**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