22-117 Asenapine: Addendum to Clinical NDA Review

NDA:	22-117
Drug:	Asenapine
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Date of Addendum:	June 26, 2008
Subject of Addendum:	Review of Deaths, Serious Adverse Events, and Selected Adverse Events
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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	8
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 [redacted]. 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).

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Robert Levin, M.D., June 27, 2008
Medical Officer,
FDA CDER ODE1 DPP HFD 130

cc: NDA 22-117
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