CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-117

MEDICAL REVIEW(S)

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: July 31, 2009

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

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

TO: File NDA 22-117
[Note: This overview should be filed with the 2-12-09 complete response to the agency's 1-13-09 CR letter.]

Note: This is an addendum to my division director memos dated 8-1-08 and 10-15-08. The purpose of this addendum is to provide an update on new information obtained since my previous memos.

CMC Data: One previous issue had been to address impurity (b) (4). The sponsor had 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 had decided that a qualification study could be a phase 4 commitment. The sponsor had in fact conducted a non-GLP segment II study in rabbits with this impurity, however, we considered this study inadequate. Therefore, we were planning to ask for an embryofetal development study in rabbits as a phase 4 commitment. The sponsor has subsequently informed us that they have in fact conducted such a study and submitted a full report to the IND on 7-10-09. The sponsor has concluded that this was a negative study with no findings of embryotoxicity or teratogenicity. We will simply reference this report in the final action letter, and review it post-approval.

There were several other minor requests for CMC information in the 1-13-09 CR letter, and these have all been resolved.

There is also agreement on labeling from a CMC standpoint, and the CMC group has recommended an approval action.

Finally, DMEPA has confirmed the acceptability of the name Saphris (7-30-09).

Carcinogenicity Data: The one remaining pharm/tox issue noted in the 1-13-09 CR letter was the fact that we had not yet had an opportunity to complete our review of additional carcinogenicity data for the rat and mouse studies. We have now completed this review, and our only remaining concern is about the suggestion of a finding for maligmant lymphomas in the mouse study. However, this finding is confounded by a high and variable background rate in the mouse strain used for this study, and of unknown human significance. We have reached agreement with the sponsor on how best to characterize this finding in labeling.

We have also reached agreement on all other labeling issues from a pharm/tox standpoint, and the pharm/tox group has recommended an approval action.

Biopharmaceutics Concerns: All remaining biopharmaceutics issues have been resolved, including agreement on labeling, and OCP has recommended an approval action.

Remaining Clinical Issues: In the 1-13-09 CR letter, we asked for a safety update, for additional clarification on the extent of exposure to asenapine in the development program, and for additional information on cases of anemia and thrombocytopenia. The sponsor's 2-12-09 submission provided responses to these requests, and these responses have been reviewed by Dr. Mathis from DPP. He concluded that the sponsor's response was adequate, and that no new safety concerns were discovered that would impact on our conclusion that asenapine has been shown to be acceptably safe. I agree with his assessment.

7-30-09 PDAC Meeting: We met with the PDAC on 7-30-09 to discuss this application. The majority of committee agreed with us and voted in favor of both the safety and efficacy of asenapine for the acute treatment of schizophrenia and mania associated with bipolar disorder.

Final Labeling: We have reached agreement with the sponsor on final labeling, and this final label will be included in the approval letter.

PREA Requirements and PMCs: We have reached agreement with the sponsor on PREA studies (for both schizophrenia and bipolar mania) and on PMCs.

The sponsor has agreed to further explore lower doses for bipolar mania, in particular 5 mg bid. They have also agreed to conduct a maintenance study in bipolar disorder. In addition, they have agreed to provide a more detailed analysis of the metabolic data for asenapine in accordance with our suggested approach. Regarding a maintenance study for schizophrenia, they have conducted such a study and will submit the results in a supplement post-approval.

At the division level, we agreed that additional studies are not needed to explore lower doses in schizophrenia because the sponsor has provided sufficient data regarding this issue.
-Study 041002 explored 3 fixed asenapine doses (0.2 bid, 0.4 bid, and 0.8 bid) vs risperidone 3 mg bid and placebo in acute schizophrenia, and found that none of these asenapine doses could be distinguished from placebo, while the risperidone group did beat placebo.
-Study 041013 explored 2 fixed asenapine doses (1.6 and 2.4 bid) vs placebo in acute schizophrenia (a 6-week study), and found that neither of these asenapine doses could be distinguished from placebo. The drug-placebo difference in change from baseline in PANSS

Total Score was about 5 units for the lower dose and about 2 units for the higher dose. This was a relatively small study, about 60 per arm, and there were substantial dropouts (only about 1/3 of patients completed for each group). However, this would not be unexpected in a trial of this disorder involving doses that are suboptimal.
-In an EOP2 meeting with the sponsor on 11-20-02, we discussed the findings from these negative studies, along with the positive findings for asenapine 5 mg bid from study 041004, and mutually concluded that the sponsor had adequately explored the lower end of the dose response curve for asenapine in schizophrenia (see meeting minutes).
-In addition, the sponsor has explored D2 receptor occupancy data (using PET imaging), and based on public domain data on receptor occupancy for other antipsychotics has argued that the level of occupancy seen with the 2.4 mg bid asenapine dose would not be expected to be effective in schizophrenia.
-Thus, I agree that we do not need to request additional studies of asenapine in schizophrenia to explore doses lower than 5 mg bid.

Conclusions and Recommendations: In my view, the sponsor has submitted data supportive of a conclusion that asenapine is effective and acceptably safe in the acute treatment of schizophrenia and mania/mixed episodes with bipolar 1 disorder. Thus, we will forward an approval letter and package to the Office.

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

DOC: Asenapine_Bipolar_Schizophrenia_Laughren_AP_Memo.doc

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22117	ORIG 1	ORGANON USA INC	SYCREST (ASENAPINE) TABLETS

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/s/

THOMAS P LAUGHREN
07/31/2009

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: 23 July 2009

FROM: Mitchell V. Mathis, M.D.
Deputy Director
Division of Psychiatry Products, HFD-130

TO: File NDA 22-117

SUBJECT: Clinical Addendum, Review of Response to CR letter of January 13, 2009 for Asenapine

The purpose of this memo is to serve as a clinical addendum to the file for asenapine sublingual tablets, an NME currently under evaluation for the acute treatment of schizophrenia in adults. The Division issued a Complete Response (CR) Letter on January 13, 2009 requesting additional information regarding clinical data in the NDA. These requests for additional data were:

1. A safety update with any new safety concerns identified.
2. A more clear delineation of extent of exposure from the clinical database.
3. A discussion of anemia and thrombocytopenia cases identified during the review and an update on any new cases.

The Sponsor submitted their response to the CR Letter on 12 February 2009 and addressed these clinical issues.

Interim Safety Update

The sponsor submitted an interim safety update report. This report includes data from 13 trials (12 clinical and one bioequivalence) that were ongoing at the time of the initial submission. Nine of these trials have been completed since the original submission and four remain ongoing. The data submitted as part of the Complete Response represent all data up to a cut-off date of 1 December 2008.

There were no substantial different findings regarding death, serious adverse events (SAEs), discontinuation due to AE, or common adverse events (AEs) that would materially change what was found during the review of the original NDA safety database. The proportion of patients treated within the relevant dose range (5 mg to 10 mg given twice daily) who experienced any adverse event was 78% in the original safety database and 78.6% in the updated database. There have been three additional deaths in the development program since the original safety data were submitted; these deaths are not likely related to drug (lung cancer, intentional overdose, and cardio-respiratory arrest 28 days after the last dose of asenapine). SAEs were largely the same as in the original submission except for some additional and likely not drug related events (e.g., road accident, pneumonia, abortion induced). Discontinuation AEs are largely related to exacerbations of

underlying disease, as was the case in the original safety database. AEs occurring in at least 2% of patients in the updated database are the same events identified in the original database. There were some small (threshold percentage of reporting between 2% and 2.5%) common adverse event differences for diarrhea, decreased weight, asthenia, ALT increased, and arthralgia. As requested, the sponsor provided an update on the anemia cases identified in the original review (seen below where this issue is addressed specifically).

In summary, there were no substantial safety findings in the updated safety report to change our original impression of the safety profile of asenapine.

Extent of Exposure

The sponsor provided the following table outlining the extent of exposure during the development program (page 185 of their safety update report).

Table 46 Updated Information Through 1 DEC 2008 - Summary of duration of exposure to asenapine (combined Phase 2/3 trial, cohort E)

Exposure Duration	Placebo (N=1064)	Asenapine <5 mg BID (N=298)	Asenapine 5-10 mg[a] BID (N=3159)	Asenapine All (N=3457)	Risp 3 mg BID (N=120)	Halo 2-8 mg BID (N=115)	Olan 5-20 mg QD (N=1139)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
≥ 1 day	1064	298	3159	3457	120	115	1139
≥ 1 week	974 (91.5)	258 (86.6)	2963 (93.8)	3221 (93.2)	106 (88.3)	104 (90.4)	1072 (94.1)
≥ 3 weeks	680 (63.9)	175 (58.7)	2557 (80.9)	2732 (79.0)	81 (67.5)	81 (70.4)	926 (81.3)
≥ 6 weeks	386 (25.5)	82 (27.5)	2171 (68.7)	2253 (65.2)	47 (39.2)	66 (57.4)	769 (67.5)
≥ 9 weeks	198 (18.6)	37 (12.4)	1851 (58.6)	1888 (54.6)	25 (20.8)	39 (33.9)	686 (60.2)
≥ 12 weeks	177 (16.6)	25 (8.4)	1681 (53.2)	1706 (49.3)	20 (16.7)	39 (33.9)	644 (56.5)
≥ 4 months	134 (12.6)	20 (6.7)	1503 (47.6)	1523 (44.1)	18 (15.0)	33 (28.7)	585 (51.4)
≥ 6 months	101 (9.5)	13 (4.4)	1301 (41.2)	1314 (38.0)	12 (10.0)	28 (24.3)	534 (46.9)
≥ 9 months	17 (1.6)	6 (2.0)	901 (28.5)	907 (26.2)	7 (5.8)	20 (17.4)	463 (40.6)
≥ 12 months	15 (1.4)	6 (2.0)	779 (24.7)	785 (22.7)	4 (3.3)	16 (13.9)	428 (37.6)
≥ 13 months	0	5 (1.7)	72 (2.3)	77 (2.2)	4 (3.3)	16 (13.9)	32 (2.8)

[a] fixed and flexible doses
Source: new data

From the table above, there were nearly 3,500 patients exposed during the phase 2/3 development program, with nearly 800 exposed for greater than a year. The majority of these exposures were within the relevant dose range of 5mg to 10 mg given twice daily.

Anemia/Thrombocytopenia

The sponsor identified all new cases of anemia and thrombocytopenia and provided case reports for all cases for our review. We had identified 5 cases of anemia and one case of thrombocytopenia in our original review and asked the sponsor to elaborate on these cases and provide narratives for these and any new cases identified in the updated safety database.

There have been six new cases of anemia and one new case of thrombocytopenia identified in asenapine treated patients since the original NDA safety data were submitted. The sponsor has clarified that the single case of thrombocytopenia identified in the original review was, in fact, a

case of thrombocytosis. Therefore, in summary, there have been a total of 11 patients with anemia, one with thrombocytopenia, and one with thrombocytosis. Several of the patients with anemia had low red cell counts before they were dosed with asenapine and none of the patients with anemia had concurrent decreases in white blood cell counts or platelets. In addition, neither of the thrombocytosis nor the thrombocytopenia cases were associated with other clinically relevant hematologic changes.

In summary, the safety update has addressed our questions and not identified any new safety information that would materially change our original conclusions about the safety profile of asenapine.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22117	ORIG 1	ORGANON USA INC	SYCREST (ASENAPINE) TABLETS

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/s/

MITCHELL V Mathis
07/28/2009

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

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

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 (b) (6) 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 (b) (6), and on (b) (6), 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 (b) (6), 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 (b) (6) 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 hypoxia, hyponatremia, and rhabdomyolysis (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) (6). 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) (6), 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) (6) and the next day (b) (6) 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) (6). 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
K Kiedrow

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

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
M Mathis
G Zornberg
K Kiedrow

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
5/15/2008 07:55:09 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 both 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

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

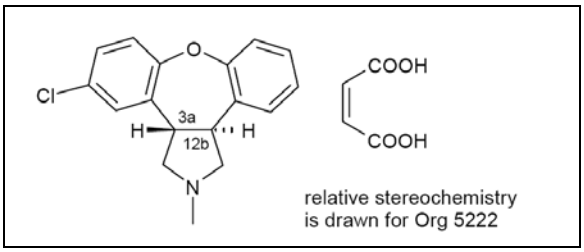
A single, small study in adolescents suggested that the pharmacokinetics of asenapine were similar between adolescents and adults. The study demonstrated that, compared to adults, adolescents swallowed a higher proportion of the asenapine dose.

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)

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 (b) (4) tablets containing 1, 2, and 5 mg asenapine, gelatin, and mannitol as a free base. The placebo for asenapine was formulated in (b) (4) 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

(b) (4)

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	

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 o (b) (4) 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 (b) (4)	07/28/06	268	Letter to FDA	Organon submits proposal regarding toxicological qualification of two asenapine degradants	

(b) (4)	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: unflavored SL tablet asenapine Route: (b) (4) Dose Regimen: (b) (4)	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) (4) tablet 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 (b) (4) (b) (4) versus freeze dried techniques	asenapine (b) (4) tablet Route: SL tablet Dose Regimen: 5 mg asenapine (b) (4) 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