mild hepatic impairment and this conclusion is supported by analyses in the original OCP NDA review.

The sponsor's signatory for this study is Larry Alphs, MD from Pfizer. Dr. Alphs was also one of the signatories to the request for the Drug Safety Monitoring Board that is contemporaneous with the SAE in the woman who may have died from agranulocytosis, but was not reported.

The information available leads this reviewer to believe that one or more individuals at Pfizer and Organon as well as others at other companies intentionally mislead the FDA as to important information regarding the safety of asenapine that would have been needed to make a decision regarding this NDA. Based on this and Chapter 18 of the United States Code this reviewer believes that the Inspector General or another criminal investigative unit must be informed.

As this reviewer was instructed by Dr. Mehta that any such requests must obtain prior approval by FDA management, this request will be included in the recommendations.

3.5.1.7 Suspicious SAEs from 120 day Safety Update

Table 21 Subjects with Suspicious SAEs from 120 day Safety Update

Study	Subject	Date	Demo	Drug	Days on Drug	SAE	Comment
25543	118012	5-7-07	41 yo WM 78.1 kg	Asenapine 5 – 10 BID	179	Ultrasound 4mm dissection of pericardial lamellas above of the anterior wall RV and 4,5mm. Dissection above the ventricule. Ultrasound 2 days later: Comparing to the previous examination, the pericardial lamellas LV 3,8 mm.	Unclear from description if this is related to stab wound or not.
25543	143006	3-13-07	67 yo WF 57 kg	Asenapine 5 – 10 BID	92	In the beginning of March control lung X-Rays were performed and this time a radiologist determined a progression of changes and assessed them as a suspicion of carcinoma metastases to the lungs **(Lung cancer metastatic)**. mild sinus tachycardia **(Sinus tachycardia)**, mild poor R wave progression **(Electrocardiogram poor R wave progression)**, mild left anterior hemiblock **(Bundle branch block left)** and mild left axis deviation **(QRS axis abnormal)** since 13 March 2007. Cardiac and respiratory insuffiency was determined as a direct cause of death. As a primary death cause atherosclerosis was registered.	
25543	194004	4-6-07	36 yo WM 95 kg	Asenapine 5 – 10 mg BID	150	Suicide attempt	
25544	121503	7-20-07 ?	59 yo M 71.8 kg Australian.	Org 5222	364 days Day 444 (80 days after drug stopped)	Epigastric pain radiating to the throat accompanied by collapse. Subj noted to have low BP, Heamatemesis (small volumes) was noted twice at admission. Interim Dx MI,, anterior ischaemia, hypotension. No cause found for haematemesis by endoscopy. 5 days after presentation Abd pain with cough inc. respiratory rate, tachypneaic, poor peripheral circ. No CP. Developed severe metabolic acidosis, inc ST in inferior and antereolateral leads. Poss further MI with ischaemic bowel or PE. Cardiac arrest with asystole. Pxt expired.	Olanzapine for 9 months prior to trial. Aug 05 – May 4, 06 Also may have have been on ranitidine. Smoker 1 PPD. Scr 4-7-06 Day Scr 1.6 11-3-06 Day Scr 1.8 Clcrest 48 ml/min
25543/ 25544	176509	5-22-07	69 yo F (germany)	Asenapine		76 days after starting asenapine subject experienced disorientation, with progressive disorientation, memory impairment and disturbance in executive functioning. 8 months after initial complaint dx by local psychiatrist with dementia, PI disagreed and attributed cognitive dysfunction to meds for EPS, after 10 months on drug subject dropped out and switched to mirtazapine.	
41512	224505	5-25-06	55 yo BF 77,6 kg	Asenapine 5 – 10 mg BID	196	Potentially Malignant hypertension. 230/130 mmHg. Headache. Also had ST & T wave abnormaliites with possible antereolateral ischchemia, Short QT interval. LVH with repolarization abnormalitiy. QT prolongagrion. Sinus bradycardia.	
	224506	4-9-06	47 yo WM	Asenapine	144	Exacerbation of Schizophrenia and Suicidal ideations. Incomplete RBBB at screening.	

			112 kg	5 – 10 mg		Prograss to RBBB,Cannot rule out lateral infarct. Poss inferior infact. Age undetermined.	
7501008	10461049	8-13-06	47 yo WM 128 kg	Asenapine 10 mg	3	Exacerbation of Depressive Sxs.	
7501009	11121003	2-21-07	65 yo M Russian	Asenapine and Li	282	Weakness, Difficulties swallowing, disarticulate speech, involuntary movements of left arm. Stroke vs. EPS?	
	11291003	9-22-06	37 yo Thai Male	Asenapine and Li	31 days.	9 previous hospitalizations for Bipolar I 4 for mania or mixed episodes. No previous hx of suicidality. Smokes heavily. Attempted suicide by jumping from overpass. 6 weeks after d/c of asenapine completed suicide by ingestion of “bathroom washing liquid”.	Presumably an akali
7501013	10751010	1-24-07	33 yo F			Szrs	
A7501021	10661002	1-22-07	74 yo F	?		Subj fell on day 15, study med stopped on day 41. Subject fell again on day 49, on day 55 subject was found on the floor and dx with fractured left hip.	6 week Elderly S/T study.
	10161002	5-22-06	76 you F			Subject took asenapine for 41 days on day 69 subject suddenly slumped forward in chair and pulse was barely palpable. CPR was unsuccessful. Dx - Cardiopulmonary arrest.	
	10231002	9-30-06	75 yo M		4	Faintness attrib to orthostatic hypotension on day 2 however ECG showed sinus bradycardia, with marked sinus arrhythmia and RBBB and left anterior fascicular block. Day 4 dx’ed with Uremia with acute mental status changes. Subj has hx of CAD, CHF, PAD, Pulm HTN, Aortic valve calcification, DJD, Patent foramen ovale.	

3.5.1.8 Other SAEs Reported in Original OCP Review

Table 22 Summary of Selected Cardiac AEs per Original OCP Review

Study	Objective	Subject	Dose	Time	AE	Comment
25506	IV study	1/2	0.7 mg IV over 30 min	15 min after end of infusion	Repeated Asystole with AV block responsive to Atropine Not vasovagel	Young healthy male. No cardiac illness found
25501	SD	1/6	30 mg PO SD	2.5 hrs	Asystole 8.7 sec with junctional escape rhythm	Young healthy male. No cardiac illness found
A7501015	Pivotal BE study		5 mg		2 subjects with "hypotension"	
A7501016	Pivotal BE study		5 mg	Telemetry monitoring	10 bradycardia 8 tachycardia 7 sinus pause 3 junctional rhythm 1 bradycardia with junctional rhythm	
41026	Pivotal BE Study		5 mg		At least 4 subjects effected Claimed that it's vasovagel orthostatic hypotension in 3 but 1 subject clearly not orthostatic in nature, and no description of another. Thus only 1 conceivably orthostatic.	
25525	Paroxetine DDI Study		5 mg SL BID		Afib requiring cardioversion with sotalol MI's (possibly 2) Hepatotoxicity Hypertension and inc HR	
25526	Imipramine DDI				Collapse and LOC of Unknown origin. Questionable relationship to asenapine, but possible.	
TQT Review					One subject died of cardiac failure in an ongoing trial	
25517						

Table 23 Selected Cardiac AEs with Additional Details per Original OCP Review

Study	Subject	Comments
A7501016		The following is from the clinical study report: *"During telemetry monitoring, 10 subjects experienced bradycardia; eight subjects experienced tachycardia; seven subjects experienced sinus pause, 3 subjects experienced junctional rhythm; and 1 Subject experienced bradycardia with junctional rhythm (Appendix B9.3)."*
41026	20	*"One subject (Subject 20) had a neurally mediated reflex bradycardia (without loss of consciousness)* ***in supine position*** *after treatment with the direct compression tablet."*
25525	101029	Subject 29. At Day 13 (07 November 2005) during Sequence A (Day 8 asenapine day after DM) atrial fibrillation was reported. The subject was dosed at 08:38 hr with 20 mg paroxetine and at 09:08 hr with 5 mg asenapine. Atrial fibrillation started 1 hr and 22 minutes after administration of 5 mg asenapine and was ended after chemical cardioversion with sotalol at 09:27 the next day. The investigator judged the SAE of mild intensity and probable related to either asenapine or paroxetine or the combination of both trial medications. After the trial, the subject visited the cardiologist of the CWZ for several assessments. The cardiologist concluded that the subject had no structural heart disease (see for more details Appendix A, narratives). In this period (lasting until March 2006) the subject was diagnosed with presumably diabetic ketoacidosis due to new-onset of diabetes mellitus at 02 March 2006. The outcome of the SAE was recovered with sequelae (diabetes). The investigator judged this SAE of severe intensity and unlikely related to asenapine, unlikely related to paroxetine and not related to dextromethorphan administered at Day 11.
	09	dropped out due to ECG changes (negative T in II, III and AVF, main reason), "non-cardiac" chest pain, pain between scapulae and shortness of breath at Day 7. (Day 2 of asenapine)
	08	dropped out at Day 15 due to persistent moderate headache (main reason), drowsiness and intermittent nightmares. (Day 10 of asenapine 1 day after paroxetine day 4 after DM
	14	dropped out due to hypertension (154/88 mmHg with a PR of 93 bpm, main reason), mental restlessness, insomnia, intermittent night sweating, emotional lability, fatigue, nightmares, myalgia shoulders and neck and headache at Day 9. (Day 4 of Asenapine)
25526	37	In this subject there was a subject who was found unconscious 1.3 days after dosing with imipramine 75 and 10 days after dosing with asenapine. Although it was not ascribed to asenapine the timing is similar to that seen in subject 37 in study 25525 and a drug interaction with one or more other drugs a week or two after a single dose of asenapine cannot be ruled out.

Table 24 Selected Adverse Events by Treatment – Study 25528[a]

	Placebo	Asenanpine	Carbamazepine		Asenapine + Carbamazepine 400 mg	Overall
			200 mg	400 mg		
Administration site conditions						
Asthenia	–	–	1 (1, 3.8%)	–	1 (1, 4.2%)	2 (2, 6.9%)
Miscellaneous						
Drug Withdrawal Syndrome	–	–	–	–	1 (1, 4.2%)	1 (1, 3.4%)
Fatigue	–	3 (2, 7.4%)	6 (6, 23.1%)	5 (5, 19.2%)	11 (11, 45.8%)	25 (17, 58.6%)
Thoracic and mediastinal disorders						
Respiratory, Total	–	–	–	4 (3, 11.5%)	5 (2, 8.3%)	9 (5, 17.2%)
Cough	–	–	–	–	1 (1, 4.2%)	1 (1, 3.4%)
Nasal Congestion	–	–	–	1 (1, 3.8%)	1 (1, 4.2%)	2 (2, 6.9%)
Pharyngolaryngeal Pain	–	–	–	2 (2, 7.7%)	2 (2, 8.3%)	4 (4, 13.8%)
Rhinorrea	–	–	–	1 (1, 3.8%)	1 (1, 4.2%)	2 (2,6.9%)

a n (y, z %): n = number of incidences of particular adverse event
y = number of subjects with particular adverse event
z = percentage of subjects with particular adverse event (refer to the number of subjects treated)
Note: Percentages refer to the number of subjects received the respective treatment at least once.

Table 25 Sponsor's Table 55 Summary of adverse events by system organ class and high level group term occurring in 10% of subjects (clinical pharmacology – healthy subjects studies, cohort F)

Adverse Event Category	Placebo	Asenapine				
		<5 mg BID	5 mg BID	10 mg BID	15 mg BID	All
n (%)	(N=96)	(N=657)	(N=64)	(N=18)	(N=6)	(N=745)
Any adverse event	39 (40.6)	562 (85.5)	63 (98.4)	18 (100)	6 (100)	649 (87.1)
Cardiac disorders	0	68 (10.4)	2 (3.1)	1 (5.6)	1 (16.7)	72 (9.7)
Cardiac arrhythmias	0	61 (9.3)	1 (1.6)	1 (5.6)	0	63 (8.5)
Gastrointestinal disorders	9 (9.4)	435 (66.2)	58 (90.6)	14 (77.8)	5 (83.3)	512 (68.7)
GI signs and symptoms	7 (7.3)	94 (14.3)	15 (23.4)	3 (16.7)	4 (66.7)	116 (15.6)
Oral soft tissue conditions	2 (2.1)	390 (59.4)	54 (84.4)	12 (66.7)	3 (50.0)	459 (61.6)
General disorders and administration site conditions	7 (7.3)	145 (22.1)	40 (62.5)	5 (27.8)	3 (50.0)	193 (25.9)
General system disorders	4 (4.2)	114 (17.4)	38 (59.4)	4 (22.2)	2 (33.3)	158 (21.2)
Nervous system disorders	21 (21.9)	452 (68.8)	52 (81.3)	15 (83.3)	6 (100.0)	525 (70.5)
Headaches	8 (8.3)	100 (15.2)	20 (31.3)	5 (27.8)	3 (50.0)	128 (17.2)
Neurological disorders	16 (16.7)	437 (66.5)	48 (75.0)	13 (72.2)	6 (100.0)	504 (67.7)
Psychiatric disorders	2 (2.1)	84 (12.8)	39 (60.9)	8 (44.4)	3 (50.0)	134 (18.0)

Source: 2.7.4 Appendix Table 2.2.FW

Table 56 Adverse events by preferred term incidence greater than or equal to 2.0% (clinical pharmacology – healthy subjects studies, cohort F)

Adverse Event Category n (%)	Placebo (N=96)	Asenapine				
		<5 mg BID (N=657)	5 mg BID (N=64)	10 mg BID (N=18)	15 mg BID (N=6)	All (N=745)
Any adverse event	39 (40.6)	562 (85.5)	63 (98.4)	18 (100)	6 (100)	649 (87.1)
Somnolence	6 (6.3)	358 (54.5)	29 (45.3)	9 (50.0)	6 (100.0)	402 (54.0)
Paraesthesia oral	1 (1.0)	245 (37.3)	38 (59.4)	9 (50.0)	3 (50.0)	295 (39.6)
Hypoaesthesia oral	1 (1.0)	205 (31.2)	22 (34.4)	12 (66.7)	0	239 (32.1)
Dizziness	6 (6.3)	140 (21.3)	12 (18.8)	3 (16.7)	3 (50.0)	158 (21.2)
Dysgeusia	0	127 (19.3)	5 (7.8)	1 (5.6)	0	133 (17.9)
Fatigue	1 (1.0)	93 (14.2)	34 (53.1)	2 (11.1)	0	129 (17.3)
Headache	8 (8.3)	99 (15.1)	20 (31.3)	5 (27.8)	3 (50.0)	127 (17.0)
Restless legs syndrome	0	72 (11.0)	5 (7.8)	0	0	77 (10.3)
Nausea	4 (4.2)	61 (9.3)	10 (15.6)	2 (11.1)	0	73 (9.8)
Dizziness postural	2 (2.1)	52 (7.9)	5 (7.8)	5 (27.8)	1 (16.7)	63 (8.5)
Dry mouth	0	60 (9.1)	2 (3.1)	0	0	62 (8.3)
Restlessness	1 (1.0)	42 (6.4)	11 (17.2)	4 (22.2)	0	57 (7.7)
Insomnia	1 (1.0)	16 (2.4)	31 (48.4)	3 (16.7)	1 (16.7)	51 (6.8)
Paraesthesia	0	26 (4.0)	6 (9.4)	3 (16.7)	2 (33.3)	37 (5.0)
Diarrhoea	0	24 (3.7)	12 (18.8)	0	0	36 (4.8)
Akathisia	0	31 (4.7)	3 (4.7)	0	0	34 (4.6)
Oral discomfort	0	34 (5.2)	0	0	0	34 (4.6)
Hypotension	0	30 (4.6)	0	1 (5.6)	0	31 (4.2)
Bradycardia	0	27 (4.1)	0	0	0	27 (3.6)
Miosis	0	21 (3.2)	0	0	0	21 (2.8)
Tachycardia	0	21 (3.2)	0	0	0	21 (2.8)
Glossodynia	0	21 (3.2)	0	0	0	21 (2.8)
Abdominal pain	2 (2.1)	17 (2.6)	2 (3.1)	1 (5.6)	0	20 (2.7)
ALT increased	0	8 (1.2)	9 (14.1)	0	1 (16.7)	18 (2.4)
Dysarthria	0	10 (1.5)	7 (10.9)	0	0	17 (2.3)
Dyspnoea	0	6 (0.9)	7 (10.9)	3 (16.7)	0	16 (2.1)
Nasopharyngitis	0	13 (2.0)	2 (3.1)	0	0	15 (2.0)

Figure 4 Hematology Values Prior to Death for Subject 132017 -Study P25520

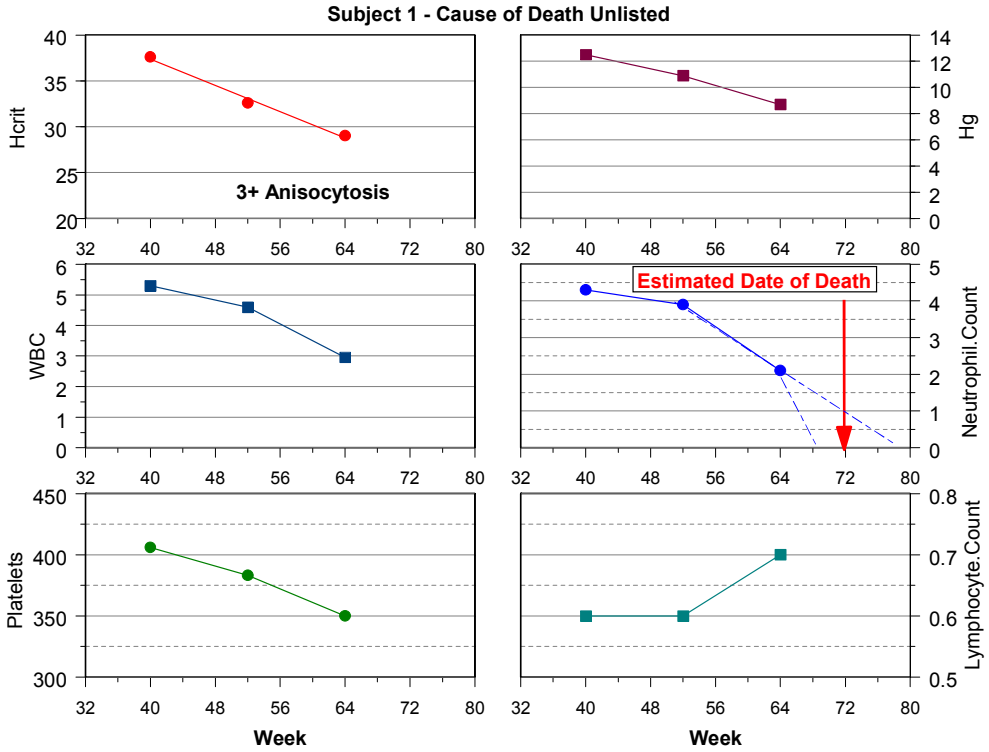
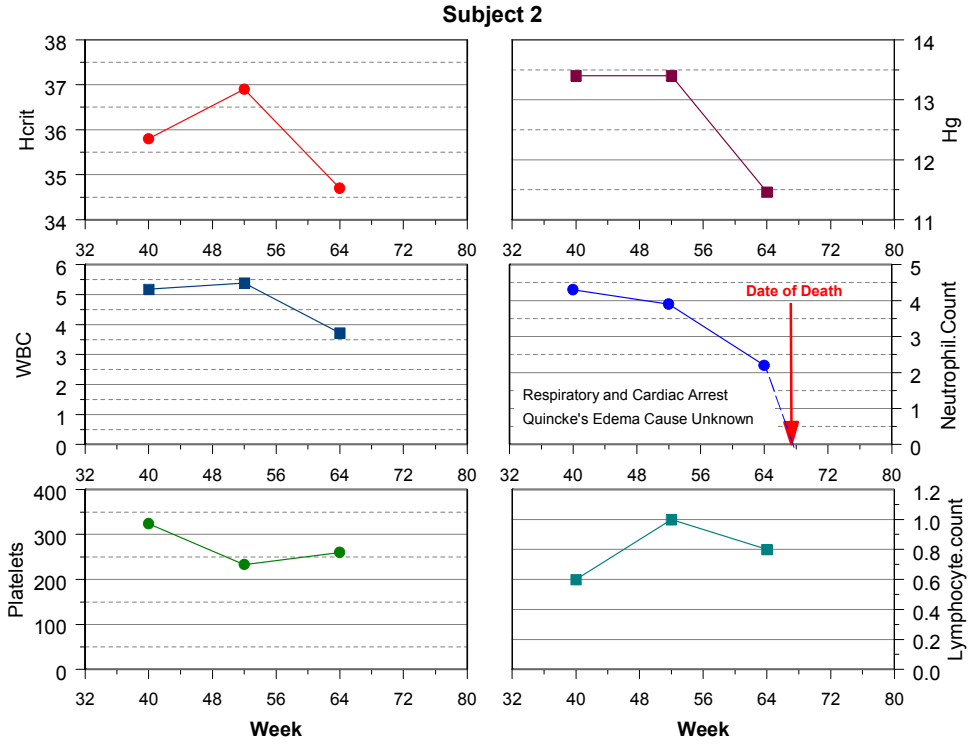


Figure 5 Hematology Values Prior to Death for Subject 241041 -Study P25520



3.5.1.9 Relative Rates of Cardiovascular and Pulmonary SAEs from Ongoing Studies

Although a preliminary assessment, Table 26 appears to indicate that the risks with asenapine are greater than the risk of similar toxicities with olanzapine. A similar pattern was noted in §3.5.1.1, Subjects who Died in Primary Efficacy and Safety Phase 2/3 Studies.

Table 26 Relative Rates of Cardiovascular and Pulmonary SAEs from Ongoing Studies

Study	# SAEs	Total N	Treatment	Relative Risk for Asenapine
41512	5	207	As/Olanz/PBO	**2.4**
25520	5	534 Rand 3:1	As/Olanz	0.9
41513	3	187	As/Hal/PBO	1.6
25543 ? / (25544)	2	124	As/Olanz	1.6
A7501012 Comparison of Suicidality	5	576	As/PBO	0.9
A7501013 & A7501014 Predominant and Neg Sxs	2+6	104	As/Olanz	**7.7**
A7501021	Elderly			
A7501007	3	218	As/Olanz/PBO	1.4
A7501008* Li VPA	3	326	As/PBO	0.9
A7501009 Li VPA	1	77	As/PBO	1.3

3.5.1.10 SAEs Reported in IND Reviews

The hypotension and syncope in the subject in study 25504 is noteworthy as structurally similar compounds also from Organon appear to result in extreme CNS depression when taken in combination with alcohol and may in whole or part be the basis for the class labeling on antidepressants and other CNS depressant medications even though the degree of the interaction may vary by drug.

Pulmonary emboli, DVTs, and strokes are c**o**mmonly seen with antipsychotics and may be mechanistically related to either vasoconstriction or effects on platelet serotonin receptors that effect aggregation.

Table 27 Subjects with SAEs in Phase I/ II Studies reported in IND Reviews per Dr. Roberta Glass

Study	Subject	Available Description
25501	?	
15501	?	Treatment emergent RBBB
25504	?	Hypotension syncope vomiting after 14 days. Sponsor questioned if this might be due to EtOH and diazepam
25505	?	New onset Sinus tachycardia Baseline incomplete RBBB
25506	?	
25511	9	
41013	28	
	48	*"Patient Died. Possible obstruction of pulmonary arteries, thrombus in lungs and/or questionable pneumonia are possible contributing factors."*
25517	186007	
41513	315504	
A7591007	50281012	
P25520	132017	
	241041	
	246021	

3.5.1.11 Other Potentially Mechanistically Related AEs

3.5.1.11.1 Connective Tissue Disorders and Fibrotic Effects

Another side effect that has been reported with asenapine is ruptured tendons. Based upon the similar cardiac effects on ECG seen with the floroquinolone antibiotics and the increased rupturing of tendons mentioned by Dr. Woodcock in the announcement of the Sentinel program.[20] This might be due to effects on the BMPR2 gene product,[21] and this might somehow also be related to schizophrenia and Parkinsonism, as well as development of brain tumors. [22], [23] Pharmacodynamic interactions of effects on sleeping have also been described for floroquinolone antibiotics and herbal Viagra.

Potential dose and time dependent hepatotoxicity was seen with asenapine, also as mentioned previously some cases of cirrhosis of the liver appear mediated through 5HT receptors.

3.5.1.11.2 Neuropsychiatric Side Effects

Effects on cognition, wakefulness, suicidality, vivid dreams, seizures, hostility and violence, and worsening psychosis have been reported to be common to a number of drugs including asenapine and other atypical antipsychotics and suggest a common mechanism. Based on effects on specific parts of the brain associated with the atypical antipsychotics, the known association of these areas with some of these functions, as well as the distribution of certain types of serotonin receptors in these areas, there may be a common underlying mechanism(s) via serotonin or other receptors.

3.5.1.11.3 Other Observations

Recently FDA issued a warning against Xiadafil 'herbal viagra' which may have a connection with effects on serotonin receptors, and similar warnings by FDA with respect to ephedra preceeded the announcement of the risks of phen-fen in 1997. More recent FDA warnings with respect to cardiotoxicity with OTC cough and cold medicines in children raise concerns regarding a possible mechanistic link between these otherwise seemingly disparate observations.

[20] http://www.nytimes.com/2008/05/23/washington/23fda.html
[21] http://ghr.nlm.nih.gov/condition=pulmonaryarterialhypertension
[22] http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1571542
[23] Am J Physiol Lung Cell Mol Physiol. 2005 Feb ;288 (2):L370-8 15516492 (P,S,E,B)

3.6 Metabolites and Other Species Potentially Responsible for Asenapine's Non-Hematologic Toxicities

When the totality of clinical pharmacology information is examined it suggests that asenpine's toxicity primarily resides in the hydroxylated metabolites, including a mono-hydroxy, a catechol, and/or one or more conjugative metabolites.[24] This includes the increased risks observed with structurally similar compounds when given in combination with MAOIs and the increased toxicities when given with carbamazepine.

This reviewer found in the pharmacology literature that for monocrotaline that toxicities in Sprague-Dawley rats are increased when given intravenously as compared to orally or by other routes of administration and that this could not be explained by differences in metabolism. This has been proposed to potentially be due to a degradation product formed in aqueous solutions however when aqueous solutions were examined none were found. Although increased toxicities have been observed when IV solutions in DMSO have been administered. It has also been noted in the literature that monocrotaline has stereoisomers that they may have different toxicities.

On Thursday June 5, 2008 at around 2:30 PM this reviewer spoke to the chemistry reviewer about the possibility of degradation products in the drug product used in the IV study with the case of cardiac asystole and requested that he obtain information on the drug substance and the diluents used in this study. The chemistry reviewer suggested that this reviewer look at his review, which this reviewer had already done for the IV drug product. Due to the lack of time, this reviewer requested that the chemistry reviewer research and provide this information.

A short time later while looking for the pharm/tox review to check some information, this reviewer serendipitously found that the day after the original OCP review was signed off, the chemistry review team, (minus the usual chemistry team leader), amended their review to request a lowering of the limit for the impurity ORG 5033 to 0.15% which based on the molar dose of asenapine is a low absolute amount. The recommendation from the amended chemistry review follows:

"I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant provided acceptable responses for the CMC deficiencies stated in the review #1 dated 11-APR-08 (see evaluation in the Chemistry Assessment section in this review). However, from the CMC point of view NDA 22-117 for Sycrest® (asenapine) Sublingual Tablets is recommended ***APPROVABLE*** *due to pending resolution of the following outstanding pharmtox issue regarding impurity Org 5033 which will have impact as the setting of acceptance limit for the drug substance specification:*

1. *The applicant proposed acceptance criteria for impurity, Org 5033, in asenapine drug substance at 0.3% which is above the ICH Q3A(R) qualification limit of 0.15%. The pharmtox reviewer (Elzbieta Chalecka-Franaszek, Ph.D.) stated in her review dated 30-APR- 08 (pp. 4) that the applicant should perform an embryofetal development study with* (b) (4) *in the rabbit to qualify this impurity during phase IV or reduce the specification of* (b) (4) *to the ICH Q3A(R) qualification limit of* (b) (4).

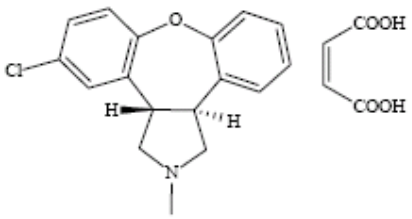
[24] Although this reviewer previous indicated that no more than approximately 4% of circulating species had been accounted for when estimates of relative exposures from asenapine glucuronide from the carbamazepine drug-drug interaction study, (3X, 7.5%), desmethyl-asenapine from the valproate interaction study, (1/3, 1%), and the 11-O-Sulfate from the fluvoxamine interaction study, (<1/3, <1%) are considered the amount of circulating specifies identified is still less than 15% of the total circulating radioactivity.

Release data for the drug substance batches used in clinical studies (20 batches) and batches used in to be marketed drug product batches (4 commercial batches) showed that process impurity (b) (4) *is present at not more than* (b) (4) *level, which is well below ICH Q3A(R) qualification limit of* (b) (4) *indicating that the applicant may be able to reduce the specification of* (b) (4) *to the ICH Q3A(R) qualification limit of* (b) (4)

Upon checking the original OCP review for the structure of (b) (4), this reviewer found that ORG (b) (4) means that it should be separable and identifiable by the sponsor in any mass balance or metabolism studies.

As this reviewer was reading the amended chemistry review this reviewer noticed the following figure, Figure 6.

Figure 6 Structure of Asenapine from Chemistry Review



Asenapine maleate (Org 5222) contains two chiral centers. Asenapine maleate is a racemate.

It then struck this reviewer that although asenapine has 2 chiral centers and although the easy way to manufacture it is to have 4 diastereomers, it is a racemic compound and thus the sponsor is specifically controlling manufacture to avoid 1 set of stereoisomers. This is highly unusual unless there is a toxicity concern. Since, N-desmethyl asenapine may be secondarily metabolized by 11-hydroxylation and since the sponsor is avoiding looking at these metabolites, and as metabolites can be active with differing activity this suggests that the toxicity with the original IV formulation might have been due to either a stereoisomer and/or a metabolite of the stereoisomer, or a contaminant or degradation product if it were dissolved in DMSO prior to secondary dilution[25].

The recommendations from the original chemistry review dated April 11, 2008 follow:

"I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC point of view NDA 22-117 for Sycrest® (asenapine) Sublingual Tablets is recommended ***APPROVABLE.*** *The outstanding issue is pending acceptable responses to the following CMC deficiencies.*

1. The acceptable limits for impurities should not be based on strength. Reduce the acceptance criteria for both strengths for the degradation product (b) (4) *and total degradation products to the levels that are more consistent with your data.*

2. Revise unspecified each individual impurity limit for both strengths to no more than (b) (4) *based on maximum daily dose of 20 mg/day.*

[25] One or more of these hypothesis can be supported if information on the drug substance and drug product used in this study is obtained.

***Note**: In e-mail (dated 26-MAR-08) and in the NDA WRAP-UP meeting (dated 07-APR-2008), the pharmtox reviewer (Elzbieta Chalecka-Franaszek, Ph.D.) indicated that the data supporting qualification of impurity Org (b) (4) was not acceptable and that additional information will be requested. However, in the WRAP-UP meeting, Dr. Barry Rosloff (Pharmtox Team Leader) stated that the limit for impurity (b) (4) is acceptable; unless the "requested" phase 4 studies (when done correctly) show a problem. If a problem is seen, then the limit for this impurity will need to be lowered."*

This reviewer did not attend the wrap-up meeting as an external contractor was supposed to attend and this reviewer did not believe it was necessary to reveal trade secrets to a contractor for evaluating business processes and thus believed that participating might be unlawful. The OCP team leader agreed that this reviewer could skip the meeting as OCP had no new information and thus the time would be better spent completing the review. The OCP TL participated by conference call from Arizona, and per this reviewer's recall reported to this reviewer something about Dr. Rosloff and an impurity with a (b) (4) level. Upon checking this reviewer cannot find / identify the management consultant on the list of participants in the Outlook calendar. This is not surprising as this reviewer does not believe the contractor had an FDA e-mail account.

Subsequent to reading the above chemistry recommendations this reviewer checked the Pharm/Tox review dated April 30, 2008 and found the following:

***"2.** Qualification of impurity (b) (4): Drug substance impurity (b) (4)) has been present in the drug substance commercial size clinical/stability batches at (b) (4). However, the Sponsor proposed to set a specification limit for this impurity in asenapine drug substance at (b) (4), thus above the ICH Q3A(R) qualification limit of (b) (4). The content of (b) (4) in relevant asenapine batches used in the preclinical program was below the limit of detection. A non-GLP pilot segment II study in rabbits was performed with this impurity; however, this study is considered inadequate for several reasons, including the following: (1) only a single dose of (b) (4) was employed which did not result in any maternal toxicity; (2) the number of animals per group was less than the recommended 16 per group, with only 34 fetuses examined in the (b) (4) group; (3) relatively high post-implantation loss was observed in the control group; (4) no information on drug analysis was provided; (5) no toxicokinetic data were obtained; (6) (b) (4)033 was administered orally, although asenapine is being administered by the sublingual route; and (7) unclear terminology was used to describe fetal findings. Moreover, a 9-fold increase in the incidence of malformations, and signs of embryotoxicity demonstrated as a 2-fold increase in post-implantation loss, were observed in fetuses of female rabbits dosed with (b) (4) at 80 mg/kg/day during the period of organogenesis in this non-GLP pilot study. The NOAEL has not been identified for these effects. Therefore, the Sponsor should perform an embryofetal development study with (b) (4) in the rabbit to qualify this impurity during phase IV or reduce the specification of (b) (4) to the ICH Q3A(R) qualification limit of (b) (4)."*

It should be noted that April 30th is after the OCP reviewer was supposed to have the review completed. Due to timelines and the amount of material this reviewer was required to review this reviewer was unable to check the reviews of other disciplines prior to sign off of the original OCP review.

It should also be noted that the ICH limits will allow amounts of this contaminant in commercial batches higher than the amount of this contaminant that has been used to define the safety profile of asenapine.

Finally on June 13, 2008 this reviewer found the information in the pharmacology /toxicology study noted in § 3.5.1.3.3, Neonatal Effects of Cis-Asenapine.

To aid in understanding the differences in the 3-dimensional changes that could result in minor alterations that could effect binding site interactions this reviewer constructed molecular models of asenapine and cis-asenapine and these are shown in Figure 7 and Figure 8.

Figure 7 shows that the trans- isomer results in a twist in the pyrroles ring that results in one carbon of the pyrroles ring standing up away from the plane of the table on which it's resting and pushes the nitrogen into the table. Whereas Figure 8 shows that in cis-asenapine the pyrroles ring and the nitrogen lie flat.

Unfortunately molecular models are constrained by the physical limits of the connecting pieces, however conceptually hydroxylation of the non-halogenated benzene on the side as the carbon in the pyrrole ring of asenapine in Figure 7 that is being pressed into the table might result in a flattening out of the pyrroles ring so the 3-D conformation is more similar to that seen with cis-asenapine in Figure 8.

To examine this and not have the physical constraints of a molecular model a 3-D chemical drawing program was used to show possible physical conformations of asenapine, cis-asenapine, and selected metabolites, (see Figure 9 to Figure 13).

Comparison of (trans-) asenapine in Figure 9 and dihydroxy-asenapine (the catechol) in Figure 11 clearly shows that the position of the pyrroles group changes, and that the position of the pyrroles group is more similar to that in cis-asenapine in Figure 12. In addition, the 3-dimensional shape of desmethyl-asenapine in Figure 10 is similar to the shape of asenapine in Figure 9. Plus addition of sulfate conjugates to the catechol, (see Figure 13), also results in a 3-dimensional shape intermediate to asenapine and the catechol.

While this reviewer realizes that this program may not be truly accurate with regards to these changes in conformation, as possibly evidenced by the change in the halogenated benzene from a planar to a boat conformation, it does help to provide some insight and does tend to support this reviewer's hypothesis for the toxic species.

Figure 7 Molecular Model of Asenapine

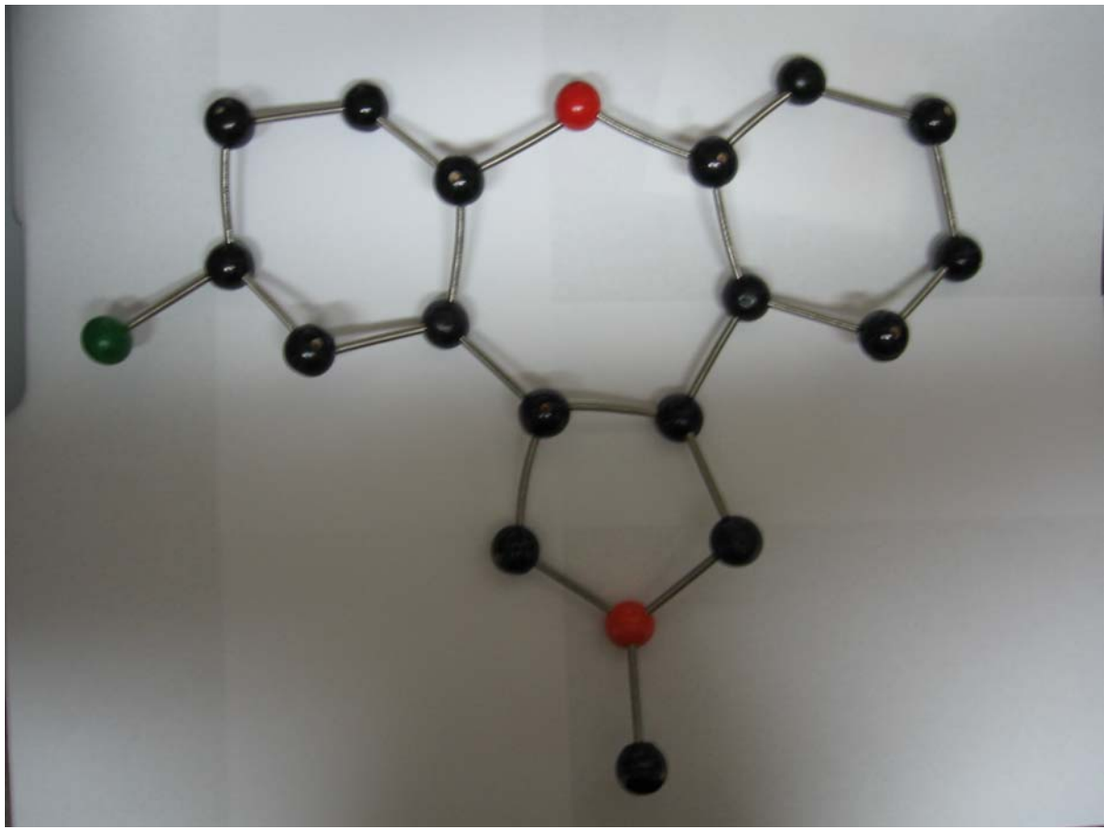


Figure 8 Molecular Model of Cis-Asenapine

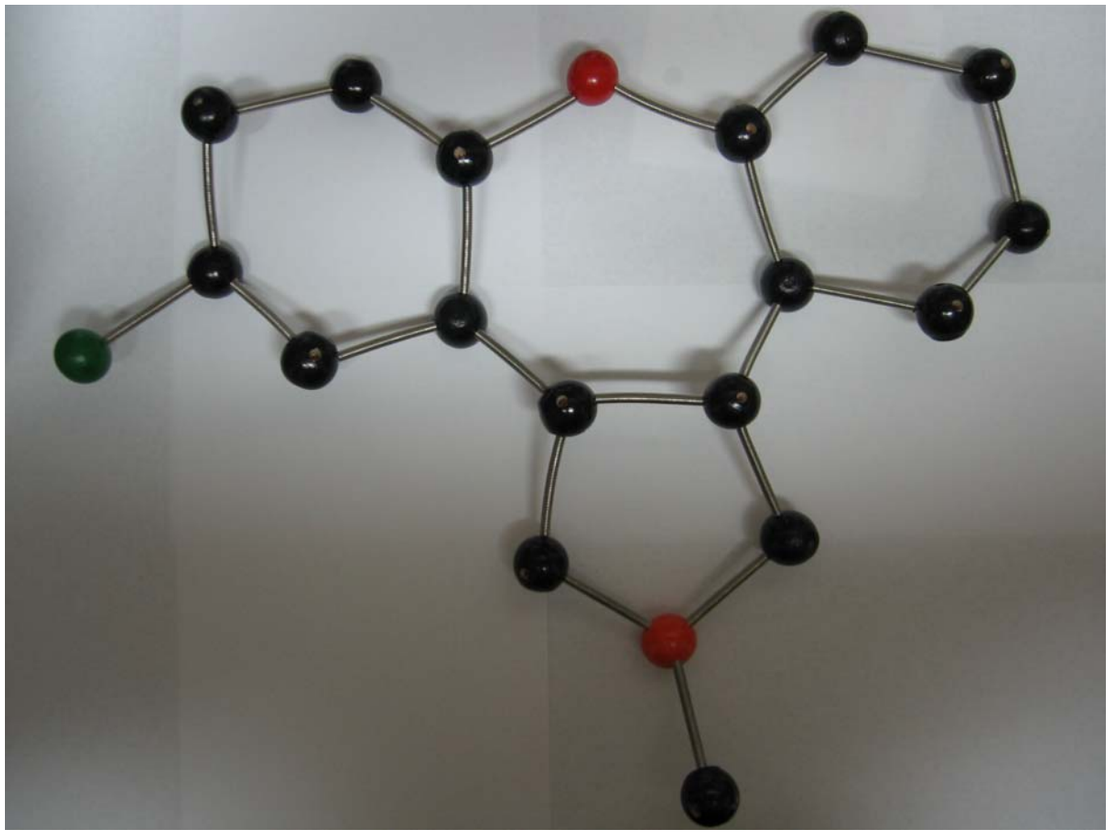


Figure 9 Asenapine

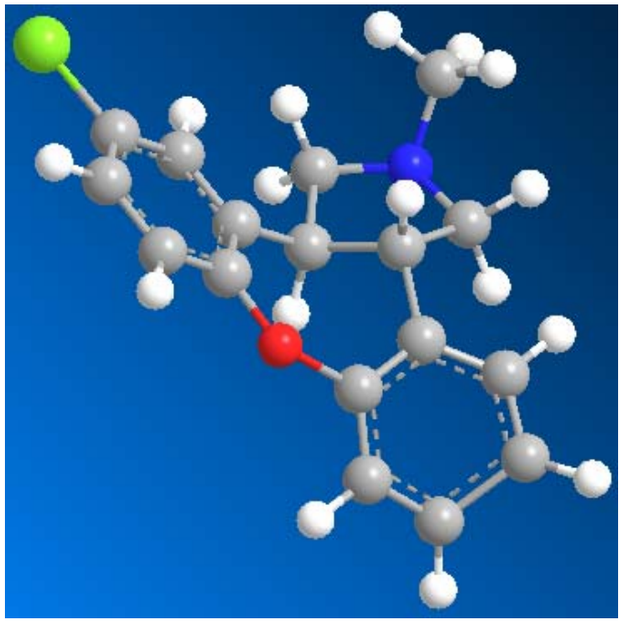


Figure 10 Desmethyl-asenapine

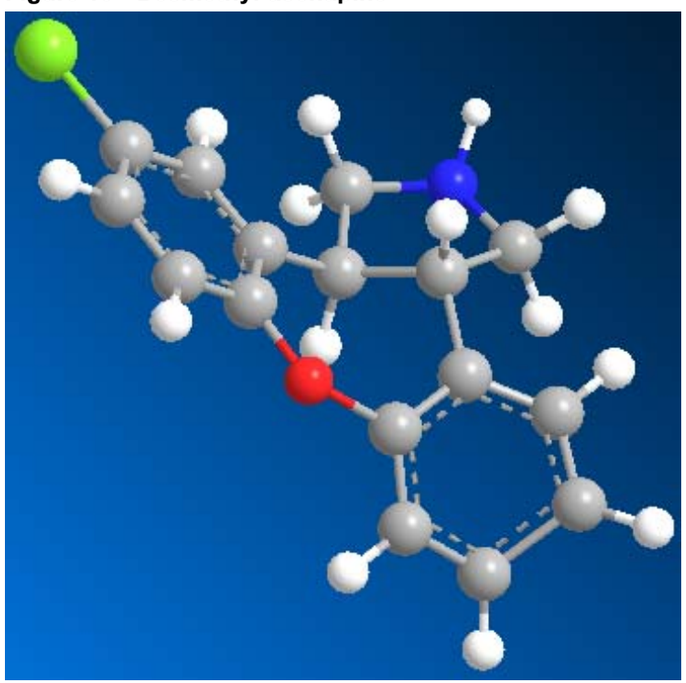


Figure 11 Asenapine Catechol

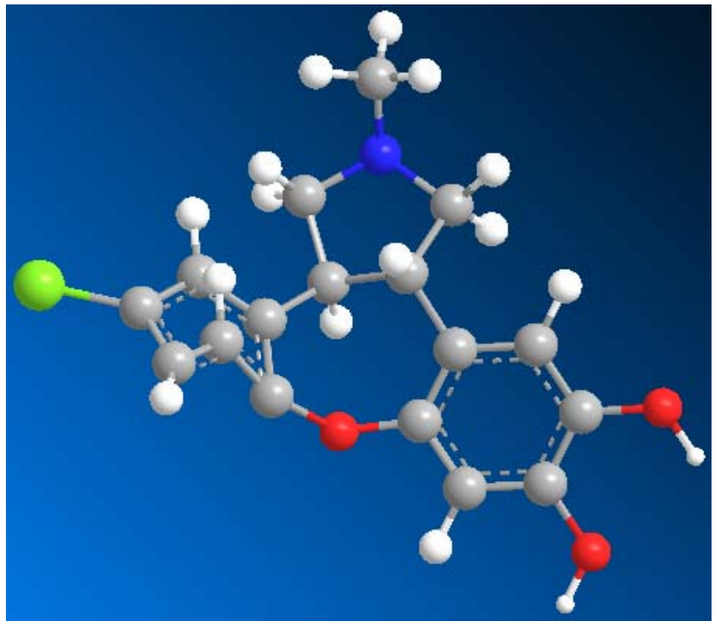


Figure 12 Cis-Asenapine

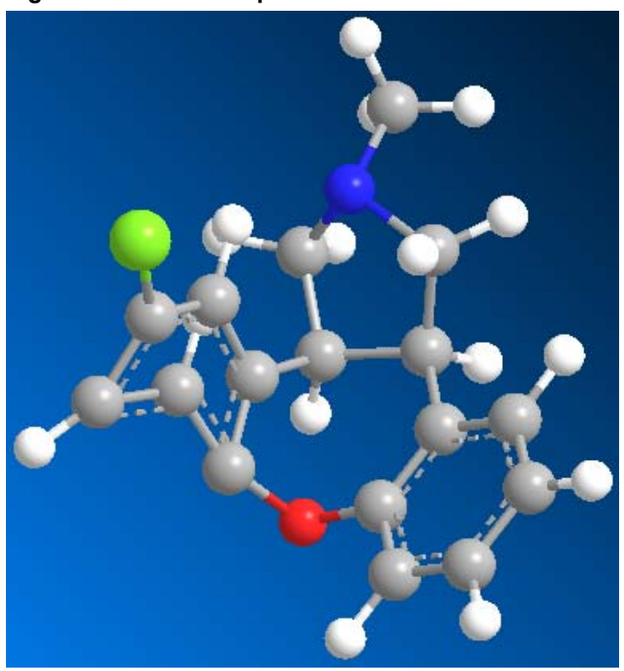
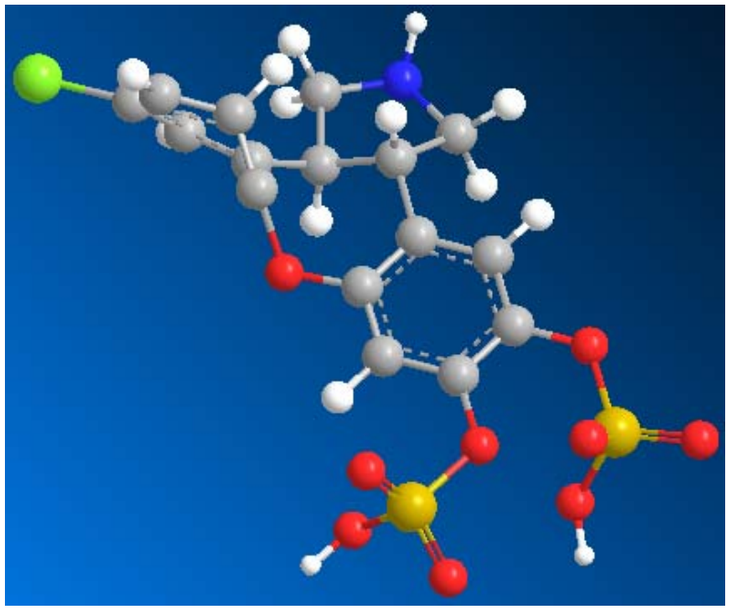


Figure 13 Desmethyl-Asenapine- DiSulfate



3.7 Major Deficiencies in NDA 21-117 and Reassessment of Approvability

Based upon the information presented so far in this amendment it is clear that there are numerous deficiencies in NDA 21-117 that appear to be intentional so as to hide critical information needed to make an informed determination of the safety of asenapine and in order to mislead the FDA. A brief description of a limited number of selected deficiencies follows. More detailed discussions may be found in the original OCP review, however conclusions regarding the clinical relevance with respect to the safety conclusions some the original OCP review including a lack of any margin of safety have now become of even great concern based on additional review.

Basic Pharmacology

The sponsor failed to provide information on the receptor activities of various metabolites and contaminants that are needed to understand the effects of both intrinsic and extrinsic factors on both safety and efficacy.

Mass Balance Phenotyping

The sponsor has not identified over 85% of the circulating species and in particular has avoided evaluation of those metabolites and pathways most likely involved with the potentially lethal toxicities of asenapine. For example even though multiple enzymes may be involved in a particular metabolic pathway without the relative contributions for all pathways and the distributions evaluation and mitigating risk is virtually impossible. This also includes prevention of the identification of pharmacogenomic factors that are expected to have an impact on safety. In addition, the sponsor clearly obfuscated the information available and in-spite of a direct request for clarification of the available information that was needed for safety review the sponsor avoided providing the information.

Basic Pharmacokinetics

Based on the detected accumulation of the potentially hematologically toxic N-oxide in the thorough QT study and the long half-lives of total radioactivity observed it appears that the sponsor has likely not adequately characterized pharmacokinetic characteristics of metabolites that might affect time dependent toxicities. The enantiomeric selective metabolism and kinetics discussed in the original submission now appears to have much greater overtones regarding potential toxicity and needs to be more fully addressed.

Subject Selection and Assessment of Chronic Toxicities

The sponsor's subject selection criteria for safety and efficacy studies, including a history of acute tolerance to similar compounds, lack of risk factors such as prior viral hepatitis, the limited number of subjects treated chronically, and the lack of long term data and placebo controls all have the effect of minimizing the detection of risks and skewing the risk benefit assessment.

Effects of Race and Ethnicity

There were few blacks included in studies and virtually none in pharmacokinetic studies except for the pediatric adolescent study. Eighty percent of African Americans express CYP3A5 as compared with 20% of white Americans. Although substrate specificity and intrinsic clearance may vary between CYP3A4 and 3A5, we must be concerned a priori that the similarity in substrate specificity between the two enzymes might result in increased formation of toxic metabolites in the African American population and thus the risk benefit profile could not have been adequately assessed in this population which is expected to be at higher risk than Caucasians. This is especially problematic as individuals in prison or children in foster care are more likely to be persons of color and individuals in prison and foster care are also more likely to be inappropriately prescribed antipsychotic medications.

Other populations that may also be at higher risks for hematologic toxicities include Finns, Ashkenazi Jews, and Thai (or possibly the 60% of the population of Bangkok that are of Han Chinese ethnicity). Finns and Ashkenazi Jews have higher risks of agranulocytosis, and Thai have higher risks of aplastic anemia with clozapine.

Effects of Gender

The effect of gender was not formally examined. Although there was some data that was found at the end of the review cycle that could have been extracted, but by the time it was realized that such data was available there was insufficient time for reanalysis and review. Unfortunately although the sponsor could have easily included this analysis in the NDA they did not do so.

Both increased CYP1A2 activity that might result in increased formation of toxic metabolites as well as smaller body mass in women would be expected to increase exposures to toxic metabolites. In addition, there could be interactions with various sex hormones including oral contraceptives. Thus any safety analyses would need to take account of these factors.

Effects of Age

There was limited information on pharmacokinetic and pharmacodynamic effects with age. The same concerns with gender are also of concern in the elderly. In addition, underlying chronic conditions such as atherosclerosis, and cardiovascular disease would be expected to increase toxicity. Increased toxicity in older adults (non-elderly) was noted in the original review for olanzapine but was not highlighted in the labeling. This subsequently resulted in a black box warning. In addition, it's possible that the cardiovascular toxicity with asenapine might be worse than with olanzapine. The elderly PK study was reported in an incomplete form and submitted to the NDA in a manner that appears designed to avoid its detection.

The original olanzapine review included studies for psychosis in dementia but it was not approved for this indication. In spite of this apparently the sponsor later pushed prescribing for this off-label indication with the known consequences of increased mortality and a black box warning for a class effect.

Pediatric Pharmacokinetics

The pediatric pharmacokinetic study only included mean and not individual data. Subjects ranged in age from 12 – 17 years of age but the weight over the entire range was at the 80^{th} percentile and thus would underpredict the exposures expected in practice. The most obvious example was the inclusion of a 200 lb. 12 year old. There were also very few subjects. Both of these demographic characteristics are common and tend to let inappropriate adult doses be used in children with the associated greater risk in toxicity. The subjects were also primarily African American. Therefore this short term study may give the sponsor some insight into potentially greater risks with African Americans but the short duration and underdosing would be likely result in an under appreciation by most readers of the study report of the risks identified. This under appreciation of the risks in the actual population that would use the drug would then likely result in mislabeling of the drug.

Effects of Smoking

The effect of induction of CYP1A2 by smoking was conducted in chronic smokers so that no increase in formation of the likely toxic metabolites would be found.

Effects of Renal Impairment

Both due to the short duration and by not examining the likely toxic species, the study was biased against elucidating the both the cardiovascular and other risks from asenapine in this population, including both effects on bone, as well as platelet aggregation, and possibly salt and water balance.

Effects of Hepatic Impairment

Without examination of the likely toxic species, this study was also biased against finding any problems. In spite of this there are indications of increased risk in even mildly impaired subjects. This hints that patients with cirrhosis or fibrotic processes may be at increased risk due to increased genetic susceptibility in addition to any increased risk due to altered pharmacokinetics.

Drug Interaction Studies

Some of the drug interaction studies appear to be designed to give some idea of the potential increased risks via surrogate examination of the effects on pharmacokinetics while at the same time minimizing the possibility of finding adverse effects by using low single doses. After identification of the risks with asenapine, the likely toxic species, and the timing of events it appears that the sponsor intentionally designed these studies in such a manner so as to allow labeling that would protect the sponsor from liability if preemption should pass the US Supreme Court. At the same time the sponsor appears to have tried to obfuscate or avoid monitoring the most pertinent information needed to mitigate risks so as to avoid detection by the FDA.

Paroxetine – An increase in pharmacodynamic adverse effects with a SSRI as expected. In fact several subjects having severe AEs with even a single dose of asenapine added to paroxetine, yet the study is ostensibly primarily a pharmacokinetic interaction study.

Cimetidine – Inhibition of multiple pathways may increase hematologic toxicities over time.

Valproate – Without examination of the likely toxic species, this study was biased against elucidating the risk of problems in this population.

Carbamazepine – Expected to induce the formation of the toxic metabolites responsible for cardiopulmonary toxicities, yet an extremely low dose was used much below what would be expected to be used clinically. In spite of this there was a several fold increase in signs and symptoms of cardiopulmonary toxicity with even a single dose of asenapine whereas toxicity is expected to be cumulative over time. In addition to a pharmacokinetic interaction a pharmacodynamic interaction is also possible.

In the second End-of-Phase II meeting held on April 27, 2004 the sponsor specifically requested whether approval would be granted for asenapine as adjunctive therapy in bipolar I disorder based only on data with lithium and valproate, (see Figure 14).

Figure 14 Minutes from April 27, 2004 EOP2 Meeting Regarding Adjunctive Therapy in BP I

Question Related to Bipolar Indication: Adjunctive Therapy

Question 1.3.1: Does the Agency agree that a study comparing asenapine treatment with placebo as adjunctive treatment to lithium or valproic acid in bipolar I disorder patients experiencing acute manic episodes is adequate for an additional labeling claim for adjunctive therapy for asenapine?

Discussion: The Agency stated that the proposal appears acceptable.

What's disturbing about these meeting minutes is by this time the sponsors appear to have already long known that there was likely an increased risk of severe and lethal toxicity with this combination and they were trying to avoid detection of this by the FDA while also getting approval for a lethal drug combination. What's even more disturbing is that one of the co-sponsors in attendance at this meeting was

simultaneously preparing to submit an NDA to treat the very same expected toxicity that would result in an increase in sales for one of their most profitable drug products, (see N21-845 submitted Dec 2, 2004, Approved June 3, 2005).

In later discussions at the pre-NDA meetings held July 18, 2006 and February 22, 2007 the sponsors appear to be trying to limit submission of longer duration safety data, especially nonserious safety data that might point to a developing chronic toxicity that might be detected prior to an initial approval. In contrast detection post approval could result in a significant increase in overall sales that might offset decreased sales from this single product.

This effect could hypothetically even be multiplied via extension of marketing exclusivity and via marketing to the pediatric population.

MAOIs - No drug interaction studies with monoamine oxidase inhibitors, yet this would be expected to result in severe toxicity, even more so if used in combination with an SSRI in a patient with refractory depression. Base on recent trends in labeling to avoid using the term contraindication, there is a good likelihood that the clinical significance of this type of interaction would be underappreciated.

Other Major Deficiencies

Thorough QT Study – Both safety and pharmacokinetic data from the TQT study was not submitted and as the highest and longer duration of study with intensive pharmacokinetics this would have been extremely useful information. Instead the lack of submitting the information, some of which was not submitted even after requested by OCP, simply in itself represents a major deficiency that according to the FD&CA must result in nonapproval.

Cumulative Toxicities – cardiopulmonary, hematologic, and connective tissue toxicities appear to be cumulative with greater risks the longer patients are on medication. In spite of this the sponsor curtailed the only study of greater than 1 year total exposure ostensibly as the study was un-interpretable without a placebo arm. In addition, the sponsor may have limited the amount of safety information provided that was available from long term studies.

Suicidality – Increased risk of suicide and suicidality in adults with bipolar disorder I treated with asenapine or olanzapine for 2 to 3 weeks. This is compared to no risk seen in patients on placebo. (Please refer to original OCP review.)

Lack of Substantial Evidence of Efficacy – Please refer to original OCP review.

3.8 Assessment of Risks Relative to Currently Approved Compounds

3.8.1 Other Antipsychotics

The following compounds are presently marketed in the US. Dr. Temple has indicated that any assessment of risk benefit will likely include a comparison to the following presently marketed compounds.

- Clozapine (Clozaril®)
- Olanzapine (Zyprexa®)
- Quetiapine (Seroquel®)
- Risperidone (Risperdal®)
- Paliperidone
- Ziprasidone (Geodon®)
- Aripiprazole (Abilify®)

Of the ones that are currently approved the first 3 are structurally most similar to asenapine. In the OCP briefing this reviewer pointed out that the side effect profile for asenapine is remarkably similar to the labeled side effect profile for both clozapine and olanzapine. Figure 15 and Figure 16 on the following page are slides from the original OCP briefing and provide an overview of the particular toxicities and structure activity relationships associated these compound. However it should be noted that asenapine is the only pyrrole and thus may have both qualitatively and quantitatively more severe AEs.

Even if asenapine is compared to clozapine which is available on a restricted basis it needs to be remembered that there is data to show that clozapine does work in some individuals with schizophrenia who did not respond to classical antipsychotics, whereas there is no such data for asenapine. Plus in this reviewer's opinion there is a lack of substantive data to support the efficacy of asenapine in schizophrenia. In addition it should be remembered that due to the variety of serotonin receptors and their various effects just because a patient will respond to clozapine when they don't respond to a classical antipsychotic does not mean that the same is true for asenapine.

Thus the most relevant compound to assess the safety of asenapine against is olanzapine.

The sponsor reported their position as to the safety of asenapine relative to olanzapine American Psychiatric Association Meeting held in Washington DC in May as described in a press release from the sponsor shown in §4.4 Appendix 4 – Schering-Plough May 8, 2008 Press Release for Asenapine. These statistics are also put forward by the sponsor in the common technical document summary sections of the NDA. While on face asenapine seems no more dangerous than olanzapine, these statistics only cover total statistics and do not address the safety data referred to in this review amendment. Specifically they do not include sufficient long term safety data and the numbers do not adequately reflect the relative incidence of serious AEs and death. When serious AEs and deaths are compared asenapine appears to be significantly less safe than olanzapine. In addition, the signal for serious long term safety problems rather than arguing for the approval of asenapine actually argues for an immediate reevaluation of the safety of olanzapine. In addition it might be more appropriate to compare the safety of olanzapine to the safety profile of other antipsychotics.

Recently published articles have raised significant concern about the long term safety of antipsychotics and in particular that the more recently introduced antipsychotics increase all cause mortality and decrease life expectancy to a greater extent than older antipsychotics[26]. This is significant as the

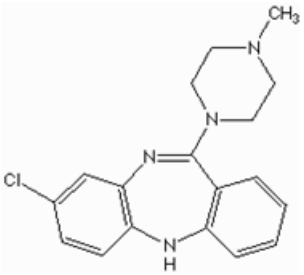
[26] Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? Arch Gen Psychiatry. 2007 Oct;64(10):1123-31.

schizophrenic population is already at an increased risk of death from all causes compared to the non-schizophrenic population[27]. Most recently there has been a publication that seems to argue for an acceptable risk benefit for the use of antipsychotics in schizophrenics[28]. However even a cursory examination of the article reveals that the benefit may be only for a subset of the schizophrenic population. For example patients who are already suicidal, who are young, who are early in the course of their illness (< 4 years) and have had only 1 or 2 psychotic episodes. In addition to the fact that the risk of suicide is lower than previously thought and decreases with the duration of illness[29], whereas the risk of death from the drugs appears to increase with time argues for as limited treatment duration as possible to simply get a psychotic episode under control with subsequent switching to non-antipsychotic disease management if possible. In addition, other publications suggest that the risk benefit may be different in different populations or with disease severity.[30]

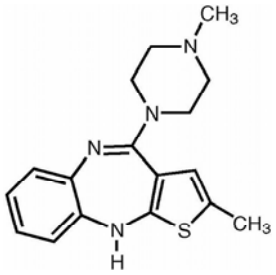
[27] Auquier P, Lançon C, Rouillon F, Lader M, Holmes C. Mortality in schizophrenia.Pharmacoepidemiol Drug Saf. 2006 Dec;15(12):873-9. Review. PMID: 17058327 [PubMed - indexed for MEDLINE]
[28] Haukka J, Tiihonen J, Härkänen T, Lönnqvist J. Association between medication and risk of suicide, attempted suicide and death in nationwide cohort of suicidal patients with schizophrenia. Pharmacoepidemiol Drug Saf. 2008 Mar 10
[29] Palmer BA, Pankratz VS, Bostwick JM.The lifetime risk of suicide in schizophrenia: a reexamination.Arch Gen Psychiatry. 2005 Mar;62(3):247-53.
[30] Thirthalli J, Jain S. Better Outcome of Schizophrenia in India: A Natural Selection Against Severe Forms? Schizophr Bull. 2008 Mar 13. [Epub ahead of print] PMID: 18339655 [PubMed - as supplied by publisher]

Figure 15 Structure Slide # 1 from OCP Briefing

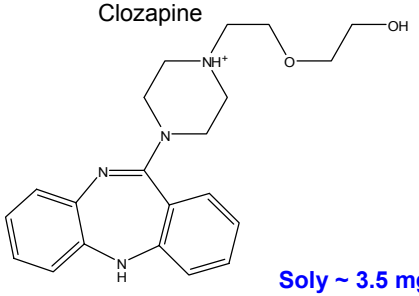
Dibenzopyrridine / Benzofuranopyrridine
Dibenzopyrrole



Clozapine

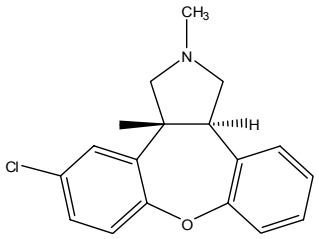


Olanzapine



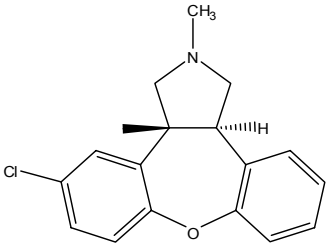
Quetiapine

Soly ~ 3.5 mg/ml

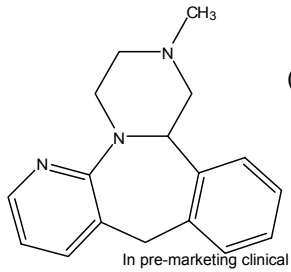


Asenapine

Figure 16 Structure Slide # 2 from OCP Briefing

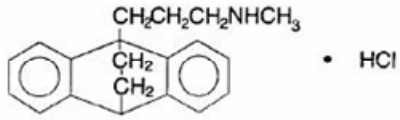


Asenapine



Mirtazapine
(**Remeron – Organon 1994)**
Antidepressant
excessive sedation with alcohol
or benzodiazepines
Agranulocytosis
DDI – MAOIs
CL dec 40% in elderly males
10% in elderly Females

In pre-marketing clinical trials of mirtazapine, 2 out of 2796 patients developed AGRANULOCYTOSIS (absolute neutrophil count (ANC) less than 500 cells/cubic millimeters with symptoms) and 1 patient developed severe NEUTROPENIA (ANC less than 500 cells/cubic millimeters without symptoms).
All 3 patients recovered after mirtazapine was discontinued.
The incidence based on these 3 cases was approximately 1.1 per 1000 patients.



Maprotiline - Ludiomil – Ciba Geigy

Discontinue therapy if the patient develops a sore throat, fever stomatitis, or signs of infection, along with a low white blood cell (WBC) count.

Other events rarely (incidence less than 1 in 1000 patients) reported in pre-marketing evaluation were PANCYTOPENIA, THROMBOCYTOPENIA, LEUKOPENIA, ANEMIA, LYMPHOCYTOSIS, lymphadenopathy, and petechia (Prod Info Remeron(R), 02a).

Extreme caution should be used when this drug is given to:
patients with a history of myocardial infarction; a history or presence of cardiovascular disease because of the possibility of conduction defects, arrhythmias, myocardial infarction, strokes and tachycardia.
Agranulocytosis
CYP2D6 MAOIs

3.8.2 Combination Products (Atypical Antipsychotics & Serotonin Reuptake Inhibitors)

As mentioned earlier there is likely an increased risk of serious and lethal life threatening adverse effects and death if asenapine or a pharmacologically similar drug were to be used in combination with a serotonin Reuptake Inhibitor, (see §3.1.4).

As mentioned in §3.1.4 Symbyax® (Lilly N21520 Approved Dec 24, 2003) a combination of olanzapine and fluoxetine is currently on the market.

Current labeling and safety information for Symbyax® may be found at the following websites[31].

http://pi.lilly.com/us/symbyax-pi.pdf

http://www.symbyax.com/prescribing/consumer_safety.jsp

http://pi.lilly.com/us/AntiDep-MedGuide.pdf

Examination of the Clinical Pharmacology, Warnings (including but not limited to orthostatic hypotension), Precautions (including but not limited to pregnancy) sections of the labeling for Symbyax® reveal similar deficiencies in the development program and labeling of Symbyax® as has been noted in the reviews for asenapine.

The following is the indications and usage section from the labeling available at this website:

*"**INDICATIONS AND USAGE***

SYMBYAX is indicated for the treatment of depressive episodes associated with bipolar disorder. The efficacy of SYMBYAX was established in 2 identically designed, 8-week, randomized, double-blind clinical studies.

Unlike with unipolar depression, there are no established guidelines for the length of time patients with bipolar disorder experiencing a major depressive episode should be treated with agents containing antidepressant drugs.

The effectiveness of SYMBYAX for maintaining antidepressant response in this patient population beyond 8 weeks has not been established in controlled clinical studies. Physicians who elect to use SYMBYAX for extended periods should periodically reevaluate the benefits and long-term risks of the drug for the individual patient."

The highlighted text in red, appears to indicate that:

a) Symbyax is approved for depression associated with any bipolar disorder.

b) Symbyax is approved for administration longer than 8 weeks but that it's at the physician's discretion, and that all pertinent information available at approval has been provided to allow for a maximally informed decision for treatment beyond 8 weeks. (This is not to imply that there may be unknown risks however the labeling implies that sufficient information is included in the labeling regarding known potential long term risks.

[31] Accessed June 15, 2008

With respect to the labeled indication selected text from the clinical studies section of the label follows:

"CLINICAL STUDIES

The efficacy of SYMBYAX for the treatment of depressive episodes associated with bipolar disorder was established in 2 identically designed, 8-week, randomized, double-blind, controlled studies of patients who met Diagnostic and Statistical Manual 4th edition (DSM-IV) criteria for Bipolar I Disorder, Depressed"

Thus although the indications and usage section indicates approval for any depression associated with bipolar disorder, which clearly implies bipolar I disorder and more recently can be interpreted to mean bipolar spectrum disorder this is clearly not the case.

This interpretation is supported by the following self-asessment tool on Lilly's Symbyax® website (http://www.symbyax.com/tools_downloads/mdq.jsp) which might induce patients to potentially identify bipolar I or bipolar spectrum disorder which may result in patient pressure on primary care providers to inappropriately prescribe Symbyax® for indications for which it was not studied in.

Even stronger evidence suggesting that the sponsor is trying to induce misuse and inappropriate prescribing is the following text from the labeling itself:

***"Screening Patients for Bipolar Disorder** — A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that SYMBYAX is approved for use in treating bipolar depression."*

With respect to item b) the evidence provided in this review indicates that Lilly was also likely aware of the long term risks and even short term risks especially when used in combination with certain other drugs such as carbamazepine.

It is this reviewer's opinion that the labeling for Symbyax® is misleading and is therefore misbranded in violation of the Food Drug and Cosmetics Act § 502 (a), (f) and (j), and that the sponsor is also in violation of FD&CA § 301.

Additional information regarding these laws, as well as preclinical evidence that both some sponsors and more importantly that FDA has been aware of some of the risks associated with both olanzapine and asenapine are included in § 4.5, (Appendix 5 – Additional Information Regarding the Approved Atypical Antipsychotic / SSRI Combination Product- Symbyax®; (Fluoxetine/Olanzapine)).

3.8.3 Quantitative Risk Benefit Analysis

This reviewer is presently working on a new approach to quantify the relative risk to benefit of a drug. This approach may allow a quantitative calculation of a particular drug's risk to benefit that also includes risks of leaving the patient untreated and as compared to presently marketed compounds. Not only may this approach be useful in determining whether the drug should be approved, it may also be useful in assessing if a drug should be removed from the market or whose indications or labeling should be altered.. It is expected that asenapine will be one of the compounds used in developing this methodology. Due to time constraints this quantitative analysis is not included in the present review. If asenapine needs to go to the Drug Safety Oversight Board, this reviewer expects that this review will need to be amended to incorporate some of these analyses.

3.9 Risks with Other Pharmacologically Active Agents

A number of other medications have been reported to have side effect profiles that suggest a common underlying mechanism with asenapine and other antipsychotics.

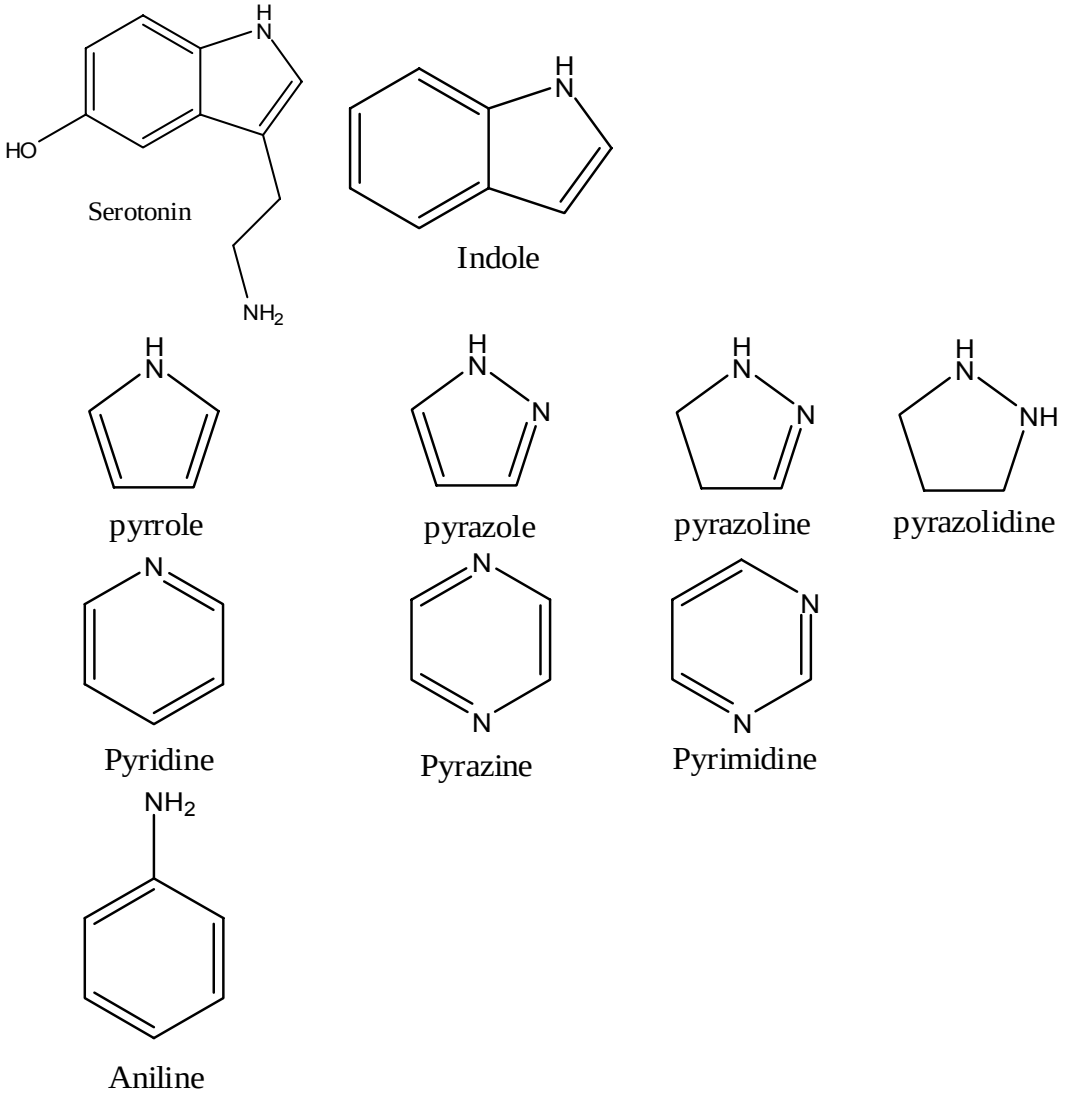
As various serotonin receptors are involved in so many different disease processes similar risks might be seen with receptor nonspecificity with other pharmacologically active agents that tend to bind to different degrees to different serotonin receptors. To this end a quick examination of possible structure activity relationships was undertaken.

3.9.1 Serotonergic Compounds

3.9.1.1 Heteroaromatic Nitrogen Containing Compounds

Figure 17 shows the structure of serotonin and other simple heteroaromatic nitrogen containing compounds that might be expected to bind to serotonin receptors and are common substructures in many drugs. It's clear that serotonin is an indole derivative.

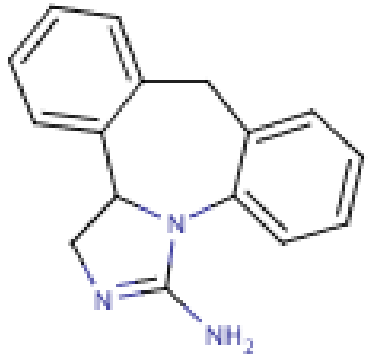
Figure 17 Simple Heteroaromatic Nitrogen Containing Compounds



3.9.1.2 Other Compounds Structurally Similar to Asenapine

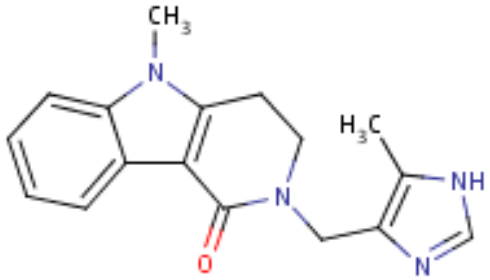
Figure 18 to Figure 20 show other compounds that are structurally similar to asenapine. One of them, epinastine, is a pyrizolidine tetracyclic compound whereas the two 5HT3 antagonists are very similar with both containing an indole and differing primarily in the pyrrazole side chain substituent, yet this change results in a significant difference in toxicity in some individuals. In addition to the potential for different 5HT3 receptor subtypes altering efficacy, either this subgroup is cleaved and has different toxicities mediated by vasoconstriction of the intestines and/or minor genetic variations between individuals result in differences in toxicity.

Figure 18 Epinastine (Elestat – Allergan)



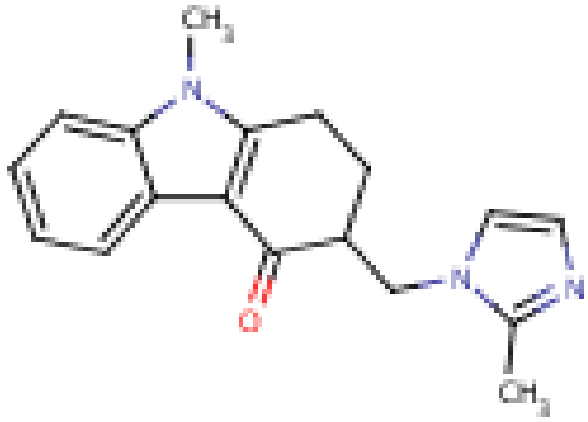
Antihistaminic Ophthalmic used or the prevention of itching associated with allergic conjunctivitis

Figure 19 Alosetron (Lotronex - Glaxo)



5HT3 antagonist used for Irritable Bowel Syndrome, Diarrhea Predominant in Women. Caused Ischemic Bowel Disease in 1 : 300 women, life threatening AE requiring emergency surgery. 4 Cases pre-approval.

Figure 20 Ondansetron (Zofran - Glaxo)



5HT3 antagonist used for the treatment of chemotherapy-induced nausea and vomiting

3.9.1.3 Other Atypical Antipsychotics

The other group of atypical antipsychotics that are structurally different from the tri- and tetracyclic antipsychotics similar to asenapine all include indole substructures and many have multiple substructures that can result in additive toxicities depending on metabolism etc. For example bifeprunox and pimozide each have one or more substructures that might inhibit serotonin reuptake transporters.

Figure 21 Indole Containing Atypical Antipsychotics

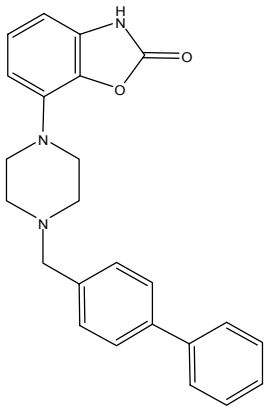
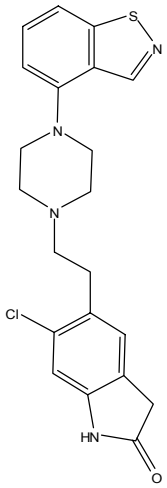
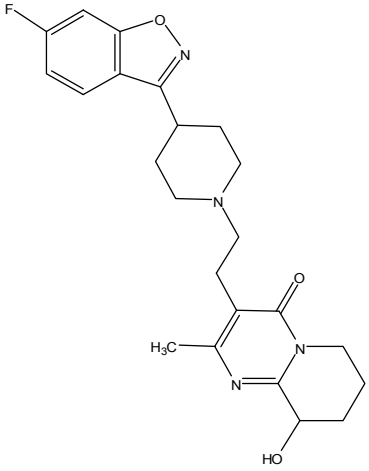
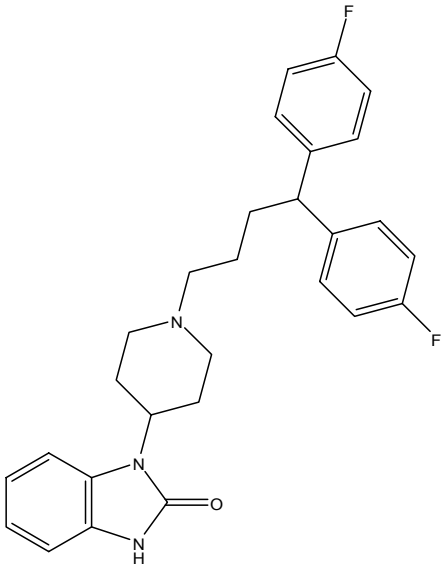
Bifeprunox N22-077	**Ziprasidone (Geodon® – Pfizer)**	**Paliperidone Invega® - J&J**
PDUFA Aug 20 mg – 40 mg QD Choreoathetosis - Common QTc minimal Wt Gain 'favorable' Hyperlipidemia 'favorable' DM 'favorable'	N 20-825 Feb 5, 2001 80 mg BID Choreoathetosis – "Common" QTc 14 mSec > risperidone Dec wt gain Hyperlipidemia Rare DM Rare	N 21-999 Dec 19, 2006 6 mg - 12 mg QD Choreoathetosis – Ris: "Rare" QTc prolonged 3% - 5% Wt gain – 6% - 9% Lipids/DM/CPK/RBC some signal
		

Figure 22 Pimozide – Jannsen (1963)



Extremely toxic. Drug of last resort. Structure could cleave at 2 different places both producing different structures that might result in adrenergic or serotonergic reuptake inhibition.

3.9.1.4 Fluoroquinolones

Fluoroquinolones are known to cause QT prolongation and effects on connective tissues, and both type of effects can be mediated by specific serotonin receptors. Of the two fluorquinolones shown in Figure 23 and Figure 24 moxifloxacin has an obvious substructure that would be expected to bind similarly to serotonin, however that does not preclude pharmacologic effects due to the other part of the molecule. Or how a particular serotonin receptor subtype is affected.

Figure 23 Moxifloxacin

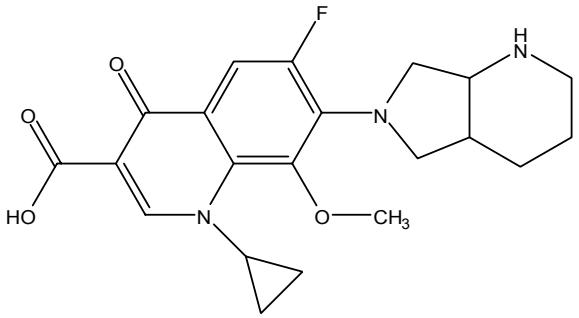
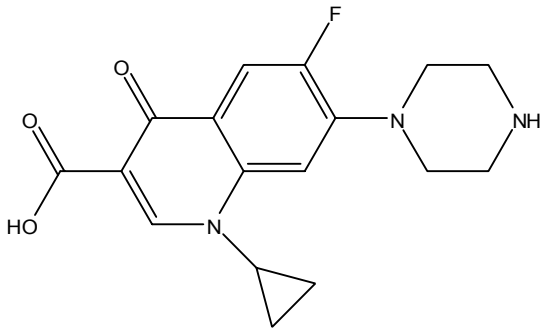


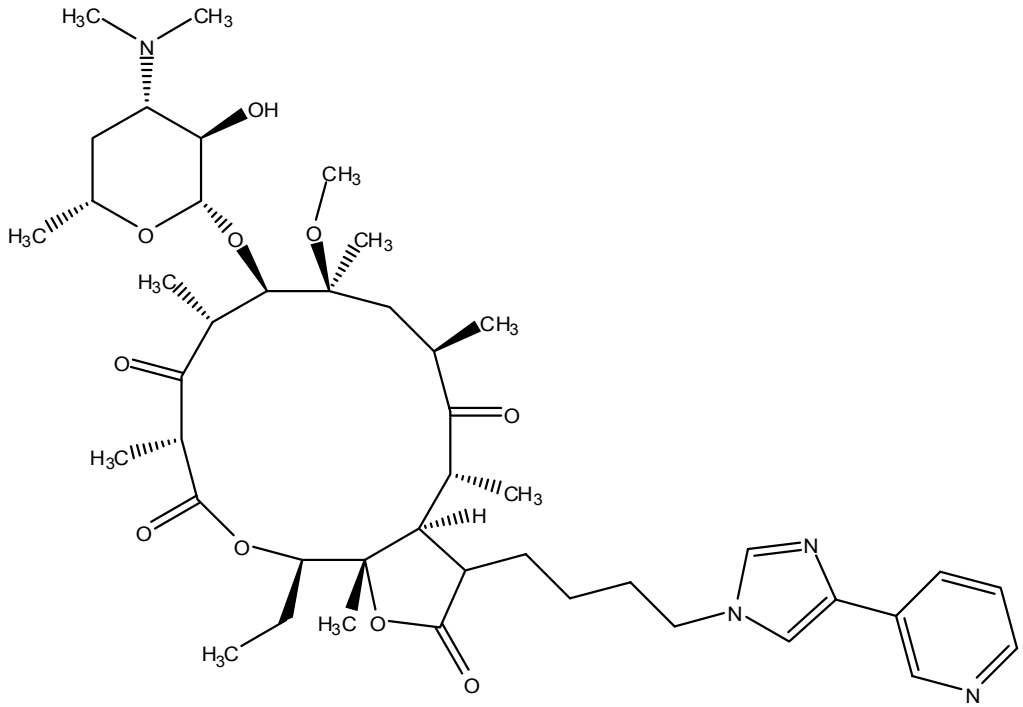
Figure 24 Ciprofloxacin



3.9.1.5 Macrolide Antibiotics

Various macrolide antibiotics also cause hepatotoxicity, the one that has most recently been in the news is Ketek® whose structure is shown in Figure 25. There are various parts of the molecure that might bind to receptors that result in hepatic fibrosis, and this could be used to predict such toxicities in the future.

Figure 25 Telithromycin Ketek®



3.9.1.6 Avermectins

Another drug that has been in the news for cardiac toxicity is moxidectin whose structure is shown in Figure 26. It's clear that moxidectin contains a serotonin like substructure, and it has a degree of similarity to monocrotaline, (see Figure 3). What's more interesting is that moxidectin is extensively used in horses. Since the mid-1990's a number of Kentucky Derby winners have been retired immediately after the Derby due to bone chips in the knee, except for ivermectin most avermectins were not approved for use that early. Avermectins are also used in livestock for food and in farmed fish, (e.g. emamectin in salmon). This raises the possibility that such drugs or compounds with similar pharmacologic activity in the food supply could be causing illness in humans.

Merck has been lauded for their donation of ivermectin to treat parasitic infections in tropical communities, (http://www.who.int/bulletin/volumes/82/8/editorial30804html/en/index.html Accessed June 18, 2008). A perhaps unintended benefit to this program is that potentially commercially valuable information has been obtained on side effects in humans and in particular in human populations with especially high genetic diversity which may shed light on the development of personalized medicine.

Figure 26 **Moxidectin (Proheart 6)**

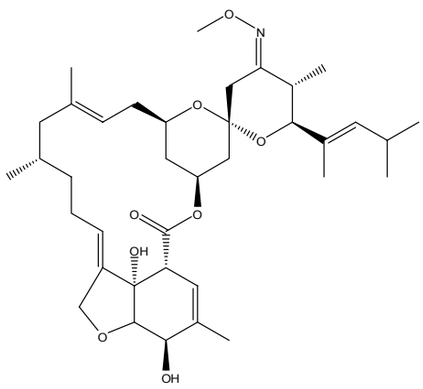


Figure 27 **Emamectin**

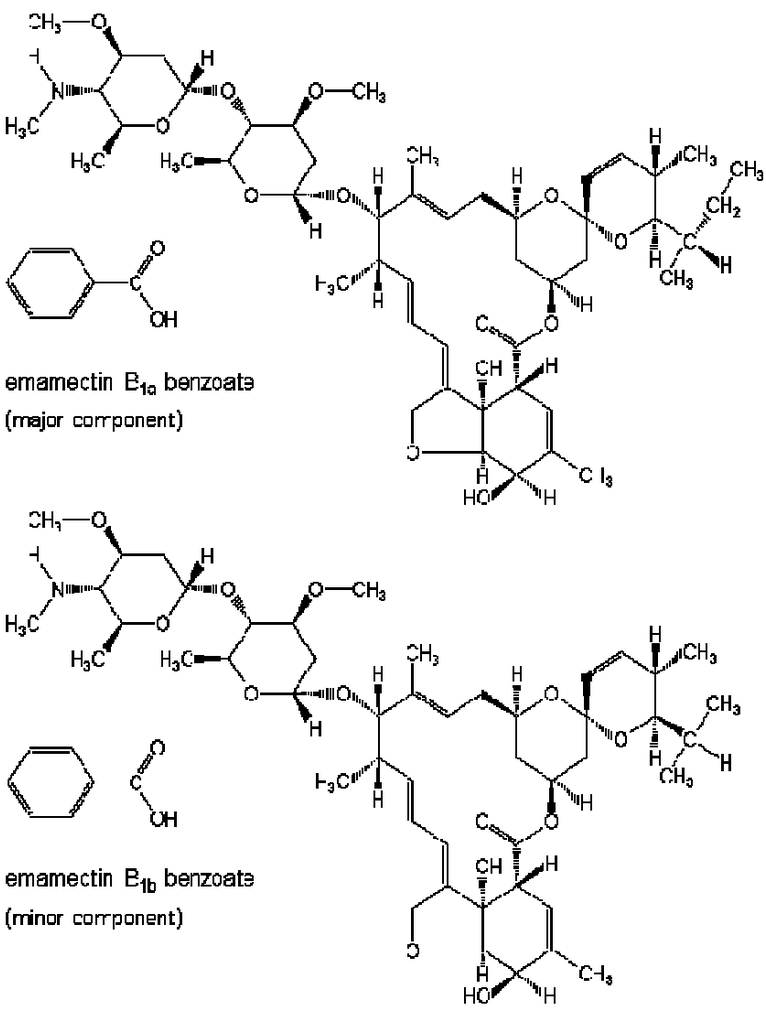
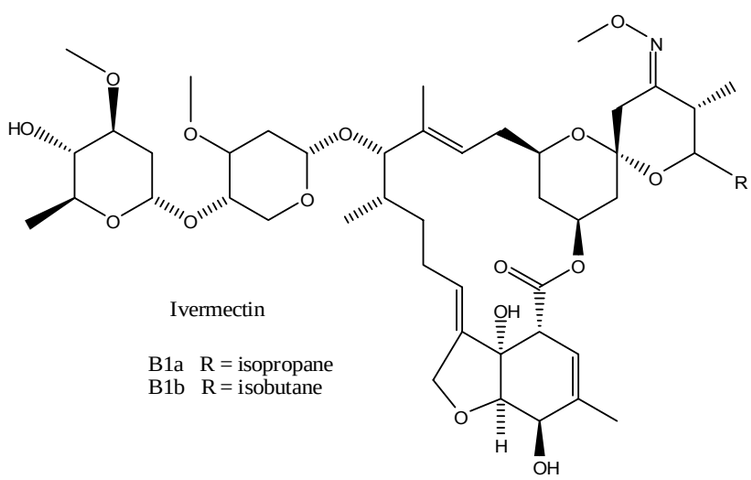


Figure 28 **Ivermectin**



3.9.1.7 Steroids and Related Compounds

Steroids are well known to have varying effects depending on structure including glucocorticoid, mineralocorticoid, estrogenic and androgenic effects depending on substituents. Steroids all contain a bicyclic 5 and 6 sided ring sub-structure, in addition estrogenic activities have been related to biphenyls. Some of the substructures suggest that some steroidal effects might be mediated via serotonergic receptors. This suggests that perhaps the recent concerns regarding pharmacy compounding of estriol may have a pharmacologic concern underlying it. It also suggests that the varying pharmacologic effects, both positive and negative, seen with conjugated estrogens may be in part mediated via serotonergic effects.

Figure 29 Estriol

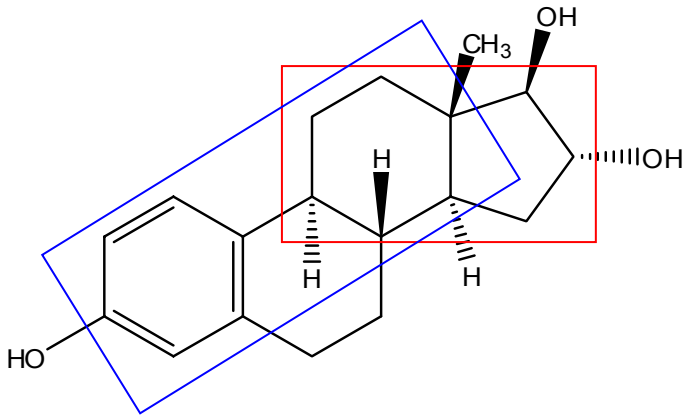
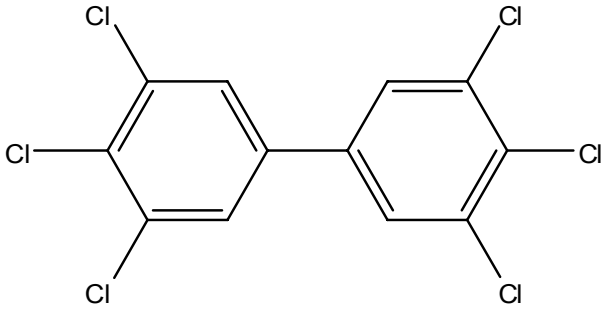


Figure 30 PCBs Polychlorinated Biphenyls



3.9.1.8 Zoloft® Like Compounds

Sertraline (Zoloft ® - Pfizer) is a NSRI antidepressant. Comparison of the structure reveals similarities to Bisphenol A, dioxins, including agent organ, and steroids. This also suggests that varying effects for environmental toxins including carcinogenic effects could conceivably be mediated via hormonal or serotonergic effects. In addition, if environmental toxins also affect the 5HT2B receptors and other receptors this provide a mechanistic basis for various maladies such as chronic fatigue syndrome, infertility, the increasing incidence of ADHD, the rising incidence of mitochondrial disorders, possibly autism, and gulf war syndrome.

Figure 31 Sertraline (Zoloft- Pfizer)

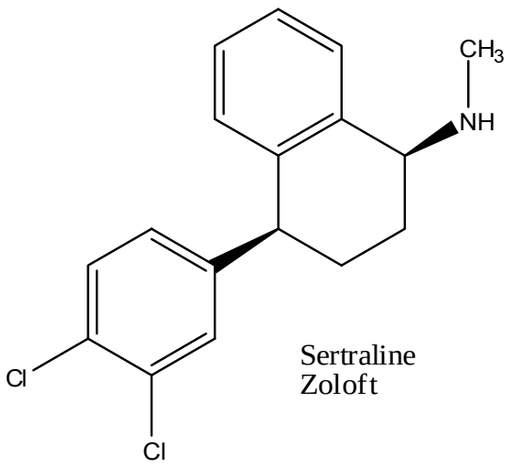


Figure 32 Dioxin 2,3,7,8-p-TCDD

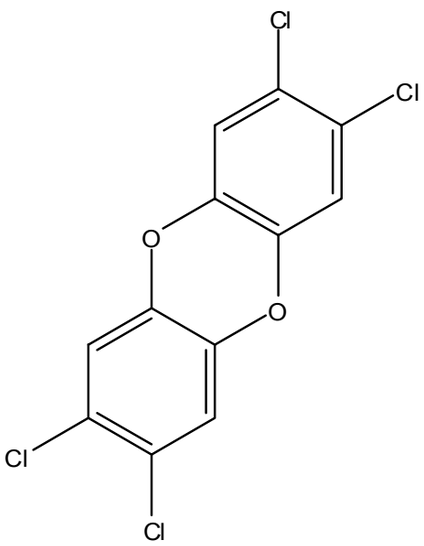


Figure 33 Bisphenol A

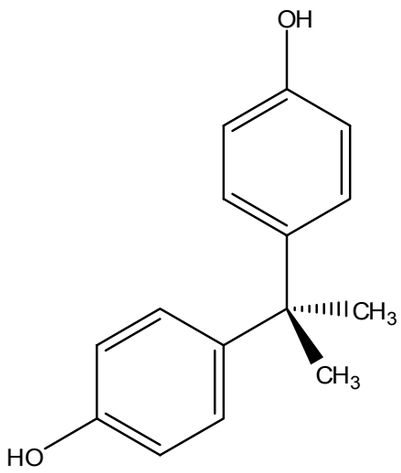


Figure 34 Modafinil

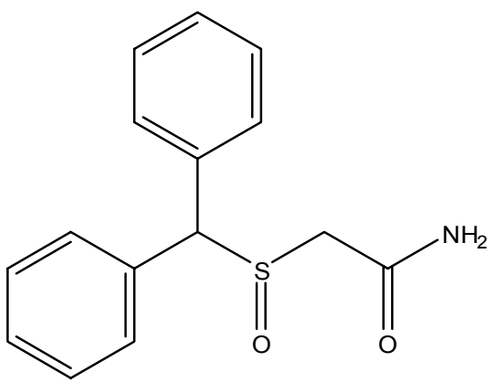
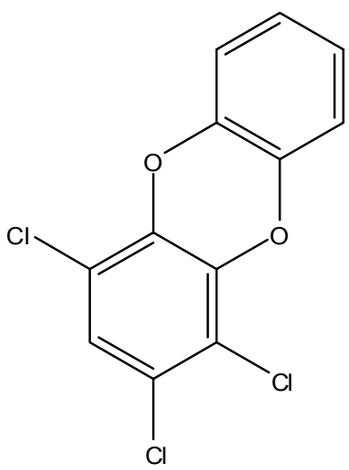


Figure 35 Agent Orange (Equal Mixture of 2,4-DCDD and 2,4,5-TCDD)



3.9.2 Other Structural and Receptor Classes

Several other structural and more importantly receptor drug classes have been shown to have complementary effects all over the body, and that interact with serotonergic systems, that in some cases increase toxicities. Only a few classes are mentioned here.

3.9.2.1 Pyrroles and Pyrrolizidine Plant Alkaloids

Pyrrolizidine plant alkaloids have been implicated in a wide variety of functions related to effects on serotonin, and pyrroles are a primary additive to cigarette tobacco and are among the primary stuctures in the development of a wide variety of new drug classes including: anti-addictive drugs, anticancer and cancer prevention drugs, drugs for Alzheimers, dementia, psychiatric illnesses, cardiovascular illness, neurologic diseases, stroke, clotting disorders, musculoskeletal disorders, pulmonary and hepatic fibrosis, preeclampsia, etc.. They may also help explain toxicities with a wide variety of drugs presently on the market as well as with tobacco [32]

3.9.2.2 Nicotinic Receptor Drugs

A number of drugs are under development that effect nicotinic receptors and indications under investigation include Alzheimer's disease and other dementias, age associated memory impairment (AAMI), mild cognitive impairment (MCI) and other disorders marked by cognitive impairment, Parkinson's disease, pain including neuropathic pain, depression, anxiety, schizophrenia, and addiction.

Recently one of these nicotinic receptor drugs has come under scrutiny for safety reasons[33]. Varenicline (Chantix® - Pfizer), has recently been implicated in dizziness, loss of consciousness, seizures, abnormal spasms and movements, and suicidality. Of particular concern are the long term side effects and 224 cases of potential heart-rhythm disturbances. Based on what has been seen in the present submission this raises concerns about effects at serotonin receptors similar to what is observed with asenapine.

Structurally asenapine and varenicline (Chantix® - Pfizer) do not appear similar with possible exception of the single pyrazino nitrogen on varenicline. Since side chain length distance of nitrogen atoms on antipsychotics has been known to affect receptor binding to dopamine receptors since the 1970's this may be involved with binding characteristics to serotonin receptors.

Figure 36 Varenicline Structure (Chantix® - Pfizer)

[32] This information was found on my own time and using my own computer equipment while looking up side effects and mechanisms related to ciprofloxacin, BMRP2, and my own or my family's personal health related to drug side effects, i.e. SSRIs, umbilical hernia, COPD, cardiovascular disease etc.. Although I am including this information in this review I want to clearly indicate that this information was not found based upon information I learned through my position and thus I believe I am able to freely discuss it outside of FDA. There will be other information in this review with other drug classes, e.g. drugs for osteoporosis, cancer, etc. that I have also learned about secondary to searches for medical information for personal purposes and although I may include some of my findings in this review, and though I may redo the same google searchs that I did at home on my work computer for inclusion in this review, it should not be construed that the searches and information gleaned were based upon information obtained in the course of my job. Therefore I believe I am free to discuss information I use in performing review work but whose origin is completely independent of that work in my private capacity outside. Note the relationship between BMRP2, Smad, and effects on 5HT receptors, etc. as well as structure activity relationships.

[33] http://www.fda.gov/cder/news/pubpress.htm

3.9.2.3 Phenylalanine Derivatives

These include the catecholamines dopamine, epinephrine, and norepinephrine.

Figure 37 Dopamine

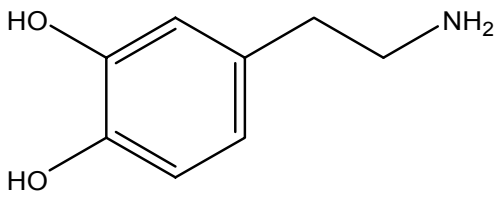
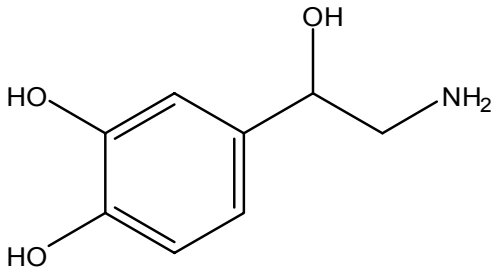


Figure 38 Norephinephrine



3.9.3 Amphetamine Like Compounds

Amphetamine like compounds include ephedra and pseudoephrine. They may have direct actions on adrenergic receptors or may disrupt cellular reuptake or vesicluar release of catecholamine neurotransmitters.

Figure 39 Amphetamine

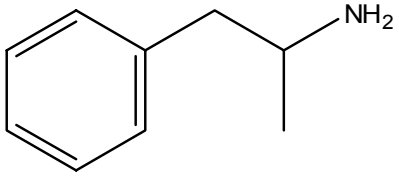


Figure 40 Ephedrine

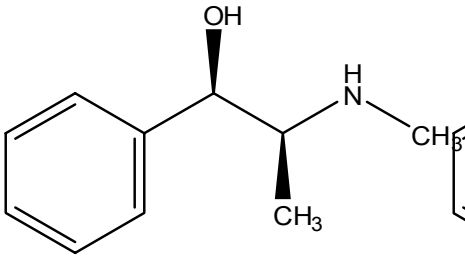
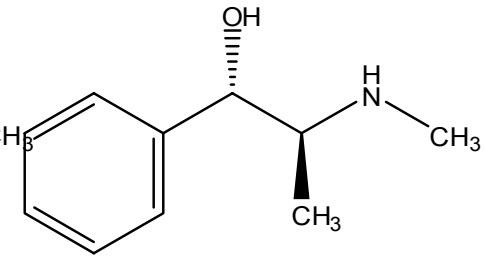


Figure 41 Pseudoephedrine



It's interesting to note that Ephedra was pulled from the market immediately prior to the FDA's warning on Phen-Fen in 1997. Similarly FDA has been issuing repeated warnings about pediatric OTC cough and cold medications that might contain pseudoephredrine since April 2007. This reviewer has also noticed that the dates of these warnings tend to coincide with significant milestones in the submission and review of asenapine, which as treatment for bipolar disorder will likely have a very high off-label market for pediatric bipolar and pediatric bipolar spectrum disorder.

3.9.3.1 Glutamine Derivatives

A number of derivatives of the amino acid glutamine also have pharmacologic effects, for example monosodium glutamate is a common flavoring enhancer and preservative and in some individuals cause intense vasoconstrictive headaches and even seizures. Whereas the structurally similar compound valproate is used as a treatment for a wide variety of seizure disorders as well as a mood stabilizer. More glutamate receptor active agents are currently under development for a variety of neuropsychiatric indications.

Figure 42 Monosodium Glutamate (MSG)

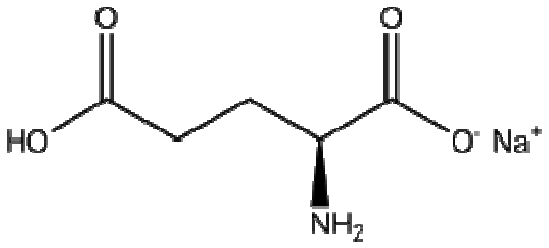
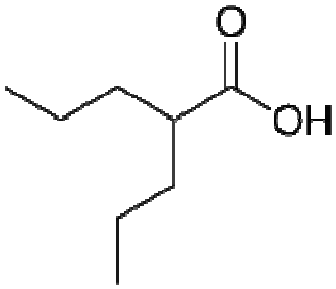


Figure 43 Valproic acid



3.9.3.2 Azo Dyes and Food Colorants

Recently the Center for Science in the Public Interest has petitioned the FDA regarding azo food dyes and has claimed that they may potentially induce or exacerbate ADHD. This seems to be a potentially plausible relationship and should be investigated.

3.9.4 Conclusions

Although still speculative in some regards, the evidence leads to a very simple and elegant unifying hypothesis, that is consistent with previous scientific theories (e.g. evolution), and it leads to important predictions.

The major points of this biologic systems hypothesis follow:

Biologic systems having developed from a limited number of small ubiquitous molecules, such as serotonin, dopamine, and acetylcholine that have over time developed various receptor subtypes in different tissues with varying effects and different degrees of interactions with other systems. Even now evolution is occurring with mutations occuring in these various receptor subsystems, some of which are silent, many of which will have a survival disadvantage, and some of which will have a survival advantage.

Many natural and man-made compounds in the environment are expected to affect these biologic systems, typically in an adverse manner. Different individuals may have different sensitivities based their personal Pharmacogenomics.

In radiation biology there are two major competing theories of toxicity, whether there is a threshold effect or simply a linear effect. A similar issue exists for drugs and it may be a combination of both. However drugs and toxins compound the problem by exposing organisms to varying amounts of different pharmacologically active agents both intentionally and unintentionally via the environment. These active substances would then be expected to have varying effects due to variations in dose and additive, synergistic, and antagonistic effects with other compounds, as well as underlying pathophysiology ad Pharmacogenomics.

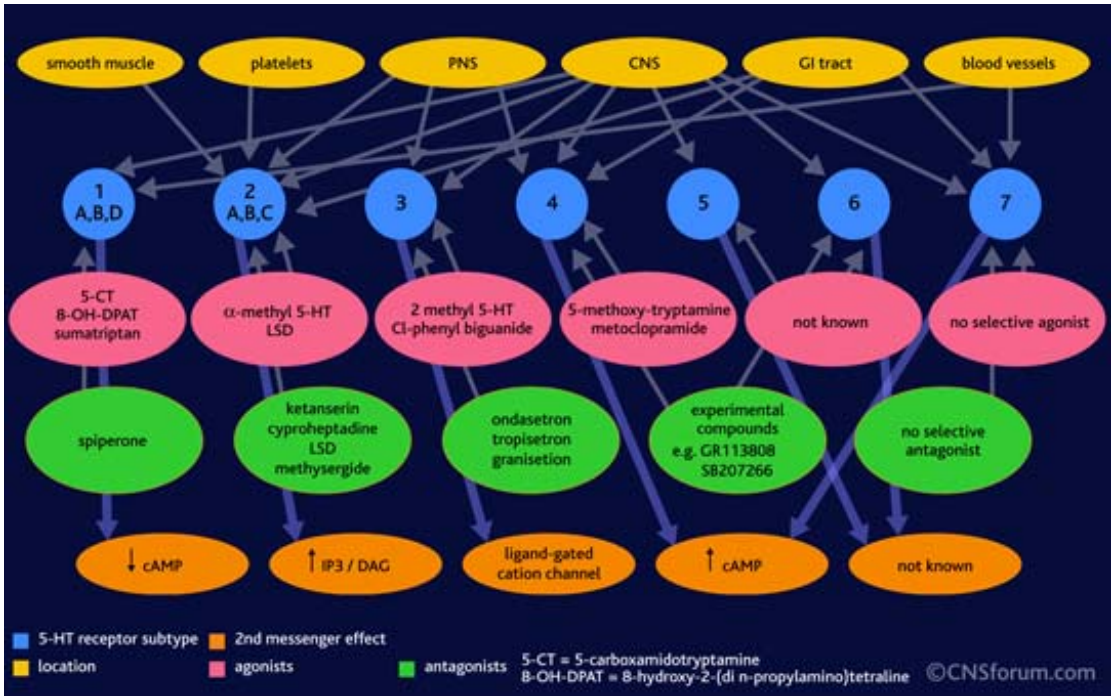
These pharmacologically active agents will enter the environment and may affect someone else. Consquently, the prudent approach would appear to be to try to minimize release and exposure in the first place, and this should include minimizing use of certain food additives, veterinary drugs in food livestock, certain fertilizers, herbacides and pesticides, and use of many drugs if not absolutely necessary.

The alternative is accumulation of environmental toxins that individually might not reach a level of concern but when the total molar exposures and especially over time are considered it becomes clear that a Malthusian effect might develop.

4 Appendices

4.1 Appendix 1 - Description of 5-HT Receptor Subtypes from the Lundbeck Institute

The actions of 5-HT are mediated by a range of different 5-HT receptors. The 5-HT receptors are classified into seven main receptor subtypes, 5-HT1–7. Six of the seven subtypes are G-protein-coupled receptors; 5-HT3 is a ligand-gated cation channel. 5-HT1 receptors occur primarily in the brain and cerebral blood vessels (5-HT1D only), where they mediate neural inhibition and vasoconstriction. They function mainly as inhibitory presynaptic receptors, linked to inhibition of adenylate cyclase. Specific agonists at 5-HT1 receptors include sumatriptan (used in migraine therapy) and buspirone (used in the treatment of anxiety). Spiperone and methiothepin are specific antagonists of 5-HT1 receptors. 5-HT2 receptors are found in the CNS and in many peripheral sites. They act through phospholisae C to produce excitatory neuronal and smooth muscle effects. Specific ligands at 5-HT sites include LSD – acting as an agonist in the CNS and as an antagonist in the periphery – and ketanserin and methysergide (both antagonists). 5-HT3 receptors occur mainly in the peripheral nervous system, particularly on nociceptive afferent neurones and on autonomic and enteric neurones. The effects of these receptors are excitatory, mediated by receptor-coupled ion channels. 5-HT3 antagonists (eg ondansetron, tropisetron) are used predominantly as anti-emetic drugs. 5-HT4 receptors are found in the brain, as well as peripheral organs like the heart, bladder and gastrointestinal (GI) tract. Within the GI tract they produce neuronal excitation and mediate the effect of 5-HT in stimulating peristalsis. A specific 5-HT4 agonist is metoclopramide used for treating gastrointestinal disorders. Little is known about the function and pharmacology of 5-HT5, 5-HT6 and 5-HT7 receptors.



References

*Other peripheral mediators: 5-hydroxytryptamine and purines. In: Pharmacology, 4th edition. Rang*see your doctor to discuss proven treatment options. [34]

[34] http://www.cnsforum.com/imagebank/item/5HT_rcpt_subtypes/default.aspx accessed June 2, 2008

4.2 Appendix 2 – Safety Signal from Original IND Submission

Figure 44 Conclusions and Recommendations from Original IND 30 Day Safety Review for Asenapine - IND 51641 SN 000

VII. Conclusions and Recommendations

At this time, it is recommended that this study be put on hold because of issues regarding safety concerns for subjects and deficiencies in the investigator's brochure(please refer above under Investigator's Brochure). The major safety concern for patients arises in light of cardiotoxic effects of this drug, which induced an asystolic event in a healthy volunteer who required emergency medical resuscitation (Study 25506/ Subject 1/1: blood concentration of 1850 pg/ml of Org 5222 after IV administration). Other studies also demonstrated subjects with asystolic events including Study 25501/Subject 1/1 (at blood concentration of 680pg/ml of Org 5222 after oral dosing), and Study 25511/Subject 9 (at blood level of 69pg/ml of Org 5222 after sublingual administration). The protocol submitted does not sufficiently address this risk or offer details of how subjects will be protected and treated if a catastrophic event such as cardiac arrest were to occur. There is a description of telemetry monitoring by a technician; however, it is unclear how involved a cardiologist will be in the monitoring and care of these subjects and how quickly the telemetry technician and other unit personal could initiate and activate a medical resuscitation if an event were to occur. A more specific plan ensuring that this study will be conducted in a safe environment is necessary to ensure that subjects are protected against possible risks. It may be desirable to enlist the assistance of a cardiology consultant to devise such a plan.

Also, because of the elevations of liver function studies observed in Study 85136, it would be important to monitor these more frequently in the proposed Study 041-001, especially in the design for Block 3. Based on these previous findings, monitoring liver function studies would be desirable in future protocols as well.

Figure 45 Conclusions and Recommendations from Original IND 30 Day Safety Review for Asenapine - IND 51641 SN 000 (Continued)

Please refer to the letter to the sponsor dated November 5, 1996 for further detail delineating the rationale for a hold at this time.

Roberta Glass 11/7/96
Roberta Glass, M.D.
Medical Officer, DNDP

CC:
Orig. IND
HAD-120 Div File
HAD-120 TLaughren/SHardeman/LFreed/GFitzgerald/AMosholder/RGlass

11-12-96

There are insufficient details for protocol 041-001 to determine if subjects will be adequately protected. The sponsor has also not adequately explored the pharmacokinetic data relative to the cardiac events of concern. In addition, the investigator handbook is deficient. I agree that a hold is appropriate.

Thomas P. Laughren, MD
TL, DDP

4.3 Appendix 3 – Skeletal Exams in Chinchilla Rabbits - Study SDG RR 2914

	GROUP 1 2X0.0 MG/KG		GROUP 2 2X0.5 MG/KG		GROUP 3 2X2.5 MG/KG		GROUP 4 2X15.0 MG/KG	
NUMBER OF FETUSES EXAMINED	130		137		140		152	
UNLISTED FINDING(S) (SHOWN ON PREVIOUS PAGE(S))	2	2%	2	1%	2	1%	4	3%
STERNUM								
INCOMPLETELY OSSIFIED								
STERNEBRA 1	0		0		0		1	1%
STERNEBRA 2	1	1%	0		2	1%	2	1%
STERNEBRA 3	0		0		0		1	1%
STERNEBRA 4	1	1%	0		1	1%	1	1%
STERNEBRA 5	70	54%	83	61%	60	43% *	104	68% **
NON-OSSIFIED								
STERNEBRA 5	24	18%	16	12%	26	19%	26	17%
ABNORMALLY OSSIFIED								
STERNEBRA 2	0		0		0		1	1%
STERNEBRA 4	0		0		0		2	1%
STERNEBRA 5	0		0		0		1	1%
RIBS								
NON-OSSIFIED								
RIB 12, LEFT	0		1	1%	0		0	
RIB 13, LEFT	89	68%	86	63%	85	61%	85	56% *
RIB 9, RIGHT	0		0		0		1	1%
RIB 13, RIGHT	94	72%	91	66%	92	66%	94	62% *
SHORTENED								
RIB 13, LEFT	6	5%	9	7%	12	9%	9	6%
RIB 13, RIGHT	3	2%	7	5%	5	4%	11	7% *
FLYING RIB								
RIB 13, LEFT	3	2%	6	4%	6	4%	11	7% *
RIB 10, RIGHT	0		1	1%	0		0	
RIB 13, RIGHT	5	4%	4	3%	1	1%	4	3%
LEFT FORELIMB								
INCOMPLETELY OSSIFIED								
METACARPALIA 1, LEFT	86	66%	86	63%	84	60%	97	64%
DIGIT 1 PROXIMAL PHALANX, LEFT	33	25%	36	26%	56	40% **	43	28%
DIGIT 2 PROXIMAL PHALANX, LEFT	1	1%	0		0		8	5% *
DIGIT 2 MEDIAL PHALANX, LEFT	77	59%	97	71% *	115	82% **	131	86% **
DIGIT 3 PROXIMAL PHALANX, LEFT	1	1%	0		0		8	5% *
DIGIT 3 MEDIAL PHALANX, LEFT	71	55%	93	68% *	98	70% **	123	81% **
METACARPALIA 4, LEFT	0		0		0		2	1%
DIGIT 4 PROXIMAL PHALANX, LEFT	2	2%	3	2%	3	2%	17	11% **
DIGIT 4 MEDIAL PHALANX, LEFT	112	86%	115	84%	115	82%	132	87%
METACARPALIA 5, LEFT	3	2%	10	7%	3	2%	23	15% **
DIGIT 5 PROXIMAL PHALANX, LEFT	31	24%	49	36% *	45	32%	73	48% **
DIGIT 5 MEDIAL PHALANX, LEFT	25	19%	40	29% *	17	12%	9	6% **
NON-OSSIFIED								
METACARPALIA 1, LEFT	4	3%	15	11% *	11	8%	32	21% **
DIGIT 1 PROXIMAL PHALANX, LEFT	12	9%	31	23% **	17	12%	40	26% **
DIGIT 2 MEDIAL PHALANX, LEFT	1	1%	2	1%	2	1%	1	1%
DIGIT 3 MEDIAL PHALANX, LEFT	1	1%	0		0		2	1%
DIGIT 4 MEDIAL PHALANX, LEFT	7	5%	12	9%	19	14% *	15	10%
DIGIT 5 MEDIAL PHALANX, LEFT	105	81%	97	71% *	122	87%	143	94% **
RIGHT FORELIMB								
INCOMPLETELY OSSIFIED								
METACARPALIA 1, RIGHT	82	63%	90	66%	83	59%	99	65%
DIGIT 1 PROXIMAL PHALANX, RIGHT	33	25%	34	25%	57	41% **	43	28%
DIGIT 2 PROXIMAL PHALANX, RIGHT	0		0		1	1%	9	6% **
DIGIT 2 MEDIAL PHALANX, RIGHT	77	59%	96	70% *	115	82% **	124	82% **
DIGIT 3 PROXIMAL PHALANX, RIGHT	0		0		0		9	6% **
DIGIT 3 MEDIAL PHALANX, RIGHT	71	55%	96	70% **	97	69% **	118	78% **
METACARPALIA 4, RIGHT	0		0		0		2	1%

* / ** : Fisher's Exact test significant at 5% (*) or 1% (**) level

	GROUP 1 2X0.0 MG/KG		GROUP 2 2X0.5 MG/KG		GROUP 3 2X2.5 MG/KG		GROUP 4 2X15.0 MG/KG	
NUMBER OF FETUSES EXAMINED	130		137		140		152	
RIGHT FORELIMB								
INCOMPLETELY OSSIFIED								
DIGIT 4 PROXIMAL PHALANX, RIGHT	4	3%	2	1%	2	1%	17	11% **
DIGIT 4 MEDIAL PHALANX, RIGHT	109	84%	115	84%	115	82%	130	86%
METACARPALIA 5, RIGHT	4	3%	11	8%	4	3%	26	17% **
DIGIT 5 PROXIMAL PHALANX, RIGHT	38	29%	54	39%	51	36%	87	57% **
DIGIT 5 MEDIAL PHALANX, RIGHT	28	22%	45	33% *	19	14%	14	9% **
NON-OSSIFIED								
METACARPALIA 1, RIGHT	6	5%	12	9%	13	9%	29	19% **
DIGIT 1 PROXIMAL PHALANX, RIGHT	14	11%	36	26% **	18	13%	45	30% **
DIGIT 2 MEDIAL PHALANX, RIGHT	2	2%	2	1%	1	1%	1	1%
DIGIT 3 MEDIAL PHALANX, RIGHT	0		0		0		2	1%
DIGIT 4 MEDIAL PHALANX, RIGHT	6	5%	12	9%	20	14% **	17	11% *
DIGIT 5 MEDIAL PHALANX, RIGHT	102	78%	92	67% *	121	86%	138	91% **
LEFT HIND LIMB								
INCOMPLETELY OSSIFIED								
CALCANEUS LEFT	10	8%	8	6%	9	6%	18	12%
TOE 1 PROXIMAL PHALANX, LEFT	1	1%	4	3%	3	2%	11	7% **
TOE 1 MEDIAL PHALANX, LEFT	52	40%	75	55% *	76	54% *	95	63% **
TOE 2 PROXIMAL PHALANX, LEFT	2	2%	5	4%	4	3%	15	10% **
TOE 2 MEDIAL PHALANX, LEFT	36	28%	57	42% *	64	46% **	81	53% **
TOE 3 PROXIMAL PHALANX, LEFT	3	2%	5	4%	5	4%	17	11% **
TOE 3 MEDIAL PHALANX, LEFT	55	42%	79	58% **	79	56% *	94	62% **
TOE 4 PROXIMAL PHALANX, LEFT	13	10%	21	15%	16	11%	30	20% *
TOE 4 MEDIAL PHALANX, LEFT	85	65%	72	53% *	69	49% **	63	41% **
NON-OSSIFIED								
CALCANEUS LEFT	0		0		0		9	6% **
TOE 1 MEDIAL PHALANX, LEFT	0		0		1	1%	2	1%
TOE 2 MEDIAL PHALANX, LEFT	0		0		2	1%	1	1%
TOE 3 MEDIAL PHALANX, LEFT	0		1	1%	1	1%	6	4% *
TOE 4 PROXIMAL PHALANX, LEFT	0		0		0		3	2%
TOE 4 MEDIAL PHALANX, LEFT	45	35%	64	47% *	71	51% **	89	59% **
RIGHT HIND LIMB								
INCOMPLETELY OSSIFIED								
CALCANEUS RIGHT	10	8%	8	6%	9	6%	18	12%
TOE 1 PROXIMAL PHALANX, RIGHT	2	2%	4	3%	3	2%	14	9% **
TOE 1 MEDIAL PHALANX, RIGHT	55	42%	76	55% *	75	54% *	93	61% **
TOE 2 PROXIMAL PHALANX, RIGHT	2	2%	5	4%	3	2%	17	11% **
TOE 2 MEDIAL PHALANX, RIGHT	37	28%	52	38%	59	42% *	74	49% **
TOE 3 PROXIMAL PHALANX, RIGHT	3	2%	5	4%	3	4%	20	13% **
TOE 3 MEDIAL PHALANX, RIGHT	51	39%	69	50% *	78	56% **	85	56% **
TOE 4 PROXIMAL PHALANX, RIGHT	13	10%	21	15%	15	11%	32	21% **
TOE 4 MEDIAL PHALANX, RIGHT	85	65%	75	55% *	67	48% **	65	43% **
NON-OSSIFIED								
CALCANEUS RIGHT	0		0		0		9	6% **
TOE 1 MEDIAL PHALANX, RIGHT	0		0		1	1%	2	1%
TOE 2 MEDIAL PHALANX, RIGHT	0		0		1	1%	1	1%
TOE 3 MEDIAL PHALANX, RIGHT	0		0		1	1%	4	3%
TOE 4 PROXIMAL PHALANX, RIGHT	0		0		0		1	1%
TOE 4 MEDIAL PHALANX, RIGHT	45	35%	61	45%	73	52% **	87	57% **

* / ** : Fisher's Exact test significant at 5% (*) or 1% (**) level

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4.4 Appendix 4 – Schering-Plough May 8, 2008 Press Release for Asenapine

Overview of Asenapine Data from Olympia Trial Program Presented at American Psychiatric Association Annual Meeting[35]

Efficacy and safety data support potential of asenapine in the treatment of schizophrenia and bipolar I disorder

WASHINGTON, May 08, 2008 /PRNewswire-FirstCall/ -- Schering-Plough Corporation today announced that an overview of asenapine clinical trials from the Olympia program was presented at the 161st Annual Meeting of the American Psychiatric Association in Washington, D.C., May 3-8. Data from the studies, involving patients with bipolar I disorder and schizophrenia, were presented in two oral presentations (Abstracts # 44 and # 80). Also presented were long-term safety and efficacy data from a clinical trial involving patients with schizophrenia and schizoaffective disorders.

Asenapine, a fast-dissolving, novel psychopharmacologic agent with a unique human receptor signature, was shown to be effective in two short-term bipolar mania studies with a nine-week extension and in two out of four short-term schizophrenia studies. In the third short-term schizophrenia study, neither asenapine nor the active control differentiated from placebo; in the fourth study, asenapine did not differentiate from placebo, while the active control did. Overall, asenapine was well tolerated in the Olympia trial program.

"Despite having effective treatments available, up to 75 percent of schizophrenia patients(1) and many bipolar disorder patients stop taking their medicines because of unwanted side effects or lack of efficacy," said Roger McIntyre, M.D., Associate Professor of Psychiatry and Pharmacology at the and head of the Mood Disorders Psychopharmacology Unit at the University Health Network, Toronto, Canada. "Therefore, new therapies that are both effective and well-tolerated would be welcome additions to the treatment options currently available for improving patient care."

Schering-Plough acquired asenapine in November 2007 through its combination with Organon BioSciences, which developed the investigational antipsychotic agent. The Food and Drug Administration is reviewing a new drug application (NDA) for asenapine in the treatment for schizophrenia and acute manic or mixed episodes associated with bipolar I disorder. The asenapine Olympia clinical trial program thus far has involved over 3,000 patients and has included bipolar mania and acute schizophrenia trials.

"Based on results from the Olympia trial program, we believe asenapine has the potential to address a clinically important unmet need for patients with schizophrenia and bipolar disorder," said Robert J. Spiegel, M.D., Chief Medical Officer and Senior Vice President, Schering-Plough Research Institute.

Olympia Data: Bipolar I Disorder

The bipolar I disorder program includes two placebo- and active-controlled, three-week trials followed by an extension study totaling one year of treatment involving nearly 1,000 patients with bipolar I disorder. Treatment response was measured using the Young Mania Rating Scale (YMRS) score, an 11-item scale used to evaluate manic symptoms.

In the trials, both asenapine and the active-control drug olanzapine* produced greater mean reductions in YMRS total scores versus placebo after three weeks of treatment. Asenapine produced 13- and 14-point reductions in the YMRS total score from baseline to day 21 ($P<0.05$ versus placebo; olanzapine was also demonstrated to be statistically superior to placebo; there was no direct comparison between asenapine

[35] http://www.drugs.com/clinical_trials/overview-asenapine-data-olympia-trial-program-presented-american-psychiatric-association-annual-4220.html Accessed June 15, 2008

and olanzapine). In a 9-week extension of the 3-week trials, asenapine was found to be noninferior to olanzapine on the primary efficacy measure, change in YMRS.

The overall incidence of treatment-related adverse events (AEs) in the trials was 60.8 percent in the asenapine group, 52.9 percent in the olanzapine group, and 36.2 percent in the placebo group. The most commonly reported adverse events (greater than or equal to 5 percent and twice the rate of placebo) with asenapine included sedation, dizziness, somnolence, oral hypoesthesia (numbness) and weight increase.

Presentation of the overview of the Olympia Program in bipolar I disorder (oral abstract #44) was on Tuesday, May 6, at 12:00 pm in Room 151A.

Olympia Data: Schizophrenia

The schizophrenia program includes four placebo- and active-controlled, six-week trials involving more than 1,300 patients with schizophrenia. In two of the trials involving almost 700 patients, asenapine produced 19- to 20-point reductions in Positive and Negative Syndrome Scale (PANSS) total score and was significantly superior to placebo. PANSS total score is a measure of positive symptoms (e.g., hallucinations and delusions), negative symptoms (such as lack of emotional expression), and general psychopathology symptoms (such as anxiety and depression).

The third study in approximately 260 patients was considered a failed trial as neither asenapine nor the active control olanzapine differentiated from placebo. A fourth trial of approximately 400 patients with acute schizophrenia was considered a negative trial, as the active-control (olanzapine) differentiated from placebo whereas asenapine did not.

The most commonly reported AEs (greater than or equal to 5 percent and twice the rate of placebo) among patients taking asenapine in the short-term schizophrenia trials were somnolence, akathisia (restlessness) and oral hypoesthesia (numbness).

"Schizophrenia is a lifelong illness that requires ongoing treatment to effectively manage the spectrum of symptoms that patients suffer from. As such, new treatments need to demonstrate an acceptable long-term safety profile," said Steven Potkin, M.D., Professor, Department of Psychiatry and Human Behavior, . "We are encouraged that in the long-term trial, asenapine had a lower incidence of clinically significant weight gain (15%) vs olanzapine (36%)."

Presentation of the overview of the Olympia Program in schizophrenia (oral abstract #80) is on Thursday, May 8, at 11:00 am in Room 101.

Long-term Safety and Efficacy Data

In a year long, double-blind, randomized study of 1200 patients with schizophrenia or schizoaffective disorder treated with asenapine or olanzapine (3:1 randomization), the safety evaluation showed that the overall rates of AEs were similar for the asenapine 5-10 mg BID arm and olanzapine 10-20 mg QD arm (drug-related AEs, 60 percent and 61 percent respectively; withdrawal due to serious adverse events, 6.3 percent and 6.8 percent, respectively). On efficacy measures, improvements in PANSS total score were greatest for both asenapine and olanzapine within the first six to eight weeks of treatment and were maintained throughout the 52-week study period. In an exploratory secondary analysis, the between-group difference at 52 weeks favored olanzapine. Most commonly reported AEs (greater than or equal to 10 percent) in both treatment groups were insomnia, worsening psychotic symptoms, weight gain and depression.

Additional Asenapine Data Presentations

Additional asenapine data were presented in poster sessions during the meeting.

About Bipolar Disorder

Bipolar disorder, commonly referred to as manic-depressive disorder, is a chronic, episodic illness characterized by mania (episodes of elevated moods, extreme irritability, and increased energy), depression (overwhelming feelings of sadness, suicidal thoughts), or a combination of both. It affects approximately 1 to 5 percent of adults, including more than 10 million adults in the U.S. and more than four million people in Europe.(2,3,4) The condition can start early in childhood or later in life, with the average age of onset between 15 and 25 years old.(5) Bipolar disorder is the sixth leading cause of disability in the world.(3) About half of the patients with bipolar disorder who recover in response to treatment experience recurrence two years later.(6)

About Schizophrenia

Schizophrenia is a chronic, disabling brain disorder characterized by hallucinations, delusions, and disordered thinking. About 24 million people worldwide (or seven in every 1,000 adults in the population) have schizophrenia,(7) including more than two million people in the U.S.(8) and more than four million people in Europe.(9) People with schizophrenia may hear voices other people don't hear or may believe others are trying to harm them. As a result, they may become socially withdrawn, fearful, and agitated.(8)

About Schering-Plough

Schering-Plough is an innovation-driven, science-centered global health care company. Through its own biopharmaceutical research and collaborations with partners, Schering-Plough creates therapies that help save and improve lives around the world. The company applies its research-and-development platform to human prescription and consumer products as well as to animal health products. Schering-Plough's vision is to "Earn Trust, Every Day" with the doctors, patients, customers and other stakeholders served by its colleagues around the world. The company is based in Kenilworth, N.J., and its Web site is www.schering-plough.com.

SCHERING-PLOUGH DISCLOSURE NOTICE: The information in this press release includes certain "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, including statements relating to the development of, and potential market for, asenapine. Forward-looking statements relate to expectations or forecasts of future events. Schering-Plough does not assume the obligation to update any forward-looking statement. Many factors could cause actual results to differ materially from Schering-Plough's forward-looking statements, including market forces, economic factors, product availability, patent and other intellectual property protection, current and future branded, generic or over-the-counter competition, the regulatory process, and any developments following regulatory approval, among other uncertainties. For further details about these and other factors that may impact the forward-looking statements, see Schering-Plough's Securities and Exchange Commission filings, including Part I, Item IA. "Risk Factors" in Schering-Plough's 2008 Q1 10-Q.

*Olanzapine is marketed as Zyprexa(R) by Eli Lilly

(1) Liu-Seifert H, Adams DH, Kinon BJ. Discontinuation of treatment of schizophrenic patients is driven by poor symptom response: a pooled post-hoc analysis of four atypical antipsychotic drugs. BMC Med. 2005;3:21. Available at www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=16375765. (Due to the length of this URL, please copy and paste it into your Internet browser to view) Accessed on April 8, 2008.

(2) National Institute of Mental Health. Available online at: www.nimh.nih.gov/publicat/bipolar.cfm

(3) Depression and Bipolar Support Alliance (DBSA). Bipolar Disorder Statistics, accessed on May 10, 2007. http://www.dbsalliance.org/site/PageServer?pagename=about_statistics_bipolar (Due to the length of this URL, please copy and paste it into your Internet browser to view)

(4) World Health Organization. WHO European Ministry Conference on MentalHealth. Available online at: http://www.euro.who.int/document/MNH/emnhqa.pdf. Accessed on October 2, 2007.

(5) National Alliance on Mental Health. Understanding Bipolar Disorder and Recovery. Available online at: http://www.nami.org/Template.cfm?Section=bipolar_disorder&template=/ContentManagement/ContentDisplay.cfm&ContentID=44951 (Due to the length of this URL, please copy and paste it into your Internet browser to view)

(6) Perlis RH, Ostacher MJ, Patel JK. Predictors of Recurrence in Bipolar Disorder: Primary Outcomes from the Systemic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Am J Psychiatry. 2006; 163:210-224.

(7) World Health Organization. Available online at: http://www.who.int/mental_health/management/schizophrenia/en/. Accessed on October 2, 2007.

(8) National Institute of Mental Health. Available online at: http://www.nimh.nih.gov/health/topics/schizophrenia/index.shtml

(9) World Health Organization. WHO European Ministry Conference on Mental Health. Available online at: http://www.euro.who.int/document/MNH/emnhqa.pdf. Accessed on October 2, 2007.

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Web site: http://www.schering-plough.com/
Company News On-Call: http://www.prnewswire.com/comp/777050.html/
Ticker Symbol: (NYSE:SGP)

4.5 Appendix 5 – Additional Information Regarding the Approved Atypical Antipsychotic / SSRI Combination Product- Symbyax®; (Fluoxetine/Olanzapine)

4.5.1 Selected Sections of the Food Drug and Cosmetics Act

FD&CA Sec. 502 [21 USC 352]

(a) False or misleading label. If its labeling is false or misleading in any particular.

f) Directions for use and warnings on label. Unless its labeling bears

> (1) adequate directions for use; and
> (2) such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users,

(j) Health-endangering when used as prescribed. If it is dangerous to health when used in the dosage or manner or with the frequency or duration prescribed, recommended, or suggested in the labeling thereof.

FD&CA Sec. 301 [21 USC 331]

Sec. 301. Prohibited acts

The following acts and the causing thereof are prohibited:

(a) The introduction or delivery for introduction into interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded.

4.5.2 Information on Risk of Phen-Fen Like and Developmental Risks with Symbyax® from FDA Reviews

The FDA recommendation for a repeat of the prenatal/postnatal development study in rats as a Phase 4 commitment is based on these findings as well as on the fact that no meaningful toxicological conclusions about these (and other) developmental endpoints in F1 generation can be made on the basis of the submitted postnatal developmental study. This study employed only two olanzapine/fluoxetine combination (OFC) dose levels: high and low. The high dose combination induced excessive mortality in the progeny early in life that did not allow assessment of postnatal developmental endpoints other than survival and body weight. For this reason, the sponsor did not provide data on developmental endpoints in the progeny (including those of the reproductive system) at the HD combination. No proper toxicological assessment or meaningful conclusion about OFC postnatal developmental toxicity can be made based on the available results at only one (LD) dose level. In conclusion, there is obviously a need for a repeated pre/postnatal study (as a phase 4 commitment) with a more appropriate dose selection that would allow a reliable assessment of postnatal developmental toxicity parameters and their dose-effect relationships and NOAEL.

6.
In the rabbit, there was no evidence of teratogenicity; however, the high-dose combination produced decreases in fetal weight and retarded skeletal ossification in conjunction with maternal toxicity.

7.
In a pre- and postnatal study conducted in rats, olanzapine and fluoxetine were administered during pregnancy and throughout lactation in combination [low-dose: 2 and 4 mg/kg (1 and 0.5 times the MRHD on a mg/m^2 basis), respectively, high-dose: 4 and 8 mg/kg/day (2 and 1 times the MRHD on a mg/m^2 basis) respectively] and alone [4 and 8 mg/kg/day (2 and 1 times the MRHD on a mg/m^2 basis), respectively]. Administration of the high-dose combination resulted in a marked elevation in offspring mortality and growth retardation in comparison to the same doses of olanzapine and fluoxetine administered alone.

Pulmonary events, including inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely. These events have occurred with dyspnea as the only preceding symptom.

FDA Comment: *Accepted with corrections (correction included in the corresponding paragraph in December 11, 2003 PI as reproduced below):*
SYMBYAX Embryofetal development studies were conducted in rats and rabbits with olanzapine and fluoxetine in low-dose and high-dose combinations. In rats, the doses were: 2 and 4 mg/kg/day (low dose) (1 and 0.5 times the MRHD on a mg/m^2 basis, respectively) and 4 and 8 mg/kg/day (high dose) (2 and 1 times the MRHD on a mg/m^2 basis, respectively). In rabbits, the doses were: 4 and 4 mg/kg/day (low dose) (4 and 1 times the MRHD on a mg/m^2 basis, respectively) and 8 and 8 mg/kg/day (high dose) (9 and 2 times the MRHD on a mg/m^2 basis, respectively).

4.6 Appendix 6 - Review of Amendment 027 Submitted June 13, 2008

Comments were apparently sent to the sponsor without the knowledge of this reviewer and that this amendment is in response to these comments. No information on what comments the sponsor is replying to is included and this reviewer can find no record of any communication of comments to the sponsor in DFS. Upon review it appears that these slides are in response to a memo to the file from the OCP team leader labeled Asenapine.Doc and dated June 10, 2008 at 1:50 PM. It is unclear why comments from a memo to the file would be sent to the sponsor without going through proper channels including being signed off on by the OCP division director. For ease of reference the comments from this memo to the file follow:

Figure 46 OCP Team Leader's Memo to File

OCP Team Leader's Memo to File

Date: June 10, 2008

From: Raman Baweja, Ph.D.
Team Leader
DCP 1, OCP

To: File NDA 22117, Asenapine

This writeup pertains to OCP dfs'ed review of May 15, 2008.

From a clinical pharmacology standpoint it should be noted that the sponsor has not adequately ascertained what moieties are circulating in plasma. In the mass balance study both the data in the table, and the figure show that the plasma concentrations of 14C asenapine (equivalents) greatly exceeds that of asenapine (cold drug) as well as the metabolites measured. Further, that the moieties looked for are asenapine, desmethylasenapine, and the N-oxide. The total AUC counts for total radioactivity (14C) is around 1550 AUC units whereas the summation of all the AUCs for the three measured moieties accounts for about 55 AUC units. There is a vast amount of circulating material in plasma that has not been ascertained. As the review indicates that at least 96.6% of the circulating species have not been identified. This is a matter for concern and the sponsor should be requested to explain this vast gap between circulating radioactivity, and, moieties circulating and identified in plasma.

Another issue that raises concern is that the mass balance has not been adequately characterized. In a generalized manner, after the administration of the radioactive dose about 88 % of the dose is recovered with 49 % in the urine and 39 % in the feces; this is like providing the generalized presentation of where did the radioactivity go. When it comes to specifics regarding what moieties are involved, what is known is that direct glucuronidation accounts for 12-21% of the dose. Further, that 5-16 % of the dose is that of unchanged drug, asenapine. When these two are added up, it represents 17–37 % of the dose. Therefore, a subtraction shows that 63-83 % of the dose has not been adequately characterized for the primary elimination pathways.

The metabolism issues mentioned above, viz., what moieties are circulating in plasma, and the characterization of elimination pathways, should be clearly and properly addressed by the sponsor.

Another area of concern stems from the administration a low single sublingual dose of 5mg to healthy subjects for the conduct of a bioequivalence (BE) study. In this BE study according to the sponsor's report, 10 subjects experienced bradycardia, 8 subjects experienced tachycardia, 7 subjects experienced sinus pause, 3 subjects experienced junctional rhythms, and one subject experienced bradycardia with junctional rhythm. Then also in another study following a 5 mg sublingual dose one subject experienced bradycardia which occurred while the subject was supine. Overall then, these adverse events raise concern about the use of this drug even when administered as low single doses based on what is seen with the administration of the drug in healthy subjects.

Nine slides were submitted in the amendment that is presumably in response to the above comments. The following table includes a description of each slide's content and review comments.

Table 28 Critique of Slides Include in Amendment 027 (BB) Submitted June 13, 2008

Slide #	Summary of Slide Content	Review Comments
Slide 1	Title Slide	
Silde 2	Sponsor claims asenapine and N-desmethyl account for only 3% of circulating radioactivity	Does not address appropriate time interval Does not address dose. Even if we accept this it is still problematic.
Silde 3	Sponsor's proposed metabolic scheme	Compare with reviewer's scheme. Neither is certain at this time. This does not change conclusions.
Slide 4	Sponsor shows comparative metabolic concentration v. time profiles of asenapine, the 11-O-Sulfate and Asenapine Glucuronide in Study 25546	Study 25546 was a 6 day multiple dose study in young healthy nonsmoking and light smoking Japanese and Caucasian males. From the raw data it's not clear what dose is represented. Neither is the race, demographics or other features. Although the 11-O-Sulfate exposure is similar to asenapine this does not address exposure to other species. Even when the reviewer did a similar analysis and estimated exposures to the 11-O-Sulfate and the glucuronide from better characterized studies the analysis revealed at least 85% of the circulating species are still unknown. Performing the same analysis again with data from study 25546 will not change the conclusions.
Slide 5	Sponsor claims radiometric quantification was difficult.	It was difficult to quantify because the sponsor apparently designed the study in such as manner so as to make it difficult. This is not a valid justification for not performing appropriately designed studies.
Silde 5 and 6	Sponsor indicates that at single time points up to 30% of the radioactivity was identified. Four species were quantified and No AUCs can be calculated.	Single time points do not represent total exposure over time which is the appropriate metric. The reason only 4 species were identified is because the sponsor a priori decided to measure these particular 4 species as cold drug by HPLC and thus did not even attempt to look at exposures via other species. No AUCs can be calculated because of the sponsor's methodology. Larger single radioactive doses could have been used and samples from a number of subject could have been pooled. In addition this does not report data from 0 to 1.5 hours after dosing and is thus skewed this is data from HPLC System 1 which is the least sensitive method the sponsor has.
Silde 7	Sponsor claims all 'major' peaks identified, the remaining peaks are minor and quantification of the pooled data is not possible.	The guidance defines major as >10% of parent (peak 20) a cursory examination reveals that the 'minor' peaks are likely greater than 10% of asenapine, the sponsor does not even include the integrated AUCs which it is possible to obtain which would help definitely answer this. Thus the sponsor hasn't even attempted to support their claim with data that they can easily go back and generate. Even 'minor' peaks or a combination of 'minor' peaks can be clinically relevant and likely are in asenapine's case. Even if what the sponsor claims is true, an alternative study design would have overcome these problems.
Slide 8	Sponsor claims 71% of dose (fully/tentatively/partly) identified via excreta.	Agree however the partly identified part is a claims mixture or multiple possible metabolites whose structures are not clear and so it is not possible to assign the relative contributions of the primary pathways. While the slide is technically correct it is misleading and the data is insufficient for assessment of safety and labeling purposes.
Slide 9	Conclusions	See previous comments.

4.7 Appendix 7 – Quality of the Submission

To be included in a separate amendment to the NDA review.

4.8 Appendix 8 – Evaluation of Pilot NDA Review Process

To be included in a separate amendment to the NDA review.

4.9 Appendix 9 – Lessons Learned and Feedback on FDA Policies, Procedures and Regulations

To be included in a separate amendment to the NDA review.

4.9.1 Future Predictions

To be included in a separate amendment to the NDA review.

4.9.2 Recommendations re: FDA Policy Procedures, Guidances, Regulations, and Laws

To be included in a separate amendment to the NDA review.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ron Kavanagh
6/18/2008 04:30:25 PM
BIOPHARMACEUTICS

Per our discussion I have cc'ed all parties reviewing asenapine for whom this might impact their reviews, as well as individuals in Neuro for whom this information may impact drugs that will eventully be used for psychiatry indications

John Duan
6/18/2008 04:34:18 PM
BIOPHARMACEUTICS

NDA Review - Asenapine
OCP Review Amendment # 2
(Memo to File)

<table>
<tr><td>NDA:</td><td>22-117</td></tr>
<tr><td>Type of Submission:</td><td>Original NDA</td></tr>
<tr><td>Submission Date:</td><td>August 30, 2007</td></tr>
<tr><td>Associated INDs:</td><td>51,641 September 30, 1996 (Treatment of Psychosis)
70,329 August 3, 2004 (Treatment of Acute Mania in Bipolar I)</td></tr>
<tr><td>Generic Name:</td><td>Asenapine Maleate</td></tr>
<tr><td>Formulation:
Strengths:</td><td>Sublingual Tablets
5 mg, 10 mg</td></tr>
<tr><td>Route:</td><td>Sublingual (N.B. Route is mislabeled in Application Form 356h)</td></tr>
<tr><td>Brand Name:</td><td>Sycrest®</td></tr>
<tr><td>Sponsor:</td><td>Organon / Schering-Plough</td></tr>
<tr><td>Additional Submissions and Dates since Original OCP Review Completed:</td><td>
<table>
<tr><th>SN</th><th>Date</th><th>Code</th><th>Descriptor</th><th>Contents</th></tr>
<tr><td>025</td><td>5-14-08</td><td>BM</td><td>Minor Amendment - Medical</td><td>Response to April 21st Request for Neutropenia & Ganulocytopenia Cases</td></tr>
<tr><td>026</td><td>5-21-08</td><td>BC</td><td>Minor Amendment - Labeling</td><td>Response to DMETS question (May 13, 2008)</td></tr>
<tr><td>027</td><td>6-13-08</td><td>BB</td><td>Minor Amendment – OCP</td><td>Asenapine Metabolite Profile</td></tr>
<tr><td>028</td><td>6-20-08</td><td>BL</td><td>Minor Amendment - Labeling</td><td>Response to June 16, 2008 Carton, Container, Blister and Label Comments</td></tr>
<tr><td>029</td><td>6-20-08</td><td>BM</td><td>Minor Amendment - Medical</td><td>Response to June 17, 2008 Information Request</td></tr>
<tr><td>030</td><td>6-23-08</td><td>BC</td><td>Minor Amendment – Chemistry</td><td>Response to Telephone Request from Office of New Drug Quality Assessment (June 19, 2008</td></tr>
</table>
</td></tr>
<tr><td>Reviewer:</td><td>Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D.</td></tr>
</table>

1 Table of Contents

2 Background

The original OCP review was essentially complete by April 30, 2008 and on that Wednesday and the following day May 1, 2008 the review was discussed with the OCP Team Leader Dr. Ray Baweja who apprised the DCP1 Division Director, Dr. Mehul Mehta, of the findings. During the following week slides for the briefing were prepared with a draft shown to Dr. Mehul Mehta on Wednesday May 7, 2008. On May 12, 2008 the OCP briefing was held and following research into requests from the Briefing the initial OCP review was placed in DFS on May 15, 2008. While working on labeling as requested post sign off of the OCP review this reviewer realized a) it was not possible to write labeling without adequate scientific data b) the CFR required nonapproval c) this reviewer had been laboring under a misconception based on previous and repeated instructions from management only to recommend acceptable or non-acceptable with regard to OCP recommendations. Consequently this reviewer wrote an e-mail on May 16, 2008 advising management of a pending change in recommendations and requested additional time in order to revise his review. After having begun writing an amended review, this reviewer discovered that OCP management was progressing with writing labeling recommendations. Consequently, on May 20, 2008 this reviewer placed a memo to the file in DFS regarding his change in recommendation. Over the next few weeks there were multiple attempts to force this reviewer to finalize a review prior to all the issues being flushed. These attempts and this reviewer's responses will not be discussed at this time. However, it is readily apparent from the sequence of events that attempts have been made to dismiss many of this reviewer's concerns without addressing the underlying scientific and clinical basis of these safety concerns.

This review amendment will briefly address many of these attempts to dismiss these concerns and will be placed in DFS prior to July 1, 2008 as a Memo to the File as specified by FDA policy and due both to time constraints and per FDA policy this memo to the file will be placed directly in DFS without secondary review by OCP management. Although this is allowed when a reviewer has a scientific dispute with FDA management this reviewer does not believe this extends to reviews by other disciplines that are in agreement with FDA management as has been done and is documented in this review. If this reviewer is in error with regards to policy this reviewer respectfully asks for the same courtesy as has already been shown to other reviewers who have not had their amended asenapine reviewers secondarily signed off.

3 New Amendments to the NDA

The following 6 amendments were made to the NDA after this reviewer completed his original review. All were made in response to communications from the FDA that do not appear to have been documented and that this reviewer was not informed of. The timing of each of them are such that this reviewer would not be able to appropriately respond to them prior to the PDUFA due date.

SN	Date	Code	Descriptor	Contents
025	5-14-08	BM	Minor Amendment - Medical	Response to April 21st Request for Neutropenia & Ganulocytopenia Cases
026	5-21-08	BC	Minor Amendment - Labeling	Response to DMETS question (May 13, 2008)
027	6-13-08	BB	Minor Amendment – OCP	Asenapine Metabolite Profile
028	6-20-08	BL	Minor Amendment - Labeling	Response to June 16, 2008 Carton, Container, Blister and Label Comments
029	6-20-08	BM	Minor Amendment - Medical	Response to June 17, 2008 Information Request
030	6-23-08	BC	Minor Amendment – Chemistry	Response to Telephone Request from Office of New Drug Quality Assessment (June 19, 2008

The first amendment requests cases of Neutropenia and Granulocytopenia, however this is different from the two cases of death this reviewer identified where neutropenia had not been achieved but the hematology values indicated that a trend was underway. Consequently this does not address the particular cases raised by this reviewer.

The asenapine metabolite profile amendment was serendiptously able to be addressed in the previous OCP review amendment.

The remaining amendments are addressed in the present amendment.

4 Discussion of Issues Raised by Other Reviews not Discussed Previously

4.1 Medical Reviews

4.1.1 Cross Disciplinary Team Leader's Review #1 – May 14, 2008

On May 14, 2008 the Cross Disciplinary Team Leader CDTL placed her review in DFS. Her remarks regarding the OCP review follow:

"The Clinical Pharmacology review to inform the regulatory processing of this application by the Division Director has not been completed as of 14 May 2008. Based on the review of the drug-drug interaction studies included in this efficacy supplement regarding adjunctive treatment, Dr. Kavanaugh and Baweja may recommend a number of hitherto unknown changes to asenapine labeling regarding drug-drug interactions with commonly used antidepressant s evaluated in the double-blind, placebo-controlled trials. If, as Dr. Kavanaugh stated on 12 May 2008 that more than 99% of circulating radioactivity has not been identified, than an approval could not be considered. This statement requires verification by OCP. The full characteristics of drug-drug interaction require clarification for labeling.

At present, biopharmaceutics issues that would preclude an approvable action for this NDA remain undefined. After the Clincial Pharmacology review is signed off and filed with confirmed pharmacokinetic data and analyses, the review and labeling recommendations will taken into consideration for regulatory processing by Drs. Laughren and then by Dr. Temple."

4.1.1.1 OCP Reviewer Comments and Recommendations

It's not known to this reviewer why the CDTL did not wait for the OCP review as she was aware that final changes were in progress and that the review needed to be finalized by OCP management first.

4.1.2 Medical Review Amendment #1 - May 15, 2008

The medical reviewer changed his conclusions from the original clinical review where he stated the acute schizophrenia study # 41004 was a failed study to a positive study with as asenapine differentiated from the negative control as the positive control did not.

4.1.2.1 OCP Reviewer Comments and Recommendations

The medical reviewer's statement is at variance with the regulatory history of the FDA going back many years. The FD&CA indicates that efficacy must be shown by 'adequate and well controlled studies'. It is common practice in science that experiments and studies need both positive and negative controls in order to be well controlled. This is especially important with treatment for certain psychiatric diseases due to the high and variable placebo response rate, which could differ between two different placebo arms.

It's also unknown why the medical reviewer did not obtain a secondary signature for this review amendment.

As with §4.1.4.1 an impartial outside medical review shall be requested as the points of contention are of such major importance to the public health.

4.1.3 OCP Reviewer Comment

This reviewer was attempting to complete the amended review by Friday June 13, 2008, the following documented amount and type of activity by other review disciplines is highly unusual and in fact has never been observed previously by this reviewer in his 10 years as a reviewer.

4.1.4 CDTL Review #2 – Recommendations – June 12, 2008

The points of contention between the CDTL and this reviewer in her review are too numerous to mention as they take up 13 pages in addition to CMC and Pharm/Tox issues.

The following note worthy statement is from this review regarding cases of possible asenapine toxicity that this reviewer would identify:

"Each case will be medically reviewed by Drs. Laughren, Mathis, Levin, and I for medical adjudication on 16 June 2008."

In addition this CDTL review included comments from the OCP TL regarding mass balance and metabolism that this reviewer was not aware of and which were communicated to the sponsor by Dr. Laughren around June 13, 2008[1].

4.1.4.1 OCP Reviewer Comments and Recommendations

This reviewer is unclear why the CDTL placed this review critiquing each point raised by this reviewer in DFS only 1 day prior to the expected completion of the amended OCP review. What is even more unclear is why this was placed in DFS before the expected completion of this reviewer's amended review why this reviewer was not notified.

As the points of contention between the CDTL and this reviewer in her review are too numerous to mention an impartial outside medical review shall be requested as the points of contention are of such major importance to the public health. However I will provide one illustration of the types of problems with the CDTL's analyses.

With regard to cardiac toxicity the CDTL makes the following statement:

"In the 15 May 2008 as well as in the 10 June 2008 OCP reviews, despite Dr. Stockbridge's conclusions in the DCRP review of 23 April 2008, OCP continued to conclude that the data supported a severe risk of cardiac toxicity associated with asenapine. On page 22 of the OCP review, in section 2.2.2, Summary of Major Conclusion), OCP opined that "There appears to be

[1] Verbal communication from OCP team leader on June 19, 2008

no margin of safety with regards to cardiac toxicity." This contradicts the conclusions of Drs. Stockbridge's and Balakrishnan's interpretations of the data and conclusions in their review.

I defer to the expertise of DCRP in the evaluation of the clinical cardiological risk profile of asenapine."

Yet the QT/IRT team in their consult of 4-23-08 clearly indicate that their assessment was based only on the sponsor's summary of clinical safety which clearly contradicts the sponsor's own earlier and more thorough analysis, and based on the thorough QT study which this reviewer has shown did not even provide all the information gathered and needed for a review. Nor did the QT/IRT team even examine any of the other clinical data that I put forward in my review. Normally I would also defer to experts in a field but when the experts admit that they haven't even examined the data I have to reject their conclusions and recommend that additional review of this information be conducted by an impartial unbiased outside adjudicator.

Per the previous section there appears to have been a meeting to adjudicate the cases raised by this reviewer. Since only Dr. Levin appears to have signed the review from this meeting it is recommended that all notes from this meeting be preserved for the outside ajudicator.

This reviewer was attempting to have the amendment to the review completed by Friday June 13, 2008. The fact that the OCP team leader was requested to write comments to the file nearly a month after the original review, that they were communicated to the sponsor without any records being kept nor without notifying the reviewer, and that the communication of the response was to be made to this reviewer after he completed his review amendment, raises concerns as to the propriety of how this was handled. Since the Secretary is responsible for assuring that the review process is without bias, this will be taken up with the appropriate authorities as required by law.

For other recommendations see XXXX.

4.1.5 Medical Review Amendment # 2 – June 27, 2008

4.1.5.1 OCP Reviewer Comments

4.1.5.1.1 Deaths

This review by the medical reviewer discusses specific safety items in more detail than discussed by him previously, although the discussion is still extremely superficial.

The medical reviewer gives a very brief description of each of the individual deaths reported and for almost every death of a patient receiving asenapine the medical reviewer indicates the death was either:

"probably unrelated to treatment with asenapine"

Or

"does not appear to be related to treatment with asenapine"

In one case where the medical reviewer does not deny the relationship is a case where the clinical investigator states that a suicide was possibly related to asenapine. For this case the medical reviewer states that "it is not clear what the (clinical investigator's) rationale was", thereby introducing doubt.

The neonatal case that this reviewer covered extensively was listed as by the medical reviewer as possibly related, and the reader is referred to the previous OCP review amendment.

In addressing suicidality the medical reviewer largely reiterates the sponsor's analysis which this review has already shown is flawed as there aren't placebo control groups in the long term studies consequently adjusting for total patient years biases the outcomes because suicides typically occur after 4-6 weeks in schizophrenics after they are discharged, and after 2-3 weeks in subjects with acute mania. In addition, this reviewer has already indicated that there is no clear increase in risk in schizophrenia.

For mania the medical reviewer inappropriately uses 12 week data which is not appropriately placebo controlled for the period beyond 3 weeks when the risk has likely largely already past.

"Mania Study (12-week)

An analysis of the ISST data was performed for the 12-week Bipolar Mania study. The results of the mean total score and change from baseline on Day 28, Day 63, and endpoint show a small increase in the mean total score across all treatment groups at endpoint (0.4 for asenapine 9- week, 0.1 for asenapine 12-week, and 0.2 for olanzapine 12-week). The results were similar between the olanzapine and asenapine groups."

This reviewer referred back to the protocols to determine how ISST was utilized. For both the acute mania studies ISST was only included at baseline, it was then included at 3 weeks as part of the 3rd protocol amendments however, by this time the enrollment was largely over and 3 weeks ISST data was not obtained. In fact at the same amendment the sponsor added a Drug Safety Monitoring Committee to ensure patient safety. This indicates that the sponsor may have had a concern about increased suicidality with during the first 3 weeks. The sponsor also added a pharmacogenomic component to this study and this information should be obtained if the sponsor decides to pursue approval.

In addition the medical reviewer requested and obtained from the sponsor information on the following cases in SN 029 June 20, 2008 provided in response to a June 17th, 2008 information request from the medical reviewer.

Schizophrenia study P041513 Subject 368509

This subject completed suicide in Sept 2006 a Suicide due to by ingestion of clozapine. The sponsor claims that the death was unlikely related to asenapine however the subject had been on asenapine 135 days, with a worsening of symptoms during July requiring coadministration of chlorpromazine. At the end of July this was discontinued, and 1 month later the patient committed suicide. This history suggests the possibility that asenapine was ineffective in this patient and thus suicide due to lack of efficacy should be considered possible in this case.

For SAEs the medical reviewer does not even appear to consider a differential diagnosis and appears to accept the sponsor's analysis at face value. Thus ven when an ECG is suggestive of an MI the medical officer still indicates that the even is reflex mediated bradycardia.

In this reviewer's opinion the medical officer's analyses are in direct contradiction to FDA guidance to reviewers in assessing safety signals observed premarketing.

4.1.5.2 Change in OCP Reviewer Recommendations

In OCP Review Amendment #1 it was recommended that the following comments to be forwarded only if asenapine is found approvable. It was thought that it was clear to FDA management hat the FD&CA required nonapproval due to the lack of this information. This can no longer be assumed by this reviewer. Consequently this reviewer now explicitly recommends that this information be required to be submitted prior to any determination of approvability and that per the FD&CA as outlined in previous reviews that the NDA not be approved as this information has not been provided.

1. Structures of all compounds with stereoisomerism and all information on receptor binding and potential pharmacologic activities of any and all metabolites and degradation products are needed including nomenclature. This will likely necessitate new mass balance studies. Please note this request is not limited to 'major' metabolites as this may eliminate clinically important species.

2. Complete drug substance and drug product information for any asenapine or asenapine derivative structure that has been used in any clinical or preclinical study is requested.

3. Complete data sets from any clinical study that has not been submitted so far is also needed. This includes data from the thorough QT study and includes pharmacokinetic, clinical laboratory, and AE data. As well as similar information that has not been submitted for early human studies or for any 'ongoing' studies should also be included. 'Ongoing' studies should be interpreted to include both studies that were ongoing at the time of the original NDA submission as well any subsequently conducted studies.

4.2 Chemistry Reviews

4.2.1 Chemistry Review Amendment #1 – May 21, 2008

On May 21, 2008 a chemistry review amendment made the following conclusions:

"I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant provided acceptable responses for the CMC deficiencies stated in the review #1 dated 11-APR-08 (see evaluation in the Chemistry Assessment section in this review). However, from the CMC point of view NDA 22-117 for Sycrest® (asenapine) Sublingual Tablets is recommended ***APPROVABLE*** *due to pending resolution of the following outstanding pharmtox issue regarding impurity* (b) (4) *which will have impact as the setting of acceptance limit for the drug substance specification:*

1. *The applicant proposed acceptance criteria for impurity,* (b) (4) *33, in asenapine drug substance at* (b) (4) *which is above the ICH Q3A(R) qualification limit o* (b) (4) *The pharmtox reviewer (Elzbieta Chalecka-Franaszek, Ph.D.) stated in her review dated 30-APR-08 (pp. 4) that the applicant should perform an embryofetal development study with* (b) (4) *in the rabbit to qualify this impurity during phase IV or reduce the specification of* (b) (4) *to the ICH Q3A(R) qualification limit of* (b) (4)

Release data for the drug substance batches used in clinical studies (20 batches) and batches used
in to be marketed drug product batches (4 commercial batches) showed that process impurity (b) (4) *is present at not more than* (b) (4) *level, which is well below ICH Q3A(R) qualification limit of* (b) (4) *indicating that the applicant may be able to reduce the specification of* (b) (4) *to the ICH Q3A(R) qualification limit of* (b) (4)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None as per this review"

4.2.1.1 OCP Reviewer Comments

This amended review was signed by the chemistry reviewer and the Branch Chief without a counter signature by the CMC team leader. This reviewer has never observed this before. It's also strange that this came more than a month after this was mentioned at a meeting this reviewer was advised not to attend, plus this review makes this reviewer wonder why it wasn't included in the original NDA review.

The timing of this relative to the OCP review should also be noted.

4.2.2 Chemistry Review Amendment #2 – May 23, 2008

Approvable. At this time, CMC is unable to accept the release criterion for the impurity (b) (4) and thereby approve the drug substance specification.

4.2.2.1 OCP Reviewer Comments and Recommendations

This is a concurrence by the Director of DPA I/ONDQA Blair A. Fraser. This reviewer does not recall ever having seen something similar to this before. In addition this reviewer does not understand why this issue of an unqualified impurity was not raised with this reviewer previously yet the pharm/tox reviewer kept insisting on metabolite information from this reviewer, when this clinical assessments should be informed by the pharm/tox data and not go purely in the opposite direction.
The timing of this relative to the OCP review should also be noted.

4.2.3 Chemistry Review Amendment #3 – June 20, 2008

4.2.3.1 OCP Reviewer Comments and Recommendations

This review was performed based on a June 19, 2008 e-mail response to a June 19, 2008 telephone request from Dr. Chhagan Tele. Again there are no records of the request and the formal submission was not submitted until June 23, 2008 in submission number 030.

From the June 19th e-mail it appears that this request and submission is only with regards to particle size in primary stability batches. This also appears to be the case from the cover letter for SN 030.

However, there was no reason at this point to have detailed particle size data for each batch as it had already been determined that this was adequately addressed during the regular review period. What is very interesting is that Dr. Chhagan in his review also includes quite a bit about changes in the chemical manufacturing process of the active pharmaceutical ingredient (API) during the development of asenapine. This reviewer had previously asked Dr. Tele for this information as prior to the new FDA policies this reviewer would review this data for clinical importance, however previously Dr. Tele would not provide specifics. This data may or may not have clinical importance and there is insufficient time to OCP to review it prior to the PDUFA goal date. In addition, the information is not cross correlated with individual phase I – III clinical studies which is needed for an appropriate review. Consequently, this review may appear to technically address previous OCP recommendations however it does not address the use of this data in interpreting clinical pharmacology and safety data.

Again this review and submission raises questions as to the reason for the delay, the lack of appropriate documentation, and the lack of communication with OCP. It should be noted that OCP management has brought up these concerns with ONDQA regarding Dr. Tele in the past, as well as with other individuals in ONDQA.

4.3 Pharm/Tox Review Amendments

4.3.1 CAC Advisory Committee Review #2 - June 16, 2008

4.3.1.1 OCP Reviewer Comments

This was essentially a reiteration of the advice provided in the previous review from this committee and included in the Pharm/Tox review. The recommendations from this review follow:

"Executive CAC Recommendations and Conclusions:

The Committee concurred that the carcinogenicity studies filed to the NDA are considered "unacceptable" without completion of the full histopathological examination of the low and mid-dose dose male and female groups in the rat carcinogenicity study and the full histopathological examination of the low and mid-dose dose females in the mouse carcinogenicity study.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC"

4.3.2 Pharm/Tox Review #3 - June 23, 2008

4.3.2.1 OCP Reviewer Comments

The following comments were made in this review by Paul C. Brown, Ph.D., ODE Associate Director for Pharmacology and Toxicology, OND IO. This reviewer cannot recall this ever occurring before. Based on these comments it seems to this reviewer that this reviewer's concerns regarding developmental and reproductive toxicities to a metabolite or impurities are being dismissed indirectly and inappropriately, while as is noncarcinogenic safety with long term usage.

"These studies were presented to the CDER executive carcinogenicity assessment committee. The committee could not fully evaluate the rat study because of the significant decrease in body weight and the lack of full histopathology examinations in all dose groups. Therefore, the committee recommended that the sponsor perform a full histopathology evaluation of the low and mid dose groups in the rat study. The committee could also not fully evaluate the mouse study because of the large variability in the lymphoma incidence in the groups evaluated. Therefore, the committee recommended that the sponsor perform a full histopathology evaluation of the low and mid dose female groups in the mouse study.

Developmental and reproductive toxicity:

The pharmacology/toxicology reviewer recommended pregnancy category C. Asenapine maleate was not teratogenic in studies in rat and rabbits although the maximum exposures tested did not greatly exceed the anticipated maximum human exposure (approximately 2 fold). Some fetal and neonatal toxicity was observed in a rat study at doses that did not exceed the human exposures. Pregnancy category C is appropriate in spite of these observed adverse effects because of the potential utility of the product in the proposed indication.

Impurities:

The sponsor proposed a (b) (4) *specification for an impurity* (b) (4) *that exceeds the ICH threshold for qualification. The impurity was qualified in genotoxicity studies and 4 week studies in rats and dogs. A non-GLP pilot segment II study was conducted with the impurity in rabbits; however, the reviewer found this study to be inadequate for several reasons. The reviewer recommends that the sponsor conduct a rabbit embryofetal toxicity study with the impurity post-approval or reduce the impurity specification to* (b) (4) *which is the qualification threshold. I concur with these recommendations.*

Conclusion:

Asenapine maleate could be used in a chronic manner in the intended indication; therefore, it is appropriate to have adequate carcinogenicity data prior to approval. I concur with the pharmacology/toxicology recommendation of the Division that this NDA not be approved until the complete information from the carcinogenicity studies is submitted, reviewed and found to support the approval."

4.3.3 Pharm/Tox Team Leader's Comments on OCP Amendment – June 24, 2008

4.3.3.1 OCP Reviewer Comments and Recommendations

The pharm/tox leader made the following comments:

"Aside from the fact that data indicate that asenapine itself is a serotonergic antagonist (although of course it is possible that its metabolites are not), the range of adverse effects which Dr. Kavanagh is speculating to be due to serotonergic agonism (as well as the wide range of drug classes he implicates) is so broad as to be useless for informing the direction of any future clinical monitoring."

This is clearly inaccurate. Most of the problems I have described are the same as occur with Phen-Fen, and clinical monitoring with serial 2D echo cardiography is a known and accepted monitoring technique and will detect changes in a large percentage of patients receiving phen-fen within a few months. While I agree that the symptoms are broad, the first thing that a clinician needs is a **'high index of suspicion'** and that is why it is imperative that public communication should be rapid, vigorous, and repeated, especially as to mechanism and the range of possible drug classes that may be involved. In addition new methods of monitoring and communication are currently in development, e.g. perhaps pharmacogenomic screening may be helpful or even the serial CAT scans that have recently been in the news as to the propriety for Medicaid and Medicare to pay for them.

With regard to the embryofetal toxicity perhaps they were not alarming to Dr. Rosloff because he is used to looking at them without considering their cause or consequence. It would be expected that we would see them consistently with psych and other drugs that effect the same receptors, especially at high doses. For as noted many centuries ago by Paracelsus (1493-1541)

"All substances are poisons; there is none which is not a poison. The right dose differentiates a poison…."

Presently we know neither the metabolite exposures in animals or humans nor their receptor activities, so we cannot even guess at the relative risk in humans. Dr. Rosloff indicates that the effects are not a malformation but rather are due to maternal weight loss, however may not be a cause and effect as he implies but rather an associated finding, as some serotonin receptors mediate control of hunger. As for skeletal muscle and ossification the exact opposite effect at the very same skeletal sites are seen with the oxaxolidinone class of antibiotics giving strength to the hypothesis that this is mediated via a specific pharmacologic action (possibly mediated by 5HT, BMRP2, or sMAD). Finally he says that it's a transient reversible delay in development. Where is the evidence? Plus if we give this to children chronically, when does he expect the children's parents will stop giving them a chronically administered drug to control behavior to allow recovery, especially if he doesn't even warn them?

4.4 Drug Marketing Evaluation Team Nomenclature Reviews

4.4.1 DMET Review # 1 – May 7, 2008

4.4.1.1 OCP Reviewer Comments

The original DMETS consult regarding the name during the review cycle was sent on September 19, 2007 and is as follows:

"Organon has submitted new NDA 22-117 for asenapine maleate sublingual tablets for use in schizophrenic and bipolar patients. Please review the proposed tradename, Sycrest, and also there proposed packaging and provide feedback."

The recommendation and signature timeline follow:

"FMEA identifies potential for confusion between the proposed proprietary name and other proprietary or established drug names, and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.

Felicia Duffy
5/6/2008 03:53:23 PM
DRUG SAFETY OFFICE REVIEWER

Kellie Taylor
5/6/2008 04:34:47 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
5/7/2008 07:17:27 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
5/7/2008 03:21:50 PM
DRUG SAFETY OFFICE REVIEWER"

The review for the brandname was placed in DFS from May 6th – 7th 2008

However, on May 6, 2008 between the time of the placing into DFS of the review by the primary Drug Safety Office Reviewer and the second signatory, a new consult was sent to DMETS regarding a new Tradename, Saphris. This consult was sent by Dr. Laughren on May 6, 2008 at 4:24 PM.

This consult sent as a response to amendment number 021 from the sponsor submitted nearly a month before on April 10, 2008. The cover letter from this submission states:

"Reference is also made to electronic mail correspondence between Dr. Kiedrow (FDA) and Dr. Paporello, in which Dr. Kiedrow advised us to submit an additional trademark for review by the Division.

In addition

As per the Division's recommendation, we are submitting the additional trademark Saphris as the proposed proprietary name for asenapine sublingual tablets. Sycrest will remain as our second choice.

We are requesting a review of the proposed proprietary name Saphris by the Division of Medication errors and Technical Support, (DMETS) for approval"

Considering that the submission was made on April 10th and was based on a request from the clinical division, this reviewer does not understand why the consult was not forwarded for nearly a month. Based on the language it seems that this new Tradename review should have been included in the original DMETS review rather than in a separate second review. This second review was signed off in DFS on June 2, 2008 and June 3, 2008.

4.4.2 DMET Review # 2 – June 3, 2008

4.4.2.1 OCP Reviewer Comments and Recommendations

The second DMETS review was placed in DFS on June 3, 2008 contained the following text (emphasis added):

"EXECUTIVE SUMMARY

*At this time, the acceptability of the proprietary name, Saphris, is dependent upon which application is approved first. The results of the Proprietary Name Risk Assessment found that the proposed name, Saphris, is vulnerable to name confusion that could lead to medication errors with the name Saforis***. Saforis*** (NDA 21-979), received an approvable letter in October 2006. If Saphris is approved first, we will recommend that the second product, Saforis***, seek an alternate name.*

We also have concerns with the proposed product's established name, asenapine, potential for confusion with olanzapine. Because established names are not regulated by FDA, we recommend the Applicant discuss this issue with USAN/INN (International Nonproprietary Name) and petition for a new established name, if they feel this is a significant safety concern with their product.

If any of the proposed product characteristics as stated in this review are altered prior to approval of the product, we rescind this Risk Assessment finding, and recommend that the name be resubmitted for review. Additionally, if the product approval is delayed beyond 90 days from the date of this review, the proposed name must be resubmitted for evaluation.

In addition, this reviewer noticed the following selected recommendation from this DMET review:

"Furthermore, the established name (asenapine) of the proposed product may be prone to potential confusion because of its similarity to the currently marketed product, olanzapine. Thus, we recommend the Applicant discuss this issue with USAN/INN (International Nonproprietary Name) and petition for a new established name, if they feel this is a significant safety concern with their product."

And the following was included as a comment to the sponsor:

"Olanzapine and asenapine share a similar orthographic prefix ('olan-' vs. 'asen-') see example below. Both names also the letter 'a' in the middle of the name, and they also share the same ending ('-pine'). Adding to our concern regarding potential confusion between olanzapine and asenapine are overlapping product characteristics in addition to their orthographic similarities. These products share several overlapping product characteristics such as indication (schizophrenia and bipolar I disorder), strength (5 mg and 10 mg), dose (5 mg to 10 mg), dosage form (solid oral: sublingual tablet/tablet), and route of administration (oral)"

In addition this second review has the following disclaimer on the front of the review and on pages 3, 10, 11, 12, 13, 14, 16, and 26 indicating that it is not to be released under FOI.

*"** Note: This review contains proprietary and confidential information that should not be released to the public. **"*

The first review did not have this disclaimer.

Most of the pages with this disclaimer also contain information on the recommended change in the nonproprietary name from asenapine. However on other pages there are recommendations regarding labeling on what to do in case of swallowing and DMETS gives the reason for this as being based on a decrease in bioavailability and makes the following statement:

"The According to the Medical Officer's review dated April 14, 2008, the bioavailability of asenapine is extremely low (2%) when swallowed, but yields a mean absolute bioavailability of 36% following sublingual administration."

Where as the real reasons is due to the dose and time dependent hepatotoxicity observed with oral dosing. This reminds this reviewer of Dr. Zornberg's question to OCP at the Scoping Meeting last fall.

This reviewer is quite concerned about the safety implications of DMETs recommendation regarding changing the nonproprietary name.

Asenapine's International Nonproprietary Name (INN) was submitted to the World Health Organization in 2002 and it was granted in 2003.[2] This must then have later gone through the United States Adopted Name to obtain the same name in the US. If a new USAN is requested it will have to follow the present naming conventions which would likely mean a –sidone suffix as it's an "antipsychotic with binding activity on serotonin (5HT2A) and dopamine (D2) receptors". Resulting in a name that is similar to ziprasidone. However, these new naming conventions ignore the difference in chemical structure that these names also implied in the past and the associated toxicologic activities associated with those particular structure groups. By changing the name from asenapine we would be removing an extremely useful tool for

[2] RECOMMENDED International Nonproprietary Names (Rec. INN): List 49

recognizing that the toxic effects are similar to olanzapine and clozapine. A change in name would also make it extremely difficult for anyone to look up any research that has been published under asenapine in the past not to mention the typical clinician who would not be familiar with the history of the name of this compound. This would also completely frustrate the typical patient who would not know to use the search term asenapine when searching Clin Trials .gov.

In addition if the US adopted name (USAN) is changed and the International Nonproprietary Name is not then for immigrants or international travelers they might accidentally be prescribed an additional dose of the exact same medication, and considering the lack of margin of safety with asenapine this could be catastrophic.

Lastly DMETs indicated that the following was the criteria that they utilize in whether to recommend a proprietary name change (emphasis added):

"3. FMEA identifies potential for confusion between the proposed proprietary name and other proprietary or established drug names, **and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice**."

The nonproprietary name would not be used under the conditions of usual clinical practice for many many years and even then for a number of years the majority of prescribers will likely use the Tradename with the option that a generic may be dispense. Consequently, it appears that DMETs did not even apply or meet their own standards when marking this recommendation.

In conclusion it is strongly recommended for safety reasons that the nonproprietary name not be changed.

4.5 Comments and Recommendations regarding Warning of Imminent Danger to the Public Health

This reviewer would like to reiterate his previous recommendations that an immediate public health warning be issued regarding suicidality with olanzapine in bipolar disorder the use of antipsychotics in individuals with less severe episodes bipolar II, bipolar spectrum disorder, and in children, and the combined use of antipsychotics with a SSRI especially for longer than 8 weeks, and use in pregnancy and breast feeding as there are imminent dangers (hazards) to the public health and in making this recommendation this reviewer would like to highlight criteria afforded by 21 CFR §2.5.

Number of injuries anticipated

Schizophrenia is approximately 1% of the population
Bipolar I disorder is approximately 1% of the population
Bipolar II disorder is approximately 1% of the population
Bipolar Spectrum Disorder is approximately 2.5% of the population
Schizoaffective Disorder 0.5% - 0.8%
In addition there is misuse especially in children with ADHD (10% of the population) and autism, and the elderly demented (> 1% of the population)

Total ~ 7.5% of the population is at risk, and with chronic use, which is expected, and most if not all patients will probably experience the some 5HT2B mediated toxicity eventually, with some even experiencing sudden death.

Nature

Heart failure, MI, Cardiac Arrest, Pulmonary Hypertension

Duration of the anticipated injury.

Many of these may be permanent.

Finally, if we compare this with the recent warning regarding 'classical' antipsychotics then this surely meets the criteria for immediate dissemination without waiting for regularly scheduled dissemination of health information per the publicity section of the FD&CA.

4.6 Comments regarding Good Review Management Pilot Process

This will be addressed in more detail in subsequent documents,

This pilot process clearly indicates that the parallel review, the early communication to the sponsor, the inability of reviewers to collaborate due to distance, the commitment of opinions prior to being able to examine data, the ability of the sponsor to overload the application with excessive, convoluted, and missing data, the problems with the new electronic datasets including miscoding, and the reassignment of certain review responsibilities away from the scientifically appropriate review discipline as well as numerous other difficulties clearly demonstrates that the GRMP is excessively easy to manipulate to game the review process in order to place dangerous and ineffective drugs onto the market.

With the expected surge in dangerous drugs coming based on the 75% increase in IND from 2003 – 2006 and the lack of input OCP was allowed on INDs for Psych and Neuro drugs during this same time frame is likely to result in immense harm to the public health.

5 Signatures

_____ _____

Ronald E. Kavanagh, B.S.Pharm., Pharm.D., Ph.D. June 29, 2008

CC list:

Robert Temple
Tom Laughren

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/s/

Ron Kavanagh
6/30/2008 09:07:28 AM
BIOPHARMACEUTICS

OCP Team Leader's Memo to File

Date: June 10, 2008

From: Raman Baweja, Ph.D.
Team Leader
DCP 1, OCP

To: File NDA 22117, Asenapine

This writeup pertains to OCP dfs'ed review of May 15, 2008.

From a clinical pharmacology standpoint it should be noted that the sponsor has not adequately ascertained what moieties are circulating in plasma. In the mass balance study both the data in the table, and the figure show that the plasma concentrations of 14C asenapine (equivalents) greatly exceeds that of asenapine (cold drug) as well as the metabolites measured. Further, that the moieties looked for are asenapine, desmethylasenapine, and the N-oxide. The total AUC counts for total radioactivity (14C) is around 1550 AUC units whereas the summation of all the AUCs for the three measured moieties accounts for about 55 AUC units. There is a vast amount of circulating material in plasma that has not been ascertained. As the review indicates that at least 96.6% of the circulating species have not been identified. This is a matter for concern and the sponsor should be requested to explain this vast gap between circulating radioactivity, and, moieties circulating and identified in plasma.

Another issue that raises concern is that the mass balance has not been adequately characterized. In a generalized manner, after the administration of the radioactive dose about 88 % of the dose is recovered with 49 % in the urine and 39 % in the feces; this is like providing the generalized presentation of where did the radioactivity go. When it comes to specifics regarding what moieties are involved, what is known is that direct glucuronidation accounts for 12-21% of the dose. Further, that 5-16 % of the dose is that of unchanged drug, asenapine. When these two are added up, it represents 17–37 % of the dose. Therefore, a subtraction shows that 63-83 % of the dose has not been adequately characterized for the primary elimination pathways.

The metabolism issues mentioned above, viz., what moieties are circulating in plasma, and the characterization of elimination pathways, should be clearly and properly addressed by the sponsor.

Another area of concern stems from the administration a low single sublingual dose of 5mg to healthy subjects for the conduct of a bioequivalence (BE) study. In this BE study according to the sponsor's report, 10 subjects experienced bradycardia, 8 subjects experienced tachycardia, 7 subjects experienced sinus pause, 3 subjects experienced

junctional rhythms, and one subject experienced bradycardia with junctional rhythm. Then also in another study following a 5 mg sublingual dose one subject experienced bradycardia which occurred while the subject was supine. Overall then, these adverse events raise concern about the use of this drug even when administered as low single doses based on what is seen with the administration of the drug in healthy subjects.

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/s/

Raman Baweja
6/10/2008 01:50:16 PM
BIOPHARMACEUTICS

OCP secondary reviewer's memo to file

From: John Duan, Ph.D., Acting Team Leader, DCP1, OCP

Through: Mehul Mehta, Ph.D., Division Director, DCP1, OCP
Ramana Uppoor Ph.D., Division Deputy Director, DCP1, OCP

To: File NDA 22-117, Asenapine

Re: Review amendment by Ronald Kavanagh, Pharm. D., Ph.D.

1. Background

Asenapine NDA is proposed for the treatment of schizophrenia or acute episodes of bipolar I disorder. The original clinical pharmacology review by Dr. Kavanagh was signed off on May 15, 2008. After the completion of the review, Dr. Kavanagh changed his recommendation to "not approvable", which is the subject of his review amendment.

Since he has broad knowledge and interest and thus the scope of his review are beyond the normal range of regular Clinical Pharmacology review, I do not think I am qualified to make appropriate judgment on the issues Dr. Kavanagh has raised. This memo will first briefly summarize his concerns and comment on these issues divided into several categories.

2. A brief summary of issues Dr. Kavanagh has raised

A glimpse on the thought flow of Dr. Kavanagh in his review may be helpful for quicker grasping his view of points.

He started with a hypothesis that correlates the adverse events mechanistically with binding on 5HT2B receptor based on his observations; followed by introducing the signs and symptoms associated with 5HT2B agonism, he emphasized on pulmonary arterial hypertension, cardiotoxicity, connective tissue disorders, and effects on neonates; then, he restates the clinical observations emphasizing the deaths, SAE and AEs in the clinical studies to provide evidences to support his hypothesis, not only from clinical, but also from preclinical data (especially for neonatal risks and bone remodeling); after that, structure-activity relationship is sought to further expand his hypothesis; finally, he puts his concerns in the context of broader picture addressing implications of his hypothesis on other drugs.

Following is a list of his major concerns.

1. Serious cardiovascular toxicities including death due to pulmonary arterial hypertension, direct and indirect effects on the myocardium, and (likely via indirect) effects on platelet aggregation.

2. Pulmonary arterial hypertension in neonates, resulting in death, maiming of children, and infant death via breast feeding by mothers taking drug postnatally.
3. Bone remodeling and ossification from Pharm/Tox data concerning the effects in pregnancy, growing children, and in other populations where bone remodeling is an issue, e.g. elderly women and renal failure patients.
4. Other connective tissue disorders, such as hernias and rupture of tendons.
5. Increase in motor activity from animal studies concerning that could induce prescribers to inappropriately increase the dose, which would increase the risk of chronic cardiopulmonary toxicity.
6. Possible risk of aplastic anemia due to agranulocytosis.
7. Effects on platelet aggregation and strokes.
8. Sudden death without warning in otherwise young healthy individuals due to arrhythmias or strokes with symptoms misattributed to something else such as orthostatic hypotension.
9. Likely cumulative serious cardiovascular toxicities resulting in Phen-Fen type toxicities especially when dosed for over a year.

Based on these concerns, Dr. Kavanagh concludes that asenapine is less safe than competing agents and offers few if any advantages. He indicates that asenapine "is unacceptably dangerous at this time" and he also mentions: "there was inadequate information submitted to assess safety."

In addition, Dr. Kavanagh believes that the entire development program of asenapine appears designed to minimize detection and quantification of risks and thereby precludes his ability to write appropriate labeling. He also believes that in several instances the sponsors' actions were unlawful and must be reported to the criminal investigators.

Therefore, he recommends that N22-117 submitted on August 30, 2007 not be approved, other drugs and drug classes be re-evaluated and the safety issue be communicated to the public. He also recommends criminal investigation of individuals in various companies and organizations for failure to report deaths, attempting to mislead reviewers. He made a formal request for such investigation.

3. Comments

Dr. Kavanagh's comments, recommendations and requests can be divided into following categories.

First of all, clinical safety and efficacy, such as cardiovascular toxicities, are his major concerns. I am not qualified to make judgments and comments on these issues.

Secondly, preclinical concerns including receptor binding activity, bone remodeling and motor activity are closely related to clinical safety issues. I am not qualified to make judgments and comments on these issues.

Thirdly, structure-activity relationship is a prosperous field in chemistry. Expert judgments on this are needed.

Fourthly, legal issues such as request of criminal investigation are unusual items in Clinical Pharmacology review. Dr. Kavanagh insists on putting it in the review, although I am not sure whether it is the right procedure to follow.

Lastly, he restates the comments from his original review regarding clinical pharmacology issues although they are not the focus of this review amendment. It is not necessary for me to reevaluate the studies submitted in the original NDA as the review memo from Team leader Dr. Raman Baweja have already made the relevant conclusions (please see the memo from Dr. Baweja).

In a word, this review amendment concentrates on the clinical safety issues, in a manner out of the range of regular Clinical Pharmacology review and beyond my qualification for a secondary review.

Recommendations

Due to the range beyond regular Clinical Pharmacology review and comprehensive nature of this review amendment, I am not qualified to make judgments and comments.

The clinical, pharm/tox, and chemistry reviewers should evaluate and consider Dr. Kavanagh's comments and recommendations.

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/s/

John Duan
6/20/2008 04:28:07 PM
BIOPHARMACEUTICS

Mehul Mehta
6/20/2008 04:34:19 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA 22117	**Sponsor : Organon USA**
Drug: Asenapine (ORG5222)	
Formulation:	**Sublingual Tablets**
Proposed Indication:	**Schizophrenia** **Acute Mania Associated w/Bipolar Disorder**
Correspondence Date:	July 25, 2008 September 4, 2008 September 23, 2008
Reviewer:	Andre Jackson

Review History of Additional Plasma Metabolic Profile Data Submitted by the Firm

HISTORY

The firm submitted a letter on July 25th 2008 making the following points related to the clarification of the metabolite profile for Asenapine (see Appendix I).

- Nearly 50% of the drug-related material in human plasma has been unequivocally identified and/or quantified by LC-MS/MS.
- The remaining radioactivity (~50%) corresponds to at least 15 different very polar peaks, none of which represent more than 6% of the plasma radiocarbon profile.
- A significant percentage (~71%) of the excreted radioactivity has been characterized by LC-MS.

The FDA responded to that July 25th correspondence with comments in the format of a review (see Appendix II).

The amount of information presented by the firm related to metabolite analysis required an in depth re-analysis of all submitted data which was completed and is presented in Appendix III.

Questions were sent to the firm on September 3, 2008 seeking further clarification (see Appendix IV).

The firm's response is presented in Appendix V.

The firm's response response to FDA questions is presented in Appendix VI.

Information presented at the internal meeting on September 15, 2008 (see Appendix VII).

The firm's final response and data summary are presented in Appendix VIII.

TABLE OF CONTENTS

OVERALL COMMENT:

The metabolite data presented by the firm is acceptable to OCP and has been included in the label text.

OCP LABEL

Metabolism and Elimination

In a mass balance study about 50% of the circulating species in plasma have been identified and they are asenapine-N-glucuronide (34%), N-desmethylasenapine (5%), N-desmethylasenapine N-carbamoyl glucuronide (7%) and unchanged asenapine (4%). There are other non-identified metabolites which account for 32% of the plasma circulating species.

SIGNATURES

Andre Jackson_____

RD/FT Initialed by Raymond Baweja, Ph.D.

Team Leader_____

Cc-NDA 22117, HFD-860(Jackson, Baweja,Mehta), Central Documents Room(Biopharm-CDR)
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APPENDIX 1 July 25th 2008 LETTER FROM FIRM

Nearly 50% of the drug-related material in human plasma has been unequivocally identified and/or quantified by LC-MS/MS. The remaining radioactivity (~50%) corresponds to at least 15 different very polar peaks, none of which represent more than 6% of the plasma radiocarbon profile. Metabolites eluting in this region have been characterized by LC-MS and correspond mostly to Phase II (sulfate, glucuronide and methylated) products. Overall more than 70% of circulating radioactivity is associated with conjugated metabolites. In addition, it should be noted that a significant percentage (~71%) of the excreted radioactivity has been characterized by LC-MS. Given the well-characterized biotransformation pathways for asenapine in the mouse, rat, rabbit, and dog, we believe that we have adequately exposed non-clinical safety species to all relevant human metabolites. A more detailed discussion of these points can be found below.

Metabolite profiling was studied in human volunteers using state-of-the-art LC-MS, LC-MS/MS and liquid scintillation techniques. All samples were derived from four healthy male subjects who had received a single radiocarbon dose (10 mg) after having been previously administered unlabeled drug for 10 days.

- The most representative profile which illustrates total exposure to plasma metabolites and unchanged drug comes from a pooled (1.5-12 hr) plasma sample. Referring to the radiochromatogram (**Figure 1**), we can see that asenapine (PC20) is extensively metabolized. While >9% the circulating radioactivity can be accounted for by asenapine and the desmethyl metabolite (PC19), an additional 40.5% is associated with asenapine N^+-glucuronide (PC12/13; 33.6%) and N-desmethylasenapine N-carbamoyl glucuronide (PC16; 6.9%). The N+-glucuronide, N-desmethylasenapine and asenapine-11-hydroxysulfate metabolites have also been quantified by validated bioanalytical assays in clinical PK trial 25546 (included in the dossier). These results reproduced the ratios found in the human ^{14}C-AME study. With the exception of the N-carbamoyl glucuronide, these metabolites have also been tested pharmacologically and showed decreased activity and/or no entrance into the brain.

- The remaining radioactivity which elutes between 13 and 25 min (**Figure 1**) corresponds to at least 15 different peaks, none of which represent more than 6% of the plasma radioprofile. As determined in urine by LC-MS, most peaks eluting before PC12/13 consisted of more than 3 metabolites, resulting in the characterization of greater than 40 metabolites. It is important to note that the majority (**Table 1**) of these metabolites correspond to phenolic sulfate and/or glucuronide conjugates and as per FDA guidance most likely pose little safety concern. The remaining unconjugated metabolites result from 10- and/or 11-hydroxylation and N-oxidation and represent no obvious structural alert. Each of these minor metabolites in turn have been detected in at least one preclinical safety species.

- In addition to very acceptable total recovery (>90%) of the radioactive dose within 7 days, a significant percentage (~71%) of the excreted radioactivity has been characterized by LC-MS. There were no major human-specific biotransformation pathways identified in plasma, urine and feces (**Figure 2**).

In summary, a majority (>70%) of the drug-related material in human plasma following sublingual administration of asenapine is associated with conjugated metabolites. Other than desmethyl-asenapine, for which adequate exposure multiples have been established with validated LC-MS/MS methods, any other unconjugated metabolite likely represents less than 6.0% of the total plasma profile. The known metabolites of asenapine have much reduced affinity for CNS receptors considered to be involved in mediating the pharmacological effects of asenapine or have low brain penetration and are thus unlikely to contribute towards the pharmacodynamic properties of asenapine. In addition, all metabolic pathways as observed in human have been observed in preclinical species. In conclusion, given the well-characterized metabolic pathways and their respective identified metabolites there is strong evidence that we have adequately exposed non-clinical safety species to all relevant human metabolites.

Figure 1. Radiochromatographic profile of a pooled (1.5 – 12hr) plasma sample following administration of ^{14}C-asenapine to 4 healthy male subjects.

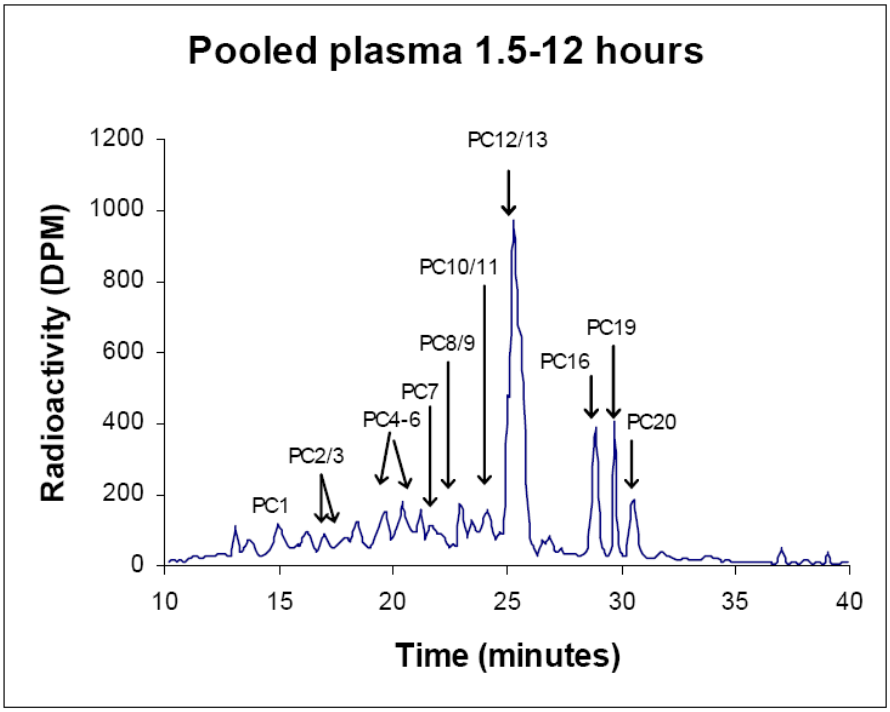
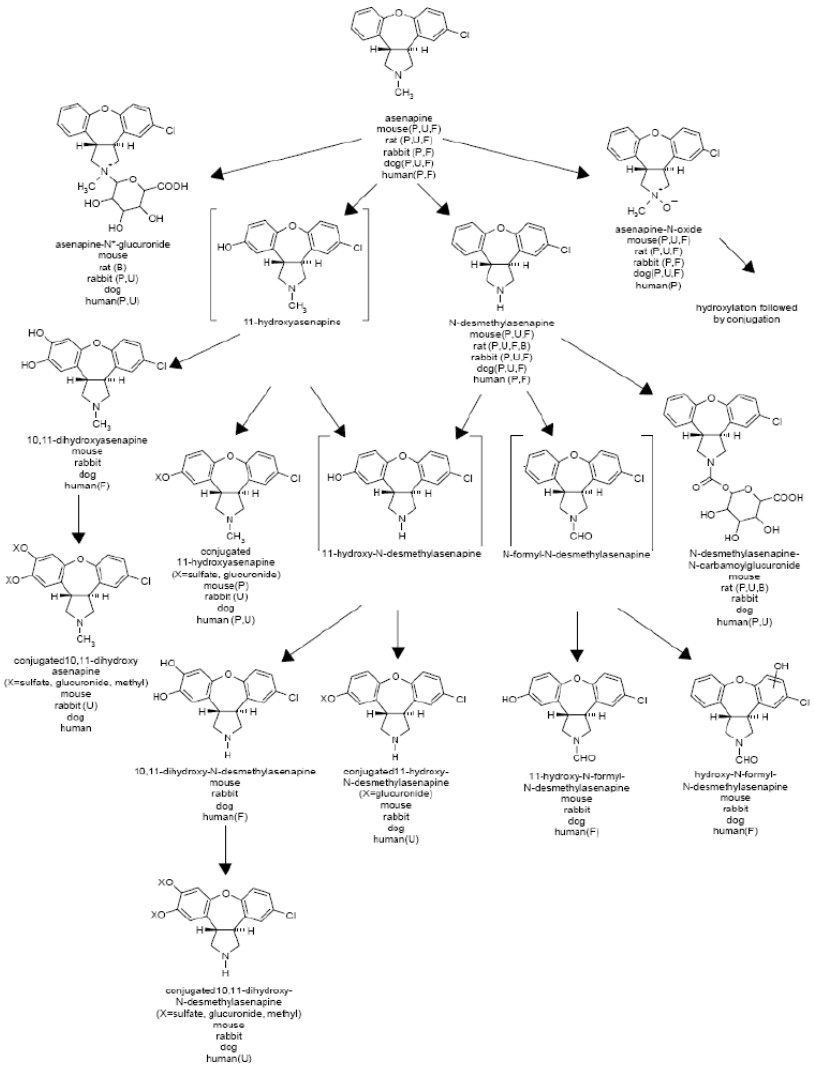


Figure 2. Major biotransformation pathways of asenapine in human and preclinical species



P= plasma, U = urine, F = feces, B = bile

Table 1: Summary of Radioactive peaks found in human plasma and urine after sublingual administration of asenapine (Org 5222 plus [^{14}C]-Org 5222) to male volunteers.

Peak Number (human)	Identity	Retention time	% radioactivity of run, corrected for noise	Presence verified in at least one preclinical species (excreta or plasma)
PC1	Unknown	15.2	3.6	+
PC2 PC3	Methyl- and glucuronide of the 10,11 dihydroxy of N-desmethylasenapine, with the positions of the conjugates 10,11 and reverse	16.6-17.6	5.1	+
PC4-PC6	Methyl and sulfate of the 10,11 dihydroxy of the N-desmethylasenapine, with the positions of the conjugates 10,11 and reverse; 11-O-glucuronide of asenapine and of N-desmethylasenapine; other conjugates (sulfates/glucuronides)	18.5-22.0	13.3	+
PC7	Unknown	22.7	2.7	+
PC8-9	Sulfates and glucuronides	23.3-23.6	5.9	+
PC10 PC11	11-O-sulfate asenapine; other sulfates and glucuronides of the N-oxide asenapine	25.1 25.6	7.4	+
PC12 PC13	N+ glucuronide	26.8 27.2	33.6	+
PC16	N-desmethylasenapine N-carbamoyl glucuronide	28.7	6.9	+
PC19	N-desmethylasenapine	29.7	5.1	+
PC20	Asenapine	30.2	4.3	+

APPENDIX II- FDA RESPONSE TO FIRM JULY 25TH LETTER

TITLE RESPONSE TO FIRM JULY 25, 2008 LETTER
CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA	**22117**
Sponsor :	**Organon USA**
Drug:	**Asenapine (ORG5222)**
Formulation:	**Sublingual Tablets**
Proposed Indication:	**Schizophrenia** **Acute Mania Associated w/Bipolar Disorder**
Correspondence Date:	July 25, 2008
Reviewer:	Andre Jackson

Review of Additional Plasma Metabolic Profile Data Submitted by the Firm

The firm has submitted a document with additional information related to the metabolite issues. This review will only focus on metabolite identification and quantitation in plasma. Feces and urine will not be discussed.

Firm Comment 1.

Nearly 50% of the drug-related material in human plasma has been unequivocally identified and/or quantified by LC-MS/MS. The remaining radioactivity (~50%) corresponds to at least 15 different very polar peaks, none of which represent more than 6% of the plasma radiocarbon profile.

FDA Reply:

OCP agrees that, "nearly 50% of the drug-related material in human plasma has been unequivocally identified and that The remaining radioactivity (~50%) corresponds to at least 15 different very polar peaks, none of which represent more than 6% of the plasma radiocarbon profile." However OCP does not agree with the use of the word quantified. The profiles were a mixture of plasma samples from (1.5-12hrs) and the firm has stated in (see Module 5.3.3.1, CTR 25532,Table 4, page 31), "At a later stage the remainder of the plasma samples 1.5-12h of all four subjects was pooled. The same was done for the 1h plasma sample. Both pooled samples were analyzed on HPLC system 2. The pooling of these samples was not performed quantitatively and therefore these chromatograms were only evaluated in a qualitative way." What is being reported is a mixture of times so one can not be sure of how much is parent and how much are metabolites. The statement "6% of the plasma radiocarbon profile" is non-informative related to the parent drug.

Firm Comment 2.

Metabolites eluting in this region have been characterized by LC-MS and correspond mostly to Phase II (sulfate, glucuronide and methylated) products. Overall more than 70% of circulating radioactivity is associated with conjugated metabolites.

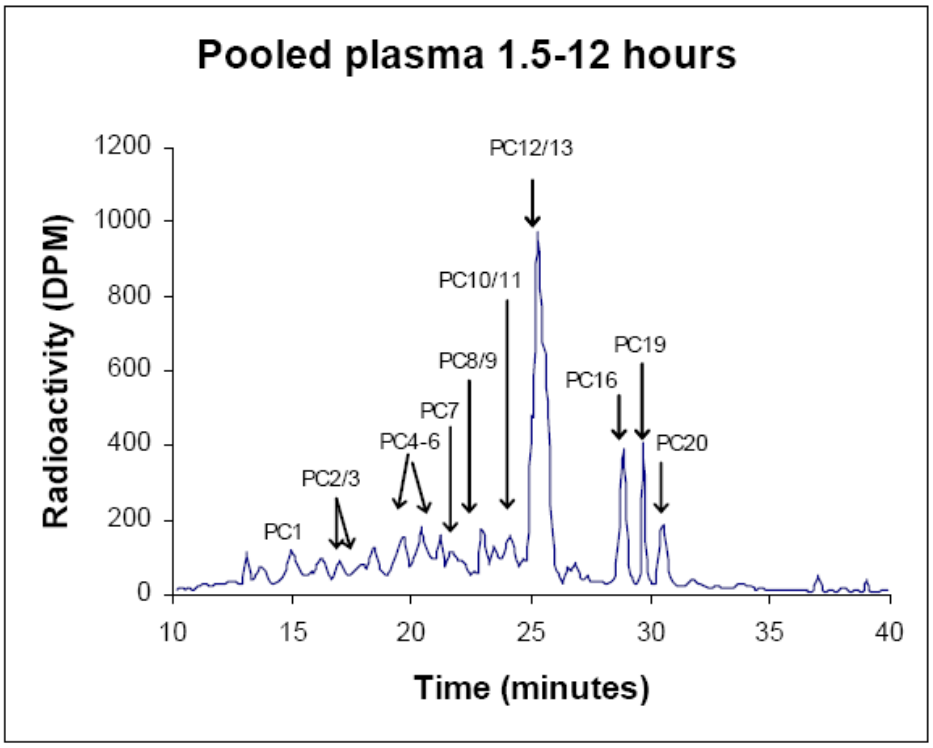
FDA Reply:

OCP agrees with this statement but it is **not quantitative** relative to the parent and the major metabolites and the time course is unknown.

Firm Comment 3.

• The most representative profile which illustrates total exposure to plasma metabolites and unchanged drug comes from a pooled (1.5-12 hr) plasma sample. Referring to the radiochromatogram (**Figure 1**), we can see that asenapine (PC20) is extensively metabolized. While >9% the circulating radioactivity can be accounted for by asenapine and the desmethyl metabolite (PC19), an additional 40.5% is associated with asenapine N^+-glucuronide (PC12/13; 33.6%) and N-desmethylasenapine N-carbamoyl glucuronide (PC16; 6.9%). The N+-glucuronide, N-desmethylasenapine and asenapine-11-hydroxysulfate metabolites have also been quantified by validated bioanalytical assays in clinical PK trial 25546 (included in the dossier). These results reproduced the ratios found in the human ^{14}C-AME study. With the exception of the N-carbamoyl glucuronide, these metabolites have also been tested pharmacologically and showed decreased activity and/or no entrance into the brain.
• The remaining radioactivity which elutes between 13 and 25 min (**Figure 1**) corresponds to at least 15 different peaks, none of which represent more than 6% of the plasma radioprofile.

Figure 1. Radiochromatographic profile of a pooled (1.5 – 12hr) plasma sample following administration of ^{14}C-asenapine to 4 healthy male subjects.



FDA Reply:

OCP agrees but there is no quantitation of the major species other than the desmethyl metabolite (PC19) and the N-oxide. What is required is a quantitative time course for the identified species (i.e., asenapine, desmethyl metabolite (PC19), asenapine N+-glucuronide, N-oxide and N-desmethylasenapine N-carbamoyl glucuronide as a function of time. This will allow for a quatitative assessment of the contribution of each species which is not possible from pooled plasma samples.

Overall FDA Comment:

The accepted good scientific standard for NME metabolites adhered to by the FDA is that a quantitative assessement of metabolites as a function of time is done so that any relevant exposure response can be determined. For Asenepine only a total quantitation for pooled samples (2-12 hr) but not a true metabolic profile for parent and major metabolites has not been done over time.

SIGNATURES

Andre Jackson_____

RD/FT Initialed by Raymond Baweja, Ph.D.
Team Leader_____

Cc-NDA 22117, HFD-860(Jackson, Baweja,Mehta), Central Documents Room(Biopharm-CDR)
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APPENDIX III-IN DEPTH RE-ANALYSIS OF ALL SUBMITTED DATA

TITLE: INITIAL REVIEW ASENAPINE DEFINING STUDY INFORMATION PRESENTED IN THE NDA DOSING

TABLE 1. Dosing schedule1: SOURCE(Module 4.2.2.5, Report INT00003211)),PAGE 2/94

Day-1	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10
Plac.	0.3 mg	1 mg	3 mg	5 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg+[14C]

FDA COMMENT :DOSING SCHEDULE-INFORMATION ONLY

HPLC SYSTEMS

HPLC system 1-SOURCE(Module 4.2.2.5, Report INT00003211)),PAGE 23/94

Radioactivity in the HPLC effluent was determined on-line (urine and feces (partly)) using a flow-through detector or off-line by the collection of fractions (plasma and feces (partly)) followed by Solid Scintillation Counting (SSC). Radioactive peaks in the HPLC metabolite profiles were assigned by visual inspection.

Gradient : 5% B isocratic during 5 minutes
5 to 35% B in 30 minutes (linear)
35 to 90% B in 20 minutes (linear)
90 to 100% B in 1 minutes (linear)
100% B isocratic during 9 minutes
100% to 5% B in 5 minutes (linear)

HPLC system 2(Module 4.2.2.5, Report INT00003211)),PAGE 24/94

Gradient : 10% B isocratic during 3 minutes
10 to 40% B in 17 minutes (linear)
40 to 90% B in 30 minutes (linear)
90 to 95% B in 1 minute (linear)
95% B isocratic during 3 minutes or 8 minutes
95 to 10% B in 1 minute (linear)

Radioactive peaks in the HPLC profiles were numbered assigned on the basis of retention time.

FDA COMMENT : The systems will have different elution patterns. Based upon information from the firm only HPLC **System 1 gives a quantitative analysis. On the other hand, "**HPLC system 2 was considered to achieve the best separation and ended up being used for all (plasma, urine and fecal) human samples so that direct comparison of radiochromatographic profiles among these matrices can be made. In addition to the qualitative information (correspondence with standard retention times and mass spectral data) embedded in these analyses, quantitative determinations from the radioactivity contained within individual peaks and total radioactivity eluted during the run were also made."

METABOLITE PROFILING

METABOLITE PROFILING-SOURCE(Module 4.2.2.5, Report INT00003211)),PAGE 2/94

Blood samples for the determination of the concentration of radioactivity in plasma (coded B)were taken from day 10 onwards at 0 (=pre-dose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60,72 h post dosing and blood samples for the metabolite profiling (coded C) were taken at day 1 at 0 h (=pre-dose (just before the first dose of asenapine)) and on day 10 at 1, 1.5, 2, 4, 8, 12 and 24 h post dosing.

They were extracted after which the metabolite profiles of [$_{14}$C]-asenapine in plasma, urine and feces samples were determined by HPLC analysis using HPLC system 1 and 2 followed by Liquid Scintillation Counting (LSC) or Solid Scintillation counting (SSC). Afterwards metabolites of asenapine were isolated from plasma, urine and feces. Identification of the isolated metabolites was performed by MS and/or NMR

(Module 4.2.2.5, Report INT00003211)),PAGE 31/94

At first plasma samples (1.5-12h) were measured per time point per subject on HPLC system 1. These data are used to give quantitative data. At a later stage the remainder of the plasma samples 1.5-12h of all four subjects was pooled. The same was done for the 1h plasma sample. Both pooled samples were analyzed on HPLC system 2. The pooling of these samples was not performed quantitatively and therefore these chromatograms were only evaluated in a qualitative way.

FDA COMMENT : These statements by the firm are confusing since they are using HLPC system 2 to profile but clearly state **“** The same was done for the 1h plasma sample. Both pooled samples were analyzed on HPLC system 2. The pooling of these samples was not performed quantitatively and therefore these chromatograms were only evaluated in a qualitative way.” OCP has interpreted this to mean that for HPLC system 2 only radioactivity was quantified.

RADIOACTIVE RECOVERY

Table 2. Radioactive recovery.
SOURCE Module 4.2.2.5, Report INT00003211)) PAGE 3/94

	Excreted Radioactivity (% of the radioactive dose)					
	Subject 1	Subject 2	Subject 3[a]	Subject 4	Mean ± SD	Mean ± SD (excluding subject 3)[a]
Urine	50.7	58.8	37.0[a]	49.0	48.9 ± 9.0	52.8 ± 5.3
Feces	36.2	37.1	34.8	47.0	38.8 ± 5.6	40.1 ± 6.0
Total	86.9	95.9	71.8	96.0	87.7 ± 11.4	93.0 ± 5.2

a: Due to a technical error (most probably loss of urine between 0-12h) the urine value of subject 3 was lower than of the other 3 subjects.

FDA COMMENT : The table clearly shows the percentage of radioactivity (ie mass balance for asenapine recovered ~90%).

RAW DATA USED FOR PLASMA PROFILES IN FIGURE 1

Table 3. Concentrations of individual peaks in HPLC chromatograms (HPLC system 1) of plasma samples per time point of male human volunteers after sublingual administration of asenapine (Org 5222 plus [$_{14}$C]-Org 5222) SOURCE Module 4.2.2.5, Report INT00003211)) PAGE 47/94

		Peaks (ng equivalents·mL^{-1} plasma)									
Peak no	Mean retention time (minutes)	Subject 1					Subject 2				
		1.5 h	2.0 h	4.0 h	8.0 h	12.0 h	1.5h	2.0 h	4.0 h	8.0 h	12.0 h
10	38.7	-	-	-	-	-	2.0	-	-	-	-
11	40.8	-	-	6.3	3.5	-	13.2	12.5	10.1	-	-
13	44.6	-	-	2.6	2.9	-	1.9	-	-	-	-
15	47.5	2.2	2.2	-	-	-	2.8	3.1	-	-	-

		Peaks (ng equivalents·mL^{-1} plasma)									
Peak no	Mean retention time (minutes)	Subject 3					Subject 4				
		1.5 h	2.0 h	4.0 h	8.0 h	12.0 h	1.5h	2.0 h	4.0 h	8.0 h	12.0 h
10	38.7	-	-	-	-	-	4.5	2.3	-	-	-
11	40.8	7.6	10.7	15.9	10.5	3.4	12.0	11.8	9.3	6.7	-
13	44.6	-	-	-	-	-	3.8	3.0	3.3	-	-
15	47.5	3.8	-	-	-	-	2.1	1.4	3.0	-	-

Peak 10 contains at least the sulfate of the 11-hydroxy of asenapine.
Peak 11 is identified as the quaternary glucuronide of asenapine
Peak 13 is identified as the carbamate glucuronide of N(2)-des-methyl of asenapine
Peak 15 is identified as asenapine
- Not detected

FDA COMMENT: The data in Table 3 is incomplete however the firm has used this data to construct Figure 1 below which is **misleading** since it is composed of the observed values from Table 3 which clearly show that none of the subjects has a complete profile not even for peak # 15 asenapine. They have only connected the dots with the limited data collected. OCP could not locate data that would support the graph past 12 hrs as shown in Table 3. The firm needs to give the location of that data.

REPRESENTATIVE MEAN PLASMA GRAPH HPLC SYSTEM 1

INDIVIDUAL ASSAY HPLC SYSTEM 1 –SOURCE (Module 4.2.2.5, Report INT00003211)),PAGE 3/94

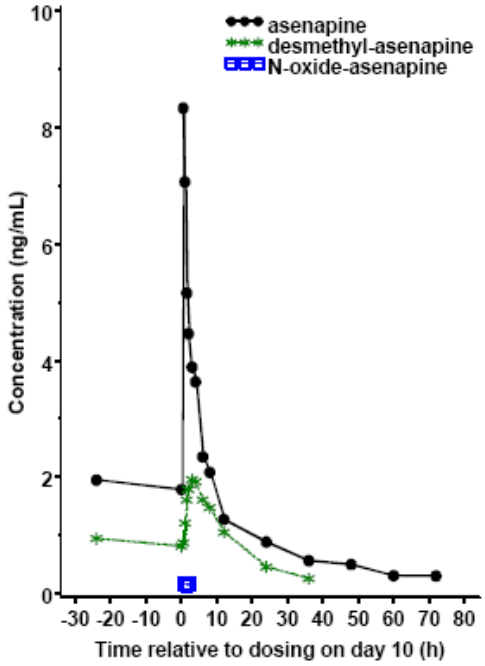
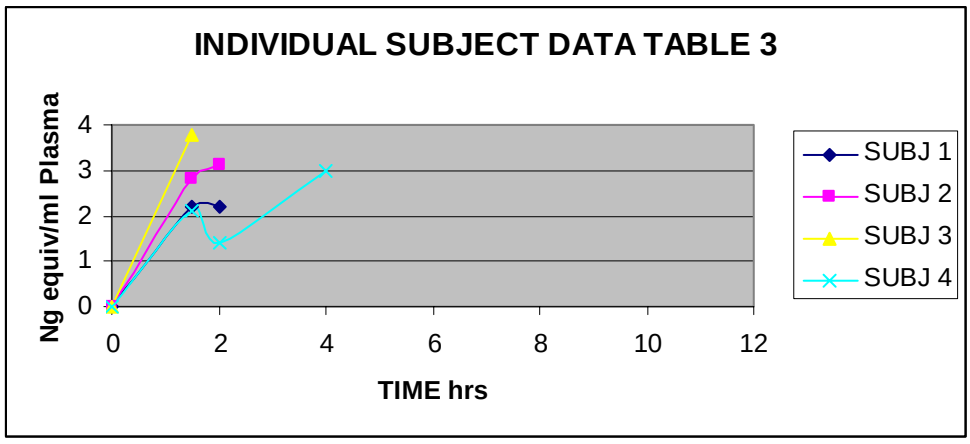


Figure 1. Profile obtained from HPLC system #1.



FDA COMMENT-See comments on Table 3.

TOTAL RADIOACTIVITY IN PLASMA

Figure 2. Profile obtained for total radioactivity. SOURCE Module 4.2.2.5, Report INT00003211)) PAGE 46/94

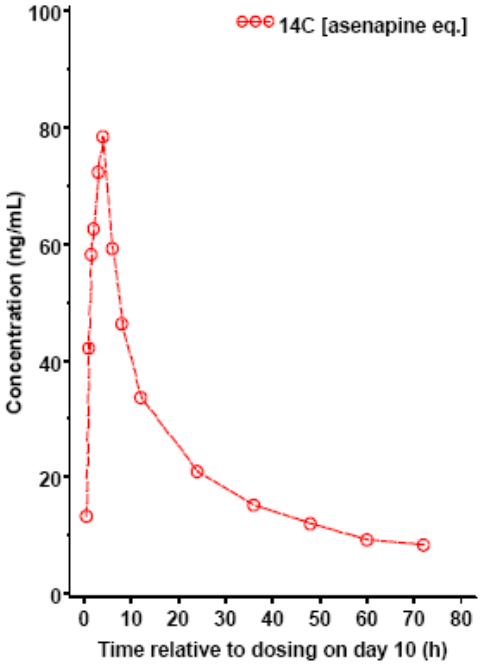


Table 4 Concentration of radioactivity in plasma samples after sublingual administration of asenapine (Org 5222 plus [14C]-Org 5222) to male human volunteers

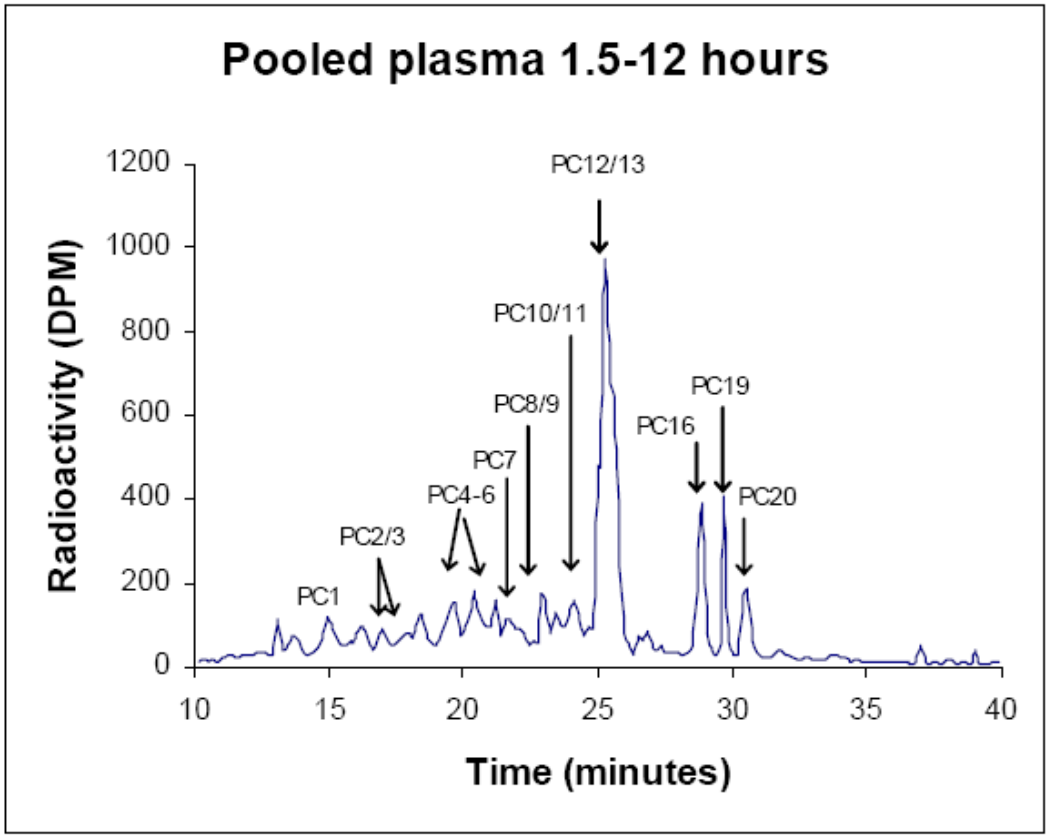
	Plasma Radioactivity (ng equivalents.mL-1)													
time (h)	0.5	1.0	1.5	2.0	3.0	4.0	6.0	8.0	12	24	36	48	60	72
Subject 1	6.68	13.7	23.6	39.8	65.7	69.7	60.5	46.9	36.1	22.9	16.2	10.9	9.01	7.00
Subject 2	19.6	53.6	64.7	64.0	61.7	64.7	43.7	30.9	27.0	16.2	13.0	10.2	7.28	8.35
Subject 3	15.1	45.2	75.3	77.4	84.4	91.4	77.1	62.1	40.9	24.6	18.1	16.2	13.5	11.3
Subject 4	11.7	55.6	69.2	68.8	77.1	87.8	55.4	45.0	30.5	19.9	13.4	10.7	7.03	6.69
Mean	**13.3**	**42.0**	**58.2**	**62.5**	**72.2**	**78.4**	**59.2**	**46.2**	**33.6**	**20.9**	**15.2**	**12.0**	**9.2**	**8.3**
SDa	5.5	19.4	23.5	16.1	10.4	13.2	13.9	12.8	6.1	3.7	2.4	2.8	3.0	2.1

a SD = standard deviation

FDA COMMENT : Figure 2 is consistent with the data in Table 4, however this is **only total radioactivity data as a function of time**. **There is no information on individual metabolites.**

REPRESENTATIVE CHROMATOGRAM

Figure 3. Radiochromatographic profile of a pooled (1.5 – 12hr) plasma sample following administration of ^{14}C-asenapine to 4 healthy male subjects. HPLC SYSTEM 2. SOURCE POOLED ASSAY 1.5-12HR SUBMITTED JULY 25 2008



FDA COMMENT : Chromatogram is acceptable to OCP.

PEAKS IDENTIFIED BASED UPON CHROMATOGRAM IN FIGURE 3.

TABLE 5. Metabolites identified in plasma and urine.SUBMITTED BY THE FIRM DATE: JULY 25 2008 HPLC SYSTEM 2

Peak Number (human)	Identity	Retention time	% radioactivity of run, corrected for noise	Presence verified in at least one preclinical species (excreta or plasma)
PC1	Unknown	15.2	3.6	+
PC2 PC3	Methyl- and glucuronide of the 10,11 dihydroxy of N-desmethylasenapine, with the positions of the conjugates 10,11 and reverse	16.6-17.6	5.1	+
PC4-PC6	Methyl and sulfate of the 10,11 dihydroxy of the N-desmethylasenapine, with the positions of the conjugates 10,11 and reverse; 11-O-glucuronide of asenapine and of N-desmethylasenapine; other conjugates (sulfates/glucuronides)	18.5-22.0	13.3	+
PC7	Unknown	22.7	2.7	+
PC8-9	Sulfates and glucuronides	23.3-23.6	5.9	+
PC10 *	11-O-sulfate asenapine;	25.1	[7.4]	+
PC11 *	other sulfates and glucuronides of the N-oxide asenapine	25.6		
PC12 *	N+ glucuronide	26.8	[33.6]	+
PC13 *		27.2		
PC16 *	N-desmethylasenapine N-carbamoyl glucuronide	28.7	[6.9]	+
PC19 *	N-desmethylasenapine	29.7	[5.1]	+
PC20 *	Asenapine	30.2	[4.3]	+

Sum of plasma metabolites in brackets=57.3%

PEAKS IDENTIFIED BASED UPON CHROMATOGRAM IN FIGURE 3.

TABLE 6. Metabolites identified in plasma and urine. TABLE SUBMITTED BY THE FIRM IN SEPTEMBER 2008 TO MY REQUEST FOR INFORMATION HPLC SYSTEM 2

Peak	**Name**	**% of total radioactivity**
PC2/3	Methyl- and glucuronide of the 10,11 dihydroxy of N-desmethylasenapine, with the positions of the conjugates 10,11 and reverse; mono conjugates of 10,11-OH-N-desmethylasenapine	5.1
PC4-6	Methyl and sulfate of the 10,11 dihydroxy of the N-desmethylasenapine, with the positions of the conjugates 10,11 and reverse; 11-O-glucuronide of asenapine and of N-desmethylasenapine; other conjugates (sulfates/glucuronides)	13.3
PC8-9	Sulfates and glucuronides	5.9
PC10	11-O-sulfate asenapine; other sulfates and glucuronides of the N-oxide	7.4
PC11	asenapine	
PC12	N+ glucuronide	33.6
PC13		
PC16	N-desmethylasenapine N-carbamoyl glucuronide	6.9
PC19	N-desmethylasenapine	5.1
PC20	Asenapine	4.3
SUM		**81.6**

Note: “BOLDED” metabolites have been unequivocally identified.
Please note that the total for those bolded the PC10 and PC 11 have been excluded so the total now becomes 57.3%-7.4%=49.9%. Nonbolded metabolites have not been found in plasma.

FDA COMMENT ON Tables 5-7 and Figure 3. OCP agrees with Figure 3 for the chromatogram. However, the firm changes the metabolites which they believe they can identify between the July and September submissions. In July P10 and P11 were included whereas in September they were excluded. This is very inconsistent and not explained by the firm. Based upon the firms statements related to the performance of HPLC System2, the results are at best semi-quantitative. Summed identifiable material in plasma for AUC 1.5-12h is either 57.3% or 49.9%. Most notable is that neither the 57.3% or 49.9% values is defining a profile only a 1.5 to 12 AUC window for a drug with a half-life of 27 hrs.

PRESENCE OF QUANTIFIED CHROMATOGRAM PEAKS AT SAMPLED TIMES

SOURCE Module 4.2.2.5, Report INT00003211)) PAGE 48/94

Table 7. Peaks found in HPLC chromatograms (HPLC system 2) of the pooled plasma samples of male human volunteers after sublingual administration of asenapine (Org 5222 plus [^{14}C]-Org 5222)

Peak code	Mean retention time (minutes)	Present yes (+)/no (-)	
		Plasma 1h	Plasma 1.5-12h
[a]	16.8	+	-
[a]	20.1	+	-
PC10/11	22.4	+	-
[a]	23.8	+	-
PC12/13	25.0	+	+
PC16	28.7	+	+
PC19	29.7	-	+
PC20	30.2	+	+

[a] No peak code was assigned because the linkage between the plasma, urine and feces metabolite profiles could not be made for these peaks.

PC10/11 is identified as the sulfate of the 11-hydoxy of asenapine plus some other conjugated metabolites (sulfates and glucuronides) of most probably the N(2)-oxide of asenapine.

PC12/13 is identified as the quaternary glucuronide of asenapine.

PC16 is identified as the carbamate glucuronide of the N(2)-des-methyl of asenapine.

Peak PC19 co-elutes with the N(2)-des-methyl of asenapine

Peak PC20 is identified as asenapine

FDA COMMENT-Table 7 shows the level of confusion that exists related to the time profile for asenapine and its metabolites. For example, metabolite PC10/11 is present at 1hr but is not found in the 1.5-12 hr pooled sample. On the other hand PC19 is not present at 1 hr but is present in the pooled sample from 1-5-12 hr. These results are very confusing.

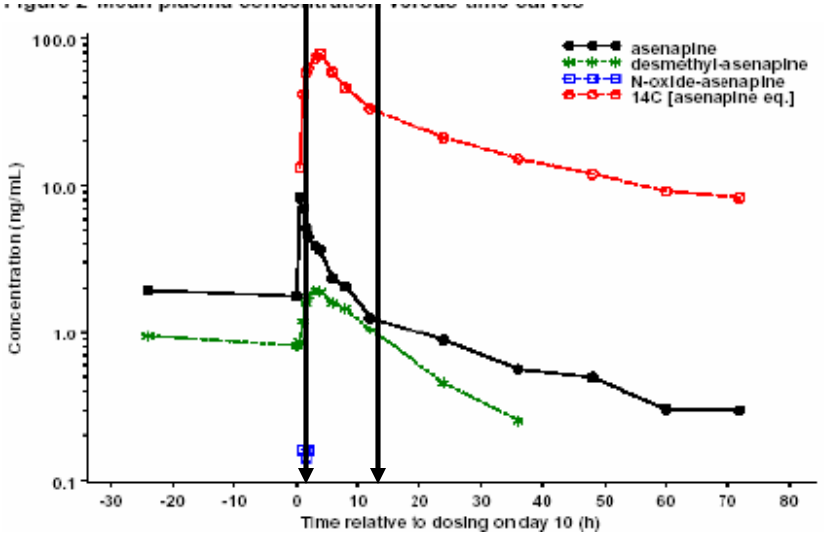


Figure 4.

1.5 -12 hrs pooled sampling time for "quantitation" of asenapine and metabolites using HPLC System 2. Source module 5.3.3.1.1 page 56

THE FIRM NEEDS TO REPEAT THE METABOLISM STUDIES WITH A QUANTITATIVE ASSAY AND COLLECT COMPLETE PROFILES.

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APPENDIX:

Results from study 25511 :
Dose-0.15 mg/BID
Cmax :0.127 ng/ml on Day 1

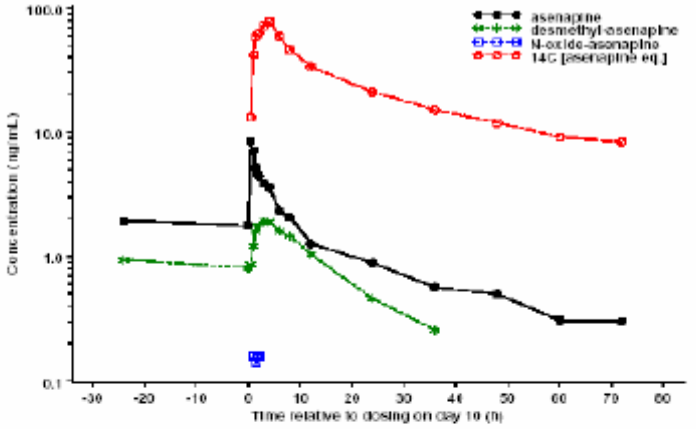
APPENDIX IV: MEAN ORG 5222 PLASMA LEVELS (pg/ml)

Table 1: Mean Org 5222 concentrations (pg/ml) in subjects receiving 150 µg sublingual Org 5222 twice daily for 6.5 days (Block 1)

Day	Protocol Time (h)	Mean	SD	N	ND	NS
1	0	-	-	0	6	0
1	0.083	-	-	0	6	0
1	0.25	32.41	10.32	4	2	0
1	0.5	74.78	22.79	5	1	0
1	0.75	92.86	41.47	6	0	0
1	1	94.08	33.12	6	0	0
1	1.5	127.89	40.81	6	0	0
1	2	94.61	38.00	6	0	0
1	3	89.15	19.68	6	0	0
1	4	71.98	14.66	6	0	0
1	6	49.79	7.20	6	0	0
1	8	32.33	6.32	6	0	0
1	12	23.58	4.99	2	4	0
3	0	41.93	10.11	5	0	1
5	0	48.47	4.32	5	0	1
7	0	44.64	13.83	5	0	1
7	0.083	48.81	15.76	5	0	1
7	0.25	86.88	29.75	5	0	1
7	0.5	134.29	35.89	5	0	1
7	0.75	134.28	42.00	5	0	1
7	1	150.40	57.08	5	0	1
7	1.5	152.62	49.99	5	0	1
7	2	129.30	32.88	5	0	1
7	3	109.48	34.48	5	0	1
7	4	98.97	33.56	5	0	1
7	6	66.17	21.99	5	0	1
7	8	46.50	6.74	5	0	1
7	12	34.42	9.99	5	0	1
8	24	24.54	-	1	4	1
8	36	-	-	0	5	1
9	48	-	-	0	5	1

Study 25532
Dose-0.27 mg
Cmax :78 ng/ml on Day 1

[$_{14}$C]-labeled asenapine was provided to PBR as an alcohol containing solution. The responsible pharmacist was to drop a volume corresponding to 50 µCi and 0.27 mg asenapine on a 10 mg tablet according to instructions provided by Organon. A test batch was prepared and analyzed prior to the final preparations.



A summary of the main pharmacokinetic parameters is presented in the following table.

Parameter (unit)*	^{14}C [asenapine equivalents]	asenapine	desmethyl-asenapine	N-oxide-asenapine
C_{max} (ng/mL)	78.4 (13)	8.40 (3.9)	2.07 (0.76)	0.211 (0.054)
t_{max} (h)	4.0 (1.5-4.0)	0.75 (0.5-1.0)	3.5 (2.0-4.0)	0.75 (0.50-1.50)
$t_{1/2}$ (h)	39.3 (7.6)	27.5 (5.0)	12.9 (4.5)	n.c.
AUC_{0-12h} (ng·h/mL)	n.a.	36.9 (9.7)	17.9 (6.9)	n.c.
$AUC_{0-\infty}$ (ng·h/mL)	2020 (467)	n.a.	n.a.	n.a.

Presented are median (minimum-maximum) for t_{max}; arithmetic mean (SD) for other PK parameters.
*:n=4; n.a.:Not applicable; n.c.:Not calculated.

Statistical analysis showed that plasma levels of asenapine and desmethyl-asenapine had reached steady state on the day of the radioactive dose. The plasma concentrations of ^{14}C (asenapine equivalents) greatly exceeded those of asenapine and its measured metabolites from the first time point (0.5 h) onwards. The peak concentration of ^{14}C was reached 4 h after dosing, which is later than for asenapine (0.75 h) and comparable to desmethyl-asenapine (3.5 h). These data indicate that asenapine is metabolized rapidly and that desmethyl- and N-oxide-asenapine constitute only a small fraction of the total of asenapine metabolites in plasma. The mean terminal half-life of plasma radioactivity was 39 h, which is longer than for asenapine (28 h) and desmethyl-asenapine (13 h)..

6.4 METABOLITE PROFILES

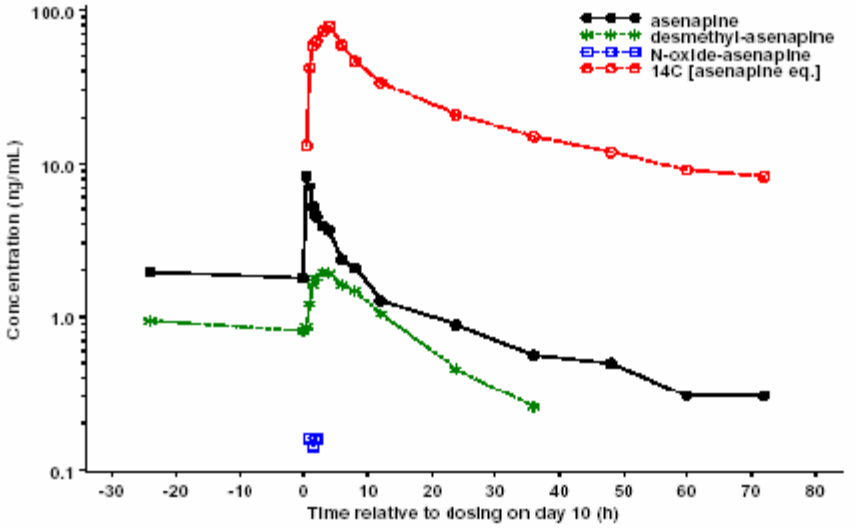
6.4.1 General

Since the resolution of the obtained metabolite signals of urine and feces samples obtained on HPLC system 1 (Section 3.3.6) was sub-optimal, the integration of the metabolite profiles appeared to be non-conclusive. The resolution on HPLC system 2 (Section 3.3.6) was much better and therefore the metabolite profiles of urine and feces, obtained with HPLC system 2 were used to give quantitative data. Indication of major or minor metabolites is done by visual inspection.

At first plasma samples (1.5-12h) were measured per time point per subject on HPLC system 1. These data are used to give quantitative data. At a later stage the remainder of the plasma samples 1.5-12h of all four subjects was pooled. The same was done for the 1h plasma sample. Both pooled samples were analyzed on HPLC system 2. The pooling of these samples was not performed quantitatively and therefore these chromatograms were only evaluated in a qualitative way.

APPENDIX IV QUESTIONS SENT TO THE FIRM

TITLE- REQUEST OF INFORMATION FROM THE FIRM
I have been reviewing your submission related to the identity of plasma metabolites and I need some clarification.
In the study Clinical Trial Report for study 25532 you produced the following graph which appears in your synopsis page 5 of 612:



A summary of the main pharmacokinetic parameters is presented in the following table.

Parameter (unit)[a]	^{14}C [asenapine equivalents]	asenapine	desmethyl-asenapine	N-oxide-asenapine
C_{max} (ng/mL)	78.4 (13)	8.40 (3.9)	2.07 (0.76)	0.211 (0.054)
t_{max} (h)	4.0 (1.5-4.0)	0.75 (0.5-1.0)	3.5 (2.0-4.0)	0.75 (0.50-1.50)
$t_{1/2}$ (h)	39.3 (7.6)	27.5 (5.0)	12.9 (4.5)	n.c.
AUC_{0-12h} (ng·h/mL)	n.a.	36.9 (9.7)	17.9 (6.9)	n.c.
$AUC_{0-\infty}$ (ng·h/mL)	2020 (467)	n.a.	n.a.	n.a.

It is not clear to me how this graph was constructed. What I would like to have from you would be an **example calculation** based upon any standard curves and dpm dated employed for all of the species represented. Please start from the raw cpm/dpm data. You can reference any data submitted in the NDA giving its location so that it can be located.

Please give all formulas. Make sure you list whether it is based upon HPLC system 1 or 2.
Please base your example only upon Cmax which would be the same procedures for the area calculation.
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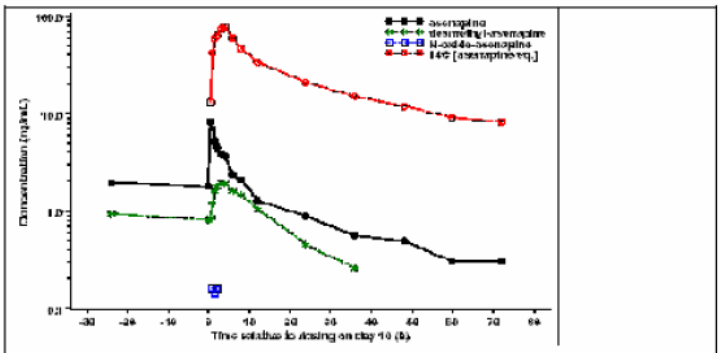
APPENDIX V FIRM'S RESPONSE TO OCP QUESTIONS

Comment 1:

I have been reviewing your submission related to the identity of plasma metabolites and I need some clarification.

In the study Clinical Trial Report for study 25532 you produced the following graph which appears in your synopsis page 5 of 612:



A summary of the main pharmacokinetic parameters is presented in the following table.

Parameter (unit)*	^{14}C [asenapine equivalents]	asenapine	desmethyl-asenapine	N-oxide-asenapine
C_{max} (ng/mL)	79.4 (13)	8.40 (3.9)	2.07 (0.76)	0.211 (0.064)
t_{max} (h)	4.0 (1.5-4.0)	0.75 (0.5-1.0)	3.5 (2.0-4.0)	0.75 (0.50-1.50)
$t_{1/2}$ (h)	39.5 (7.6)	27.5 (5.0)	12.9 (4.5)	n.c.
$AUC_{t_1-t_2}$ (ng h/mL)	n.a.	36.9 (9.7)	17.9 (6.9)	n.c.
$AUC_{0-\infty}$ (ng h/mL)	2020 (467)	n.a.	n.a.	n.a.

It is not clear to me how this graph was constructed. What I would like to have from you would be an **example calculation** based upon any standard curves and dpm dated employed for all of the species represented. Please start from the raw cpm/dpm data. You can reference any data submitted in the NDA giving its location so that it can be located.

Please give all formulas. Make sure you list whether it is based upon HPLC system 1 or 2. Please base your example only upon Cmax which would be the same procedures for the area calculation.

Response 1:

First, we would like to point out that in the human ADME study different methods have been used for: 1) determination of ^{14}C in plasma, 2) determination of asenapine, N-desmethylasenapine and asenapine N-oxide concentrations in plasma and 3) metabolite profiling. Samples for the different assessments were taken at the same time points in each subject (see Module 5.3.3.1, CTR 25532, Table 4, page 32).

The asenapine (black symbols/curve), N-desmethylasenapine (green symbols/curve) and N-oxide asenapine (blue symbols/curve) plasma concentration data as presented in this graph have been quantified bioanalytically, i.e. by means of LC-MS, as described in the bioanalytical report for this study (Module 5.3.3.1, CTR 25532, Appendix BII-1, page 125), and are not based on radioactivity data. These LC-MS methods are different methods than those used for metabolite profiling (as described in the metabolite profiling report (Module 4.2.2.5, Report INT00003211)), but are the exact same methods as have been applied for the determination of plasma concentrations of these compounds throughout the clinical program for asenapine (Module 2.7.1, Section 2.7.1.1.2.2, page 13).

In other words, the concentration data for the different analytes presented in the above graph are a direct reflection of the bioanalysis results, and no calculations have been performed on them (other than averaging by time point). Further, it should be noted that these 'cold', bioanalytical concentration data reflect the complete multiple dose (10 mg BID) asenapine regimen, whereas the radioactivity data are associated with the final, single ^{14}C-labeled asenapine dose of 10 mg.

The ^{14}C total radioactivity data in the above graph (red symbols/curve) are based on liquid scintillation counts of the plasma samples. A calculation has been made on these count data to translate them into 'asenapine equivalents'. This has been done using the specific activity of the administered radiolabeled asenapine, which was 0.08296 ng/dpm. All individual count data (corrected for baseline radiation) were transformed into asenapine equivalent plasma concentrations as follows:

$$C_{\text{asenapine equiv.}}[\text{ng/mL}] = \frac{\text{counts [dpm]}}{\text{aliquot analyzed [mL]}} \cdot \text{specific activity [ng/dpm]}$$

As an example, the calculation of the C_{max} of total radioactivity in asenapine equivalents (concentration at 4 h) for subject 1 is presented below. For reference, see also the table below from the bioanalytical report on ^{14}C (Module 5.3.3.1, CTR 25532, Appendix BII-2, page 173) with the ^{14}C data from this particular subject.

$$C_{\text{asenapine equiv.}} = \frac{210\ \text{dpm}}{0.25\ \text{mL}} \cdot 0.08296\ \text{ng/dpm} = 69.7\ \text{ng/mL}$$

Table **^{14}C radioactivity in plasma at individual time points for subject 1 (Trial 25532)**

29-Oct-04

ANALYSIS RESULT REPORT - PLASMA ^{14}C-RADIOACTIVITY — PHARMA BIO-RESEARCH

Title (short) : [^{14}C]-Asenapine mass balance study
Pharma Bio-Research code : PBR-043723 (Clinical code: PBR-041201)
Sponsor code : 25532
Sponsor : N.V. Organon, The Netherlands
Subject: Number : 01 Initials : NM
Technician(s) : XBo
Conversion factor dpm to ng equivalent : 0.08296 Apparatus: Liquid Scintillation Analyzer (Tri-Carb 3100TR)

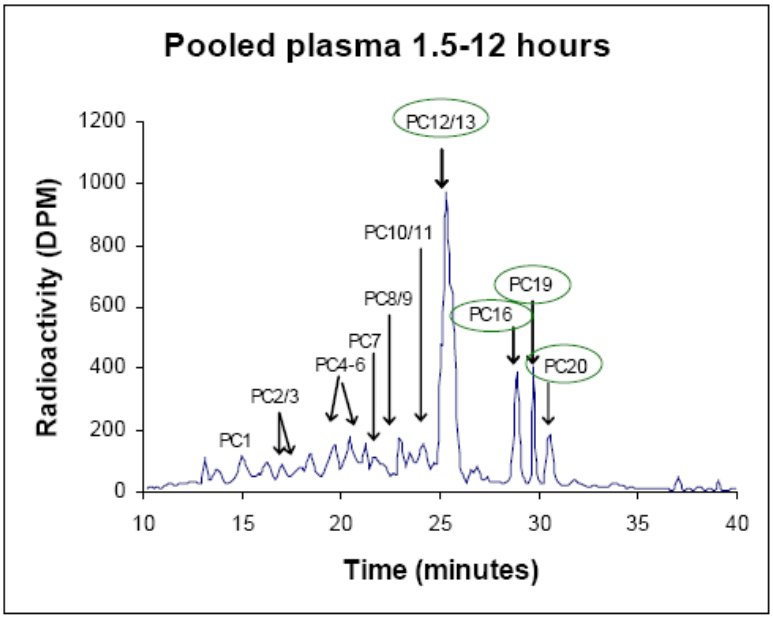
Sample Identification		Analysis	Analytical	Analysed	Background	Count	^{14}C-Radioactivity			
Sample Number	Scheme Time (h)	Date	Run Number	Aliquot (mL)	(cpm)	Number	Measured Counts*) (dpm)	Derived Counts (dpm.mL^{-1})	Calculated (Bq.mL^{-1})	Calculated (ng eq.mL^{-1})
B-4	0.00	31Aug04	AN-01	0.250	3.42	5	1.40	< LLQ	< LLQ	< LLQ
B-5	0.50	31Aug04	AN-01	0.250	3.42	6	20.1	80.6	1.34	6.68
B-6	1.00	31Aug04	AN-01	0.250	3.42	7	41.2	165	2.75	13.7
B-7	1.50	31Aug04	AN-01	0.250	3.42	8	71.2	285	4.75	23.6
B-8	2.00	31Aug04	AN-01	0.250	3.42	9	120	479	7.99	39.8
B-9	3.00	31Aug04	AN-01	0.250	3.42	10	198	792	13.2	65.7
B-10	4.00	31Aug04	AN-01	0.250	3.42	11	210	840	14.0	69.7
B-11	6.00	31Aug04	AN-01	0.250	3.42	12	182	730	12.2	60.5
B-12	8.00	31Aug04	AN-01	0.250	3.42	13	141	566	9.43	46.9
B-13	12.00	31Aug04	AN-01	0.250	3.42	14	109	435	7.25	36.1
B-14	24.00	31Aug04	AN-01	0.250	3.42	15	69.0	276	4.60	22.9
B-15	36.00	31Aug04	AN-01	0.250	3.42	16	49.0	196	3.26	16.2
B-16	48.00	31Aug04	AN-01	0.250	3.42	17	32.9	131	2.19	10.9
B-17	60.00	31Aug04	AN-01	0.250	3.42	18	27.2	109	1.81	9.01
B-18	72.00	31Aug04	AN-01	0.250	3.42	19	21.1	84.3	1.41	7.00

*): corrected for background radiation

Identity of plasma metabolites (metabolite profiling):

In addition to the quantitative LC-MS bioanalytical measurements of asenapine, N-desmethylasenapine and N-oxide asenapine metabolites, qualitative metabolite profiling of a representative pooled (0.5-12 hr) plasma sample was completed. As can be seen from the following figure and table, greater than 80% of the plasma drug-derived radioactivity has been identified in this sample: approximately 50% unequivocally and approximately 30% based upon retention time comparison with urinary metabolite profiling chromatograms.

Figure: **Radiochromatographic profile of a pooled (1.5 – 12hr) plasma sample following administration of ^{14}C-asenapine to 4 healthy male subjects.**



Peak	Name	% of total radioactivity
PC2/3	Methyl- and glucuronide of the 10,11 dihydroxy of N-desmethylasenapine, with the positions of the conjugates 10,11 and reverse; mono conjugates of 10,11-OH-N-desmethylasenapine	5.1
PC4-6	Methyl and sulfate of the 10,11 dihydroxy of the N-desmethylasenapine, with the positions of the conjugates 10,11 and reverse; 11-O-glucuronide of asenapine and of N-desmethylasenapine; other conjugates (sulfates/glucuronides)	13.3
PC8-9	Sulfates and glucuronides	5.9
PC10 PC11	11-O-sulfate asenapine; other sulfates and glucuronides of the N-oxide asenapine	7.4
PC12 PC13	N+ glucuronide	33.6
PC16	N-desmethylasenapine N-carbamoyl glucuronide	6.9
PC19	N-desmethylasenapine	5.1
PC20	Asenapine	4.3
SUM		**81.6**

Note: "Circled" metabolites have been unequivocally identified.

APPENDIX VI :RESPONSE FROM FIRM ON SEPTEMBER 18, 2008 FOR FDA QUESTIONS AND FDA REPLY

TITLE-RESPONSE TO FIRM 9-19-08

1. The representative chromatogram presented for the pooled 1.5-12h plasma sample has several major peaks i.e., PC10/11, PC12, PC13, PC16, PC19, and PC20 which accounts for 57% of the observed AUC (0-72h) based upon the total radioactivity profile presented in Module 4.2.2.5.1, Report INT00003211, page 57/94. We would like to know what percent of the total radioactivity in plasma is represented by the other peaks in the chromatogram. Do the peaks account for 43% of the AUC?

Firm Response:
No, the linking between the radioactive profile and the AUC(0-72h) is not valid. The above mentioned peaks in the pooled plasma (1.5-12 hr) metabolite profile, (PC10/11, PC12, PC13, PC16, PC19 and PC20) collectively account for 57% of the total chromatographic radioactivity detected within this sample rather than the observed AUC(0-72h).

FDA RESPONSE A-

I don’t quite understand their point but it is not essential to the other problems presented by the data.

Firm Response:

Additional characterization, totaling 25% (PC2/3, PC4-6, PC8-9) of the total chromatographic radioactivity, was accomplished and is described below. The remaining radioactivity is unknown and represents multiple compounds throughout the 0-40 min run time chromatogram.

Figure: **Radiochromatographic profile of a pooled (1.5 – 12hr) plasma sample following administration of ^{14}C-asenapine to 4 healthy male subjects.**

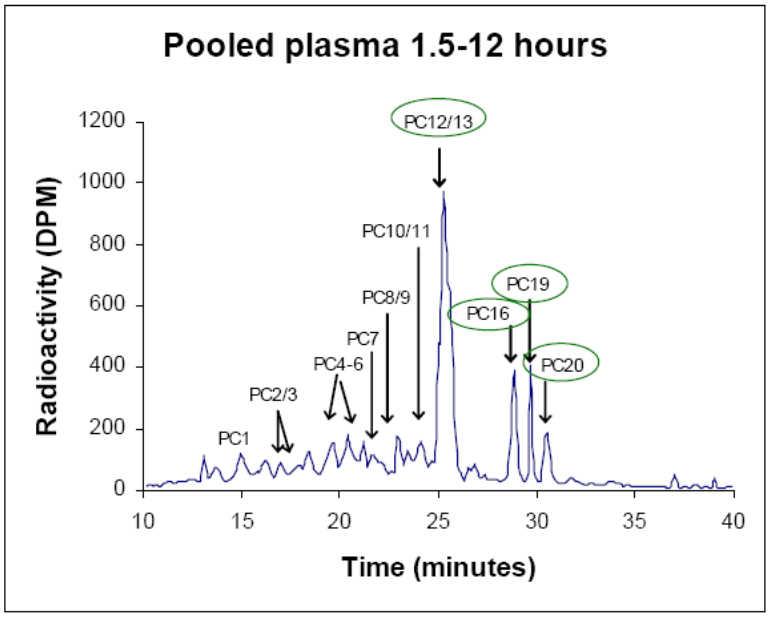


Table 1: Summary of Radioactive peaks found in human plasma and urine after sublingual administration of asenapine (Org 5222 plus [^{14}C]-Org 5222) to male volunteers.

Peak Number (human)	Identity	Retention time	% radioactivity of run, corrected for noise	Presence verified in at least one preclinical species (excreta or plasma)
PC1	Unknown	15.2	3.6	+
PC2 PC3	Methyl- and glucuronide of the 10,11 dihydroxy of N-desmethylasenapine, with the positions of the conjugates 10,11 and reverse.	16.6-17.6	5.1	+
PC4-PC6	Methyl and sulfate of the 10,11 dihydroxy of the N-desmethylasenapine, with the positions of the conjugates 10,11 and reverse; 11-O-glucuronide of asenapine and of N-desmethylasenapine; other conjugates (sulfates/glucuronides)	18.5-22.0	13.3	+
PC7	Unknown	22.7	2.7	+
PC8-9	Sulfates and glucuronides	23.3-23.6	5.9	+
PC10 PC11	11-O-sulfate asenapine; other sulfates and glucuronides of the N-oxide asenapine	25.1 25.6	7.4	+
PC12 PC13	N+ glucuronide	26.8 27.2	33.6	+
PC16	N-desmethylasenapine N-carbamoyl glucuronide	28.7	6.9	+
PC19	N-desmethylasenapine	29.7	5.1	+
PC20	Asenapine	30.2	4.3	+

FDA RESPONSE B-

This response was interpreted to mean that for the pooled 1.5-12 h chromatogram that an additional 25% of the total chromatographic radioactivity could be described by(PC2/3, PC4-6, PC8-9). The only point of concern was that the firm's statement "of the total chromatographic radioactivity" **did not** refer specifically to the pooled 1.5-12 h chromatogram. However that was the inference taken by FDA. If they are referring to the pooled 1.5-12 h chromatogram then the total per cent in the sample quantified is 57%+ 25%=82% which is a good quantitation.

2. A Table was presented in Module 4.2.2.5 Report INT00003211, page 48/94 which shows if a peak was present or absent at 1h or in the 1.5-12h pooled sample. We would like for you to explain why these peaks at 1 h were not quantified since they do appear in the 1h chromatogram in Module 4.2.2.5.1, Report INT00003211, page 57/94. A quantitative profile for the 1 hr sample as was provided for the 1.5 - 12 h pooled sample would be helpful.

Table 7 SOURCE Module 4.2.2.5, Report INT00003211)) PAGE 48/94

Table 7. Peaks found in HPLC chromatograms (HPLC system 2) of the pooled plasma samples of male human volunteers after sublingual administration of asenapine (Org 5222 plus [^{14}C]-Org 5222)

Peak code	Mean retention time (minutes)	Present yes (+)/no (-)	
		Plasma 1h	Plasma 1.5-12h
[a]	16.8	+	-
[a]	20.1	+	-
PC10/11	22.4	+	-
[a]	23.8	+	-
PC12/13	25.0	+	+
PC16	28.7	+	+
PC19	29.7	-	+
PC20	30.2	+	+

[a] No peak code was assigned because the linkage between the plasma, urine and feces metabolite profiles could not be made for these peaks.

PC10/11 is identified as the sulfate of the 11-hydoxy of asenapine plus some other conjugated metabolites (sulfates and glucuronides) of most probably the N(2)-oxide of asenapine.

PC12/13 is identified as the quaternary glucuronide of asenapine.

PC16 is identified as the carbamate glucuronide of the N(2)-des-methyl of asenapine.

Peak PC19 co-elutes with the N(2)-des-methyl of asenapine

Peak PC20 is identified as asenapine

Firm Response:

The three peaks observed at retention time 16.8 min, 20.1 min and 23.8 min in the 1 hr pooled plasma metabolite profile sample could not be identified or characterized by LC-MS. Therefore, no additional analysis of these peaks was completed, including quantification.

FDA RESPONSE

This is **not** consistent with the statement from #1, "Additional characterization, totaling 25% (PC2/3, PC4-6, PC8-9) of the total chromatographic radioactivity, was accomplished and is described below". The peaks can not total 25% if they could not be analyzed nor quantified. The firm needs to explain this inconsistency in their description

of the quantitation of these peaks and if "characterization" means quantitation or something else?

Firm Response:

All other identified peaks in the 1 hr sample were observed in the corresponding pooled (1.5-12hr) plasma sample as well as additional drug-derived metabolites which were identified or characterized by comparison to urine and fecal metabolite profiles.

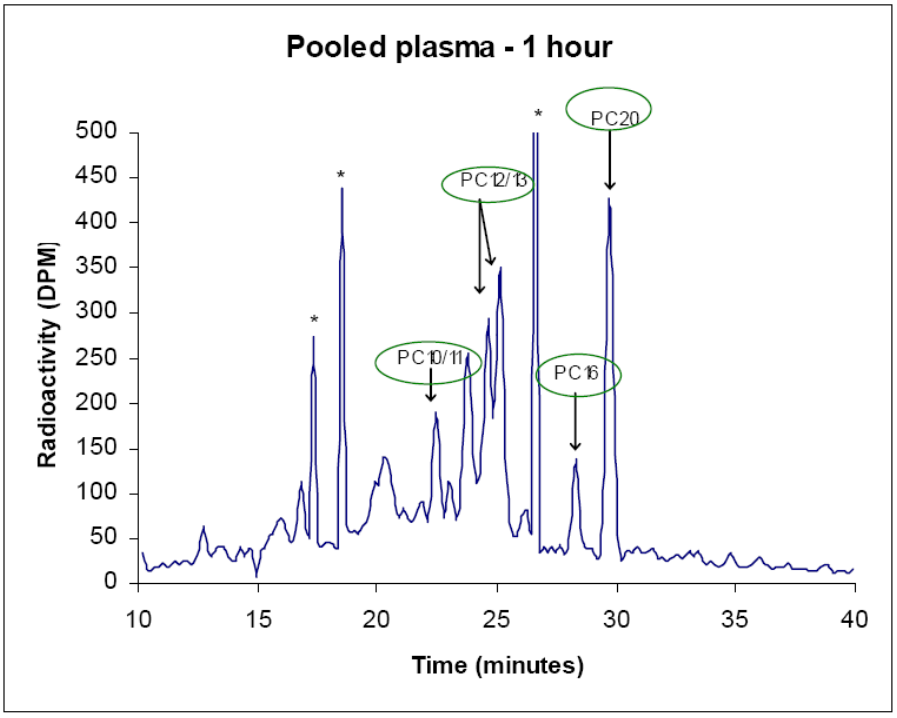
FDA RESPONSE

This statement is okay but there was peak PC 19 which was not seen at 1h but present in the 1.5-12h pooled sample. The firm should address this discrepancy since they stated, "All other identified peaks in the 1 hr sample were observed in the corresponding pooled (1.5-12hr) plasma sample." OCP does not want to consider urine and feces at this time.

Firm Response:

Figure 1, below shows the radiochromatographic profile of pooled 1 hr plasma and the percent of total chromatographic radioactivity of the peaks detected.

Figure 1. Radiochromatographic profile of a pooled (1 hr) plasma sample following administration of ^{14}C-asenapine to 4 healthy male subjects.



Peak nr	Name	% of Total Chromatographic radioactivity
RT=16.8	Unknown	3.3
RT=20.1	Unknown	9.5
RT=23.8	Unknown	8.0
PC10 PC11	11-O-sulfate asenapine; other sulfates and glucuronides of the N-oxide asenapine	5.7
PC12 PC13	N+ glucuronide	17.7
PC16	N-desmethylasenapine N-carbamoyl glucuronide	3.6
PC20	Asenapine	10.8
SUM		**58.6**

Prominent radioactive spikes identified with an asterisk in the 1 hr pooled plasma sample are artifactual peaks and are not related to asenapine based upon LCMS analysis of the fractions. These appeared during solid scintillation counting used for measuring radioactivity in the plasma fractions and are thus not relevant.

FDA RESPONSE

The table shows that you have quantified 37.8% of the metabolites at 1h. However, you can not use the RT 16.8 , RT 20.1 and RT 23.8 peaks for your total since it was pointed out previously that this is not consistent with Table 7 above. You have stated, with a subscripted 'a' " No peak code was assigned because the linkage between the plasma, urine and feces metabolite profiles could not be made for these peaks." The firm needs to explain this statement.

3. We would like you to provide information specifying that the metabolites quantified in the 1.5-12 h pooled sample is representative/quantitative for the (0-1 h) and (12-72 h) time intervals (i.e. not sampled).

Response:
We believe that the 1.5-12 hr pooled plasma is most representative of the plasma metabolic profile because it encompasses the greatest, feasible time interval of samples with sufficient radioactivity concentrations to allow metabolite profiling. Because only low levels of radioactivity were detected in plasma at 24, 36, 48, 60 and 72 hr post-dose, plasma obtained from these timepoints was not included in the pooled sample to minimize any dilution of the radioactivity signal. The 1.5 - 12 hr sample represents the most technically feasible and representative plasma metabolite profile.

FDA RESPONSE
OCP agrees with this response.

Response:

All identified peaks in the 1 hr sample were observed in the corresponding pooled (1.5-12hr) plasma sample as well as additional drug-derived metabolites which were identified or characterized. Because the 1.5-12 hr pooled plasma metabolite profile was determined using the remaining plasma volumes (i.e. 79 mL, not necessarily equal volumes from each subject at each timepoint contributed to the pooled sample), a direct quantitative comparison to the 1 hr plasma metabolite profile is not appropriate. Also, because of the low levels of radioactivity in the plasma after 12 hr, neither a qualitative or quantitative assessment was possible.

FDA RESPONSE

The firm's Table 9-5 Module 4.2.2.5 page 48/94 (i.e., Table 7 above) clearly refutes this statement. Peaks at retention times of 16.8 min, 20.1 min and 23.8 min have ' plus' signs at 1h but 'minus' signs at 1.5-12h meaning that they were not present. Furthermore the firm has labeled a superscript 'a' meaning ," No peak code was assigned because the linkage between the plasma, urine and feces metabolite profiles could not be made for these peaks. This statement is clearly contradictory to the firm's response and should be clarified by the firm.

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APPENDIX VII: INFORMATION PRESENTED AT INTERNAL FDA MEETING

ON 9-15-08

TOTAL RADIOACTIVITY IN PLASMA

Figure 1. Profile obtained for total radioactivity. SOURCE Module 4.2.2.5, Report INT00003211)) PAGE 46/94

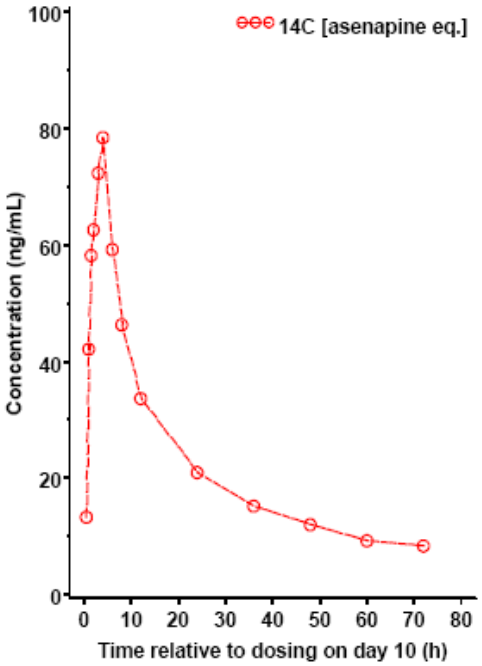


Table 1 Concentration of radioactivity in plasma samples after sublingual administration of asenapine (Org 5222 plus [14C]-Org 5222) to male human volunteers

Plasma

Radioactivity (ng equivalents.mL-1)

time (h)	0.5	1.0	1.5	2.0	3.0	4.0	6.0	8.0	12	24	36	48	60	72
Subject 1	6.68	13.7	23.6	39.8	65.7	69.7	60.5	46.9	36.1	22.9	16.2	10.9	9.01	7.00
Subject 2	19.6	53.6	64.7	64.0	61.7	64.7	43.7	30.9	27.0	16.2	13.0	10.2	7.28	8.35
Subject 3	15.1	45.2	75.3	77.4	84.4	91.4	77.1	62.1	40.9	24.6	18.1	16.2	13.5	11.3
Subject 4	11.7	55.6	69.2	68.8	77.1	87.8	55.4	45.0	30.5	19.9	13.4	10.7	7.03	6.69
Mean	**13.3**	**42.0**	**58.2**	**62.5**	**72.2**	**78.4**	**59.2**	**46.2**	**33.6**	**20.9**	**15.2**	**12.0**	**9.2**	**8.3**

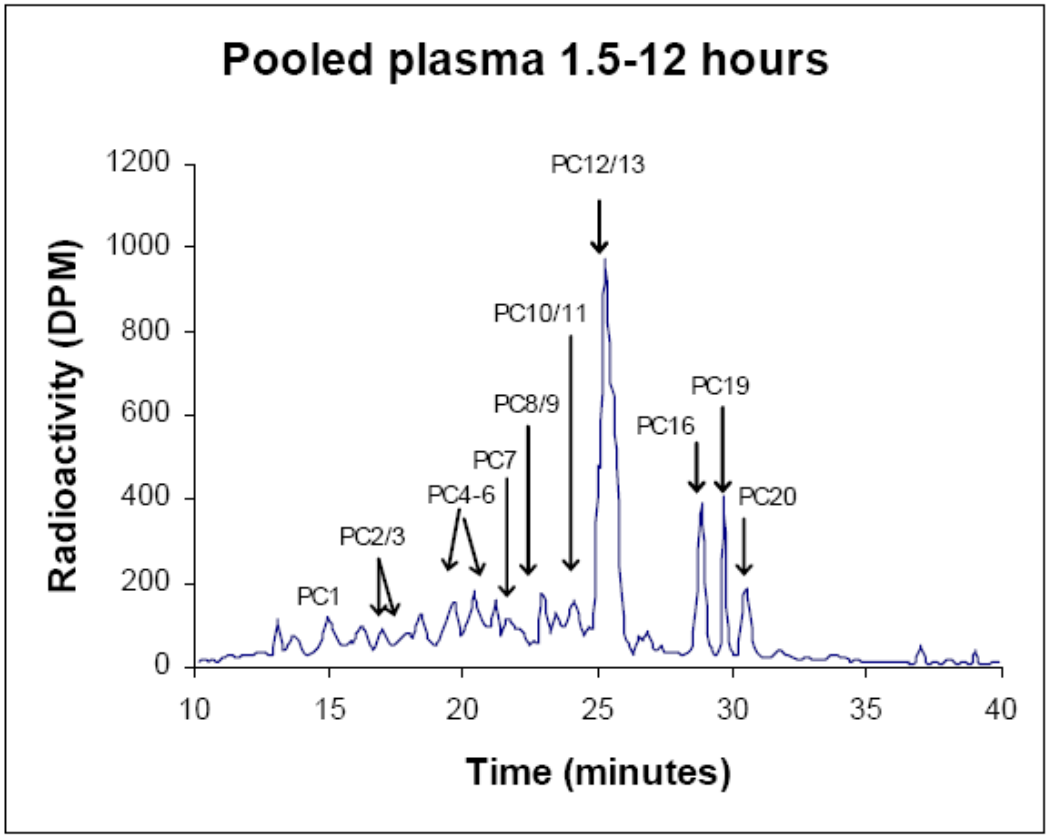
SDa	5.5	19.4	23.5	16.1	10.4	13.2	13.9	12.8	6.1	3.7	2.4	2.8	3.0	2.1

a SD = standard deviation

FDA COMMENT : Figure 1 is consistent with the data in Table 1, however this is **only total radioactivity data as a function of time**. **There is no information on individual metabolites.**

REPRESENTATIVE CHROMATOGRAM

Figure 2. Radiochromatographic profile of a pooled (1.5 – 12hr) plasma sample following administration of ^{14}C-asenapine to 4 healthy male subjects. HPLC SYSTEM 2. SOURCE POOLED ASSAY 1.5-12HR SUBMITTED JULY 25 2008



FDA COMMENT : Chromatogram is acceptable to OCP.

PEAKS IDENTIFIED BASED UPON CHROMATOGRAM IN FIGURE 2.

TABLE 2. Metabolites identified in plasma and urine.SUBMITTED BY THE FIRM DATE: JULY 25 2008 HPLC SYSTEM 2

Peak Number (human)	Identity	Retention time	% radioactivity of run, corrected for noise	Presence verified in at least one preclinical species (excreta or plasma)
PC1	Unknown	15.2	3.6	+
PC2 PC3	Methyl- and glucuronide of the 10,11 dihydroxy of N-desmethylasenapine, with the positions of the conjugates 10,11 and reverse	16.6-17.6	5.1	+
PC4-PC6	Methyl and sulfate of the 10,11 dihydroxy of the N-desmethylasenapine, with the positions of the conjugates 10,11 and reverse; 11-O-glucuronide of asenapine and of N-desmethylasenapine; other conjugates (sulfates/glucuronides)	18.5-22.0	13.3	+
PC7	Unknown	22.7	2.7	+
PC8-9	Sulfates and glucuronides	23.3-23.6	5.9	+
PC10 *	11-O-sulfate asenapine;	25.1	[7.4]	+
PC11 *	other sulfates and glucuronides of the N-oxide asenapine	25.6		
PC12 *	N+ glucuronide	26.8	[33.6]	+
PC13 *		27.2		
PC16 *	N-desmethylasenapine N-carbamoyl glucuronide	28.7	[6.9]	+
PC19 *	N-desmethylasenapine	29.7	[5.1]	+
PC20 *	Asenapine	30.2	[4.3]	+

Sum of plasma metabolites in brackets=57.3%

PEAKS IDENTIFIED BASED UPON CHROMATOGRAM IN FIGURE 2.

TABLE 3. Metabolites identified in plasma and urine. TABLE SUBMITTED BY THE FIRM IN SEPTEMBER 2008 TO MY REQUEST FOR INFORMATION HPLC SYSTEM 2

Peak	**Name**	**% of total radioactivity**
PC2/3	Methyl- and glucuronide of the 10,11 dihydroxy of N-desmethylasenapine, with the positions of the conjugates 10,11 and reverse; mono conjugates of 10,11-OH-N-desmethylasenapine	5.1
PC4-6	Methyl and sulfate of the 10,11 dihydroxy of the N-desmethylasenapine, with the positions of the conjugates 10,11 and reverse; 11-O-glucuronide of asenapine and of N-desmethylasenapine; other conjugates (sulfates/glucuronides)	13.3
PC8-9	Sulfates and glucuronides	5.9
PC10	11-O-sulfate asenapine; other sulfates and glucuronides of the N-oxide	7.4
PC11	asenapine	
PC12	N+ glucuronide	33.6
PC13		
PC16	N-desmethylasenapine N-carbamoyl glucuronide	6.9
PC19	N-desmethylasenapine	5.1
PC20	Asenapine	4.3
SUM		**81.6**

Note: “BOLDED” metabolites have been unequivocally identified.
Please note that the total for those bolded the PC10 and PC 11 have been excluded so the total now becomes 57.3%-7.4%=49.9%. Nonbolded metabolites have not been found in plasma.

FDA COMMENT ON Tables 2-3 and Figure 2. OCP agrees with Figure 2 for the chromatogram. However, the firm changes the metabolites which they believe they can identify between the July and September submissions. In July P10 and P11 were included whereas in September they were excluded. This is very inconsistent and not explained by the firm. Based upon the firms statements related to the performance of HPLC System2, the results are at best semi-quantitative. The total sum of identifiable material in plasma for AUC 1.5-12h is either 57.3% or 49.9%. Most notable is that neither the 57.3% or 49.9% values is defining a profile only a 1.5 to 12 AUC window for a drug with a half-life of 27 hrs.

Table 4. FRACTION OF TOTAL AUC(0-72h) REPRESENTED BY AUC 1.5-12 h FOR EACH SUBJECT.

SUBJECT	AUC(0-72h) ng/mlxh	AUC(1.5-12h) ng/mlxhr	AUC(1.5-12H) / AUC(0-72h)
1	1522.71	893.9	0.58
2	1282.06	716.22	0.55
3	1951.65	1113.67	0.57
4	1470.95	886.9	0.60
MEAN	1556.84	902.67	**0.57**

Table 5. OBSERVED METABOLITES IN THE 1.5-12 h POOLED PLASMA SAMPLE

OBSERVED METABOLITES	OBSERVED FRACTION IN POOLED 1.5-12h SAMPLE	OBSERVED FRACTION x MEAN RATIO OF AUC(1.5-12H) / AUC(0-72h) =**0.57**	PER CENT OF OBSERVED FRACTION IN AUC(0-72h)
PC10	0.074	0.042	4.29
PC12	0.333	0.19	19.30
PC16	0.069	0.04	4.00
PC19	0.051	0.029	2.95
PC20	0.043	0.024	2.49
TOTAL PER CENT OF METABOLITES IN THE 1.5-12h POOLED SAMPLE RELATIVE TO THE TOTAL AMOUNT OF AUC (0-72 h)			33.04

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APPENDIX VIII-FIRM'S FINAL RESPONSE AND DATA SUMMARY

CONFIDENTIAL

Organon

Schering-Plough

September 23, 2008

Electronic Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA No. 22-117
Asenapine Sublingual Tablets
Serial No. 0038
SUMMARY OF ASENAPINE METABOLITE PROFILE AS DISCUSSED ON SEPTEMBER 19, 2008

Dear Sir of Madam:

Reference is made to the New Drug Application No. 22-117 for Asenapine Sublingual Tablets received on August 31, 2007. References are also made to our submissions dated June 13, 2008 (Serial No. 0027), July 25, 2008 (Serial No. 0031), September 4, 2008 (Serial No. 0034), September 11, 2008 (Serial No. 0035), September 15, 2008 (Serial No. 0036), and September 18, 2008 (Serial No. 0037).

Lastly, reference is made to the teleconference that was held with the Division of Psychiatry Products on Friday, September 19, 2008, to discuss the asenapine metabolite profile. At the conclusion of the teleconference, Dr. Laughren asked that we submit a summary of the discussion. Our summary is enclosed. The key points are below.

The metabolism of asenapine was studied in healthy volunteers using state-of-the-art LC-MS, LC-MS/MS and liquid scintillation techniques.

- This is an extensively metabolized drug with well over 40 metabolites (most of which are polar conjugates) observed in plasma, urine and feces.
- The drug metabolism data presented in the NDA are typical of the state of the art for a drug with this extensive metabolite profile.
- The extensive metabolism of asenapine resulted in a complex metabolic profile with analytical challenges.
- Analytical limitations and extensive metabolism have precluded complete characterization of plasma samples beyond 12 hours.
- In terms of plasma metabolite profiling specifically, we have characterized ~ 80% of circulating drug-derived radioactivity in the 1.5 - 12 hour time period.

This submission is being provided in electronic format. The electronic files are supplied on one [1] CD-ROM and the submission has been checked for viruses during the creation using Symantec Netbackup Version 5.1 Windows Servers and found to be virus free.

Summary of Asenapine metabolism as discussed during September 19, 2008 teleconference:

The metabolism of asenapine was studied in healthy volunteers using state-of-the-art LC-MS, LC-MS/MS and liquid scintillation techniques.

- This is an extensively metabolized drug with well over 40 metabolites (most of which are polar conjugates) observed in plasma, urine and feces.
- The drug metabolism data presented in the NDA are typical of the state of the art for a drug with this extensive metabolite profile.
- The extensive metabolism of asenapine resulted in a complex metabolic profile with analytical challenges.
- Analytical limitations and extensive metabolism have precluded complete characterization of plasma samples beyond 12 hours.
- In terms of plasma metabolite profiling specifically, we have characterized ~ 80% of circulating drug-derived radioactivity in the 1.5 - 12 hour time period.

The 1.5-12 hr pooled plasma sample is the most representative profile of total exposure to plasma metabolites and asenapine.

Ideally, the metabolite profile would be obtained using pooled plasma samples from 0 to 72 hr. However, because mean plasma radioactivity concentrations at 24 hr were low (approximately 20 ng eq/mL) and decreased to approximately 8 ng eq/mL by 72 hr, metabolite profiling was not technically feasible after 12 hr and arguably not important to the overall metabolite profiles.

The most representative profile of total exposure to plasma metabolites and unchanged drug comes from a pooled (1.5-12 hr) plasma sample. The majority of the metabolites in this pooled sample remained above the detection limits for radioactivity which was necessary to provide quantitative estimates. Adding plasma from beyond 12 hr would have significantly diluted the sample and limited the ability to obtain a meaningful radiochromatographic profile. The 1.5 to 12 hr pooled plasma sample was obtained by combining the remaining, available plasma from all subjects at all time points and did not contain an equal contribution from each subject and necessarily every time point. This rigorous attempt to profile low levels of circulating metabolites was qualitatively successful; but only feasible for the 1.5-12 hr pooled sample.

By comparison, the 1 hr metabolite profile provided limited information presumably because sampling was too early and the plasma concentrations of some metabolites may not have reached the detection limits of the radioactivity profiling method.

Asenapine is extensively metabolized and its metabolites have been well characterized using LC-MS or by retention time comparisons.

Greater than 80% of the total chromatographic radioactivity in the 1.5-12 hr pooled plasma metabolite profile has been characterized. Metabolites representing about 50% of the profiled radioactivity were unequivocally (MS and NMR) identified and those representing another 31.7% of the chromatographic radioactivity were characterized by retention time comparisons. No one peak corresponds to more than 6% of the plasma radiocarbon profile in the remaining 18.3% of the radiochromatogram.
Referring to the radiochromatogram (Figure 1), it can be seen that asenapine (PC20) is extensively metabolized. The unequivocally identified peaks in the 1.5-12 hr radiochromatogram are shown in Table 1.

Table 1: Asenapine metabolites unequivocally identified in a pooled (1.5 – 12hr) plasma sample following administration of ^{14}C-asenapine to 4 healthy male subjects.

Metabolite Designation	% of radioactivity in chromatogram*	Unequivocally identified in plasma by**
PC12/13: Asenapine N+glucuronide	33.6	LC-ES-MS
PC16: N-desmethylasenapine N-carbamoyl glucuronide	6.9	LC-ES-MS
PC19: N-desmethylasenapine	5.1	LC-ES-MS
PC20: asenapine	4.3	LC-ES-MS
SUM of the total chromatographic radioactivity	**49.9**	

Most of the remaining chromatographic radioactivity which elutes between 13 and 25 min (Figure 1), corresponds to at least 15 different peaks (multiple metabolites coeluting within peaks observed within the radiochromatogram), none of which represents more than 6% of the plasma radioactivity profile. Most of these peaks have a discernible mass ion and have been, at a minimum, partially characterized by LC-MS. These peaks of interest are detailed in Table 2 and tabulated below:

Table 2: Asenapine metabolites characterized or partially characterized in a pooled (1.5 – 12hr) plasma sample following administration of ^{14}C-asenapine to 4 healthy male subjects.

Metabolite Designation	% of radioactivity in chromatogram*	Identified by retention time comparison **
PC2/3: Methyl- and glucuronide of the 10,11 dihydroxy of N-desmethylasenapine, with the positions of the conjugates 10,11 and reverse; mono conjugates of 10,11-OH-N-desmethylasenapine	5.1	LC-ES-MS and deconjugation in urine fractions
PC4-6: Methyl and sulfate of the 10,11 dihydroxy of the N-desmethylasenapine, with the positions of the conjugates 10,11 and reverse; 11-O-glucuronide of asenapine and of N-desmethylasenapine; other conjugates (sulfates/glucuronides)	13.3	LC-ES-MS and deconjugation in urine fractions
PC8-9: Sulfates and glucuronides	5.9	LC-ES-MS in urine fractions
PC10/11: 11-O-sulfate asenapine; other sulfates and glucuronides of the N-oxide asenapine	7.4	LC-ES-MS in urine fractions
SUM of the total chromatographic radioactivity	**31.7**	

*: data provided in Serial No. 0031
**: data provided in Report INT0003211

It was not possible to simultaneously obtain mass spectral data from the pooled 1.5 to 12 hr plasma sample. Nonetheless, by analyzing urine with the same LC-MS method as was used for plasma, retention time comparisons were made between known urine metabolites and plasma radioactivity peaks. Using these comparisons, it was determined that most of the radioactive peaks eluting before PC12/13 consisted of more than 3 metabolites. In total, this resulted in the characterization of more than 40 different asenapine metabolites in biological matrices.

In the 1-hr pooled plasma metabolite profile (Figure 2), approximately 32.1% of the circulating radioactivity has been identified unequivocally. The unequivocally identified peaks in the 1-hr radiochromatogram are shown in Table 3.

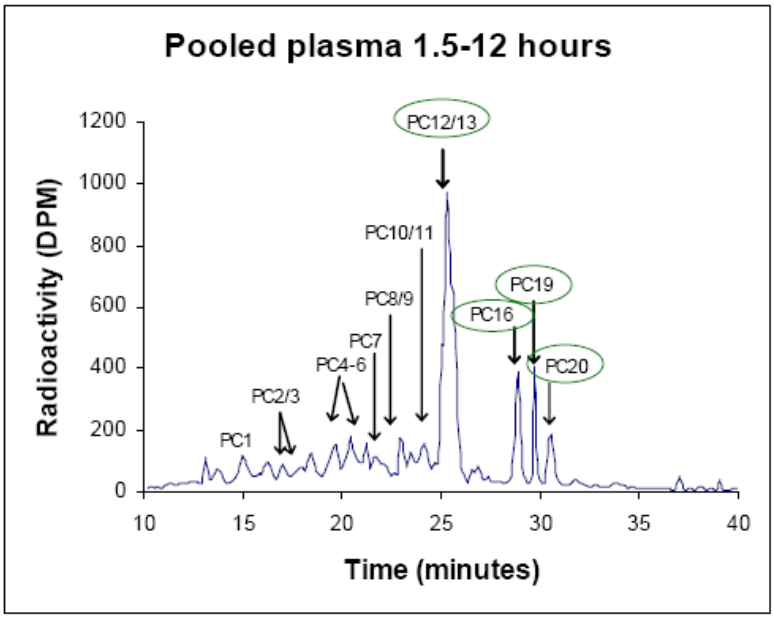
Table 3: Asenapine metabolites unequivocally identified in a pooled (1-hr) plasma sample following administration of ^{14}C-asenapine to 4 healthy male subjects.

Metabolite Designation	% of radioactivity in chromatogram*	Unequivocally identified in plasma by**
PC 12/13: Asenapine N+glucuronide	17.7	LC-ES-MS
PC16: N-desmethylasenapine N-carbamoyl glucuronide	3.6	LC-ES-MS
PC20: asenapine	10.8	LC-ES-MS
SUM of the total radiochromatographic radioactivity	**32.1**	

PC10/11 (5.7%) has been partially identified with LC-ES-MS in this 1-hr pooled plasma sample. Also, three peaks were detected which could not be identified by mass spectrometry (at retention times 16.8, 20.1 and 23.8 min) and can only be quantified based upon their contribution to the total chromatographic radioactivity. These peaks were not obvious in the 1.5 to 12 hr pooled plasma sample (and hence were indicated as not present in Table 9-5, page 48/94 of Report INT00003211) possibly due to dilution, or alternatively, they may also represent rapidly cleared metabolites. It should also be noted that PC 19 (N-desmethylasenapine) was not detected as a distinct peak in the 1-hr pooled plasma sample. Its presence was measured directly using a validated LC-MS/MS assay where Tmax ranged between 2 and 4 hours. It is probable that the plasma concentration of this metabolite at 1 hr post-dose was not yet above the detection limit for the radioactivity profiling method.

The metabolism data are described in Report INT0003211, except for quantification of the contribution of each peak to the overall radioactivity in the 1-hr and 1.5-12 hr pooled plasma samples, which was submitted to NDA 22-117 on September 18, 2008 (Serial No. 0037) and July 25, 2008 (Serial No. 0031), respectively.

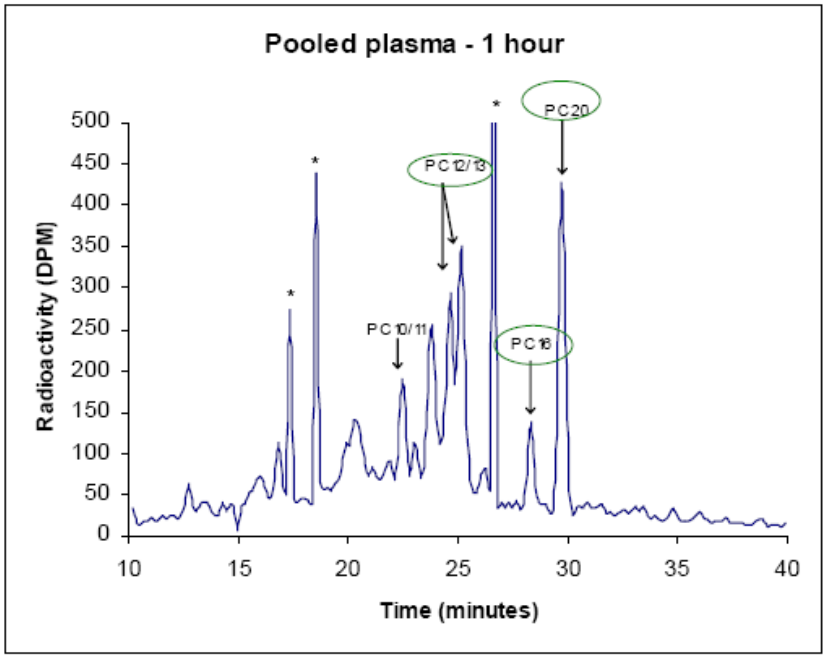
Figure 1. Radiochromatographic profile of a pooled (1.5 – 12hr) plasma sample following administration of ^{14}C-asenapine to 4 healthy male subjects.



Peak nr	Metabolite Designation	% of Total Chromatographic radioactivity
PC2/3	Methyl- and glucuronide of the 10,11 dihydroxy of N-desmethylasenapine, with the positions of the conjugates 10,11 and reverse; mono conjugates of 10,11-OH-N-desmethylasenapine	5.1
PC4-6	Methyl and sulfate of the 10,11 dihydroxy of the N-desmethylasenapine, with the positions of the conjugates 10,11 and reverse; 11-O-glucuronide of asenapine and of N-desmethylasenapine; other conjugates (sulfates/glucuronides)	13.3
PC8-9	Sulfates and glucuronides	5.9
PC10 PC11	11-O-sulfate asenapine; other sulfates and glucuronides of the N-oxide asenapine	7.4
PC12 PC13	Asenapine N+ glucuronide	33.6
PC16	N-desmethylasenapine N-carbamoyl glucuronide	6.9
PC19	N-desmethylasenapine	5.1
PC20	Asenapine	4.3
SUM		**81.6**

- >80% of the radioactivity known: 50% unequivocally (⬭), 30% based on RT comparison with urinary compounds as analyzed using NMR and LCMSMS.

Figure 2. Radiochromatographic profile of a pooled (1 hr) plasma sample following administration of ^{14}C-asenapine to 4 healthy male subjects.



Peak nr	Metabolite Designation	% of Total Chromatographic radioactivity
RT=16.8	Unknown	3.3
RT=20.1	Unknown	9.5
RT=23.8	Unknown	8.0
PC10 PC11	11-O-sulfate asenapine; other sulfates and glucuronides of the N-oxide asenapine	5.7
PC12 PC13	Asenapine N+ glucuronide	17.7
PC16	N-desmethylasenapine N-carbamoyl glucuronide	3.6
PC20	Asenapine	10.8
SUM		**58.6**

* = artifactual peak not related to asenapine based upon LC-MS analysis of the fraction
RT = HPLC retention time in minutes

Asenapine is extensively metabolized and the metabolism has been well characterized using plasma, urine and feces samples.

A majority of the circulating drug-derived radioactivity has been characterized or at a minimum partially characterized. Most of the drug-derived material in human plasma following sublingual administration of asenapine is associated with polar, conjugated metabolites.

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