CLINICAL REVIEW

Application Type	sNDA
Application Number	22-117 S-019
Priority or Standard	Priority
Submit Date	September 12, 2014
Received Date	September 12, 2014
PDUFA Goal Date	March 12, 2015
Division / Office	DPP/ODE I
Reviewer Name	Greg Dubitsky, M.D.
Review Completion Date	February 17, 2015
Established Name	Asenapine
Trade Name	Saphris
Therapeutic Class	Antipsychotic
Applicant	Forest Laboratories
Formulation	Sublingual Tablets
Dosing Regimen	2.5mg BID to 10mg BID
Indication	Bipolar I D/O (manic or mixed)
Intended Population	Pediatric Patients (ages 10-17)

Template Version: March 6, 2009

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is recommended that this supplement be approved for the use of asenapine in the treatment of manic or mixed episodes associated with bipolar I disorder in pediatric patients ages 10-17.

1.2 Risk Benefit Assessment

The benefits of asenapine treatment of pediatric patients with manic or mixed mood episodes associated with bipolar I disorder are felt to outweigh the risks.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None are recommended at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

No further PMRs or PMCs are recommended.

2 Introduction and Regulatory Background

2.1 Product Information

Asenapine is an atypical antipsychotic that was first approved in the U.S. under the tradename Saphris on August 13, 2009. It is approved for the treatment of schizophrenia and for the acute treatment, either as monotherapy or adjunctive therapy, of manic or mixed episodes associated with bipolar I disorder. The approval of these indications was based on clinical trials in adult patients.

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently approved treatments for manic or mixed episodes in pediatric patients with bipolar I disorder include: Risperdal (risperidone), Abilify (aripiprazole), Seroquel XR (quetiapine extended-release), and Zyprexa (olanzapine). These drugs were studied in patients ages 10-17 years except for Zyprexa, which was studied in 13-17 year olds.

2.3 Availability of Proposed Active Ingredient in the United States

Asenapine has been available in the U.S. since 2009.

2.4 Important Safety Issues With Consideration to Related Drugs

Important risks associated with the use of atypical antipsychotics are:

• metabolic changes including hyperglycemia and diabetes mellitus, dyslipidemia, and weight gain.
• cerebrovascular events (e.g., stroke) in elderly patients with dementia-related psychosis.
• orthostatic hypotension and syncope.
• neuroleptic malignant syndrome.
• tardive dyskinesia.
• leukopenia, neutropenia, and agranulocytosis.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The approval of Saphris in 2009 carried a number of Postmarketing Requirements (PMRs) for pediatric trials to satisfy PREA requirements:

PMR 1496-1 - a deferred study to obtain pharmacokinetic (PK) data and provide information relevant to asenapine dosing in pediatric patients (ages 13-17) with schizophrenia.

PMR 1496-2 - a deferred study of the efficacy and safety of asenapine in pediatric patients (ages 13-17) with schizophrenia.

PMR 1496-3 - a deferred study to obtain pharmacokinetic (PK) data and provide information relevant to asenapine dosing in pediatric patients (ages 10-17) with manic or mixed episodes associated with bipolar I disorder.

PMR 1496-4 - a deferred study of the efficacy and safety of asenapine in pediatric patients (ages 10-17) with manic or mixed episodes associated with bipolar I disorder.

A waiver of PREA study requirements for ages 0-12 years for schizophrenia and 0-9 years for bipolar I disorder was granted because studies would be highly impractical because of the low incidence of disease in those age ranges.

A Written Request (WR) to obtain pediatric information on the use of asenapine in patients (ages 13-17) with schizophrenia and in patients (ages 10-17) with bipolar I disorder was issued by the Agency on September 23, 2009. The WR was formally

amended on June 2, 2010; October 22, 2010; and August 30, 2013. An administrative/ editorial change to the last amendment was issued on February 6, 2014.

Trials intended to address PMR 1496-3 and PMR 1496-4 as well as the requirements of the WR with respect to bipolar disorder were conducted under IND 70,329.

A pre-sNDA teleconference was held with the sponsor on July 23, 2013. The planned supplement would encompass a total of 6 trials: 2 PK studies of asenapine in pediatric patients, 2 trials in patients ages 12-17 with schizophrenia (an 8-week RCT and a 26-week open label study), and 2 trials in patients ages 10-17 with bipolar I disorder (a 3-week RCT and a 26 plus-week open-label study). An admonition against pooling safety data because of the diverse designs of these trials was communicated to the sponsor. The Agency had no objection to including 12 year old and 18 year old patients in the analyses for trial P05896 and 12 year old patients in the analyses of trial P05897. The Agency also advised the sponsor to propose an amendment to the WR to clarify that the minimum number of patients exposed for 6 months (N=100) could be derived from the pool of the two long-term studies in schizophrenia and bipolar disorder and not that number from each study. Other advice pertained to the evaluation of demographic factors on efficacy and safety findings, the analysis of C-SSRS data, and information regarding investigational sites to be submitted to the Office of Scientific Investigations (OSI) regarding clinical site inspections.

This supplement is intended to convey the information accrued from the 4 trials relevant to bipolar disorder.

2.6 Other Relevant Background Information

On January 31, 2014, the Agency was notified that ownership of NDA 22-117 had been transferred from Organon USA, Inc., a subsidiary of Merck, Sharp & Dohme Corp., to Forest Laboratories, Inc.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The consistency of adverse event information in this application was evaluated by comparing information across the following documents for a sample of 6 patients from the two Phase 3 bipolar trials: Case Report Forms (CRFs), Narrative Summaries (NSs), and adverse event data listings (ae.xpt files). The 6 patients audited were:

- P06107-0010-100123.
- P06107-0018-100461.
- P06107-0018-100475.

• P06107-0035-100845.
• P05898-0048-100021.
• P05898-0104-101025.

Adverse event data was found to be consistently documented for these patients.

Additionally, the sponsor's coding of adverse event verbatim terms (AELIT) to preferred terms (AEDECOD), as documented in the adverse event data files (ae.xpt) for trials P06107 and P05898, was audited. No inaccuracies in adverse event coding were detected. However, as will be discussed in Section 7.1.2, because MedDRA allows splitting of closely related verbatim terms to multiple coded terms, related preferred terms have been combined into common terms for purposes of this review.

3.2 Compliance with Good Clinical Practices

Trials P06107 and P05898 were both conducted in accordance with Good Clinical Practice standards.

I requested that the Office of Scientific Investigations (OSI) conduct inspections of sites 18 and 45 in trial P06107. These sites were inspected on January 12-15, 2015, and January 12-21, 2015, respectively. A Clinical Inspection Summary was completed on February 9, 2015, by Dr. Jenn W. Sellers of OSI. There were no deviations from regulations identified and the data from both sites were felt to be acceptable. The preliminary classification for both sites was NAI.

3.3 Financial Disclosures

Clinical Investigator Financial Disclosure
Review Template

Application Number: 22-117 S-019

Submission Date(s): September 12, 2014

Applicant: Forest Laboratories

Product: Saphris

Reviewer: Greg Dubitsky, M.D.

Date of Review: February 17, 2015

Covered Clinical Study (Name and/or Number): P06107

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)

Total number of investigators identified: 92		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*. Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

No investigators in trial P06107 had disclosable financial information.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

There is no new information in this supplement regarding the mechanism of action of asenapine in treating schizophrenia.

4.4.2 Pharmacodynamics

There is no new information on the pharmacodynamics of asenapine.

4.4.3 Pharmacokinetics

The sponsor conducted two studies to explore the safety and PK of asenapine in the pediatric population (A70501022 and P06522). In addition, a pediatric population PK analysis was performed using data from these two PK studies and from the 2 pediatric RCTs, one in schizophrenia (P05896) and one in bipolar I disorder (P06107), to develop a population PK model for asenapine in pediatric patients.

Study A70501022 was a randomized, double-blind, placebo-controlled, parallel group study of multiple dose sublingual asenapine in 40 adolescents (ages 12-17) with a psychotic disorder. Doses of 1, 3, 5, and 10mg q12 hours were administered for 10 days. Eight patients took asenapine and 2 took placebo in each dose group.

Study P06522 was an open-label, rising multiple dose study in 30 patients age 10-17 years with schizophrenia or a manic or mixed episode associated with bipolar I disorder. Patients with autism, conduct disorder, oppositional defiant disorder, or other condition requiring antipsychotic treatment were allowed in some cohorts. Patients ages 10-11 (N=6) were treated with in sequential sublingual asenapine dose groups of 2.5mg bid for 7 days, 5mg bid for 7 days, or 10mg bid for 12 days (N=6 per cohort), with a decrease from 10 to 5mg bid for 7 days if intolerance emerged in the 10mg bid cohort. Patients ages 12-17 received a sublingual dose of 10mg bid for 8 days in 3 parallel age cohorts (12-13, 14-15, and 16-17), with 4 patients per cohort.

The Office of Clinical Pharmacology (OCP) reviewer, Dr. Andre Jackson, concluded that asenapine exposure was similar in adults, adolescents, and children 10-11 years old.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The following studies were conducted to support a claim for manic and mixed mood episodes associated with bipolar I disorder in the pediatric population.

Table 1: Table of Studies in Pediatric Bipolar Disorder	
Phase/Study	**Study Design**
Phase 1	
A70501022	Randomized, double-blind, placebo-controlled, parallel group safety and PK study of multiple dose asenapine in 40 adolescents (ages 12-17) with a psychotic disorder. Dosing was 1, 3, 5, and 10mg q12 hours for 10 days.
P06522	Open-label, rising multiple dose safety and PK study in 30 patients (ages 10-17) primarily with schizophrenia or bipolar I disorder. Dosing was 2.5, 5, and 10 mg/day for 7-12 days.
Phase 3	
P06107	3-week, randomized, double-blind, placebo-controlled safety and efficacy trial in 403 patients (ages 10-17) with manic or mixed mood episodes associated with bipolar I disorder using fixed doses of 2.5mg BID, 5mg BID, 10mg BID, or placebo.
P05898	50-week, open-label extension safety study for completers of trial P06107 using flexible dosing with 2.5mg BID to 10mg BID.

Hereafter in this review, the 2.5mg BID, 5mg BID, and 10mg BID doses will be referred to as 2.5mg, 5mg, and 10mg, respectively.

This information was contained in the following submissions:

Table 2: Submissions to the sNDA		
Submission Date	**Sequence #**	**Contents**
Sep 12, 2014	0171	Original sNDA
Jan 8, 2015	0196	Four-Month Safety Update Report
Jan 21, 2015	0197	Requested conversion of laboratory data from SI to conventional units.
Jan 23, 2015	0198	Requested information regarding the sponsor's literature search and cumulative exposure.
Feb 3, 2015	0201	Requested patient laboratory data.

5.2 Review Strategy

The efficacy review of this supplement is based solely on the results of trial P06107.

The safety review of this supplement is comprised of two components: 1) an examination of serious adverse events (SAEs) and adverse events that led to dropout in all 4 studies (including limited safety information from study P05898 contained in the Four-Month Safety Update Report submitted on January 8, 2015) and 2) an evaluation of supportive safety findings from analyses of data primarily from trial P06107, to include an assessment of common adverse events, laboratory tests, vital signs, and ECGs.

6 Review of Efficacy

Efficacy Summary

The efficacy of asenapine 2.5mg BID, 5mg BID, and 10mg BID in patients ages 10-17 with bipolar disorder in a manic or mixed state was evaluated in one clinical trial (P06107). Superiority over placebo was demonstrated for all three doses on both the primary endpoint (change from baseline to Day 21 in the Young-Mania Rating Scale (Y-MRS)) and the key secondary endpoint (change from baseline to Day 21 in the CGI-Bipolar (CGI-BP) score) after appropriate adjustment for multiple comparisons. In terms of dose-response, the 5mg BID dose was superior to 2.5mg BID but approximately equal to the 10mg BID dose. The biometrics reviewer, Dr. Jialu Zhang, completed a Statistical Review and Evaluation on February 5, 2015, and concurs with this conclusion.

6.1 Efficacy in Pediatric Schizophrenia

6.1.1 Methods

The demonstration of the efficacy of asenapine in pediatric patients (ages 12-17) with bipolar disorder is based on a single clinical trial (P06107). Because asenapine is approved for the treatment of adults with bipolar disorder and it is felt that bipolar illness is essentially the same in older children, adolescents, and adults, a single efficacy trial is deemed to be sufficient.

P06107 was an 3-week, randomized, double-blind, placebo-controlled, parallel group trial. This investigation was conducted at 58 sites in the U.S. and 9 sites in Russia.

Important inclusion criteria for this trial were:

• age ≥10 years when providing assent/consent and ≤17 years when randomized.

• diagnosis of bipolar I disorder in a current manic or mixed state by DSM-IV-TR criteria confirmed by a structured clinical interview (K-SADS-PL) at screening.
• at least one manic-specific symptom: elation, grandiosity, flight of ideas/racing thoughts, decreased need for sleep, or hypersexuality.
• Y-MRS total score ≥20 at screening and baseline.
• CGI-$BP_{overall}$ severity score ≥4 at screening and baseline.

Relevant exclusion criteria were:

• diagnosis of a psychotic disorder.
• known or suspected mental retardation, organic brain disorder, or an IQ <70.
• meets DSM-IV-TR criteria for substance abuse or dependence (except for nicotine or caffeine) within the prior 6 months.
• behavioral disturbance thought to be substance-induced.
• at imminent risk of self-harm or harm to others in the opinion of the investigator.
• suicidal ideation with intent, with or without a plan, in the past 2 months or suicidal behavior in the past 6 months as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS).
• history of tardive dyskinesia, tardive dystonia, or NMS.
• an uncontrolled or unstable and clinically significant medical condition that might interfere with safety and efficacy evaluations in the investigator's opinion.
• females who are pregnant or breast-feeding or intend to become pregnant during the course of the trial.
• known or suspected seizure disorder.
• unwillingness or inability to taper off prohibited medication.

Eligible patients were randomized in a 1:1:1:1 ratio to treatment with asenapine 2.5mg BID, asenapine 5mg BID, asenapine 10mg BID, or placebo (referred to as the 2.5mg, 5mg, 10mg, and placebo groups, respectively). All treatments were supplied as fast-dissolving black cherry-flavored sublingual tablets to be taken daily at approximately 8AM and 8PM. Patients assigned to the 5mg group received 2.5mg BID until their Day 4 visit, when the dose was increased to 5mg BID and continued until the end of the treatment period. Patients assigned to the 10mg group received 2.5mg BID until their Day 4 visit, when the dose was increased to 5mg BID and continued until Day 7. On Day 7, these patients began 10mg BID which was continued to the end of the treatment period.

The primary efficacy variable was the change from baseline to Day 21 in the Y-MRS total score. The key secondary measure was the change from baseline to Day 21 in the severity of bipolar illness as measured by the CGI-$BP_{overall}$. Both the primary and key secondary assessments were performed at screening and baseline and on Days 4, 7, 14, and 21. The statistical analysis for both was done using MMRM (Mixed Model for Repeated Measures) on the FAS (Full Analysis Set, defined as all randomized patients who received at least one dose of trial medication and had a baseline and at least one

post-baseline on-treatment Y-MRS assessment). Multiplicity adjustment for the three comparisons (2.5mg vs. placebo, 5mg vs. placebo, and 10mg vs. placebo) was performed using the Hochberg procedure with a 2-sided alpha level of 5%. Only if the primary efficacy null hypothesis is rejected for all three comparisons would the key secondary hypotheses be tested.

The trial was monitored by an independent, external Data Monitoring Committee (DMC) on an ongoing basis to evaluate the trial safety data, among other responsibilities, and to make recommendations as to whether the study should continue to recruit patients, be modified, or be terminated. The DMC consisted of 4 voting members representing the fields of psychiatry and statistics.

6.1.2 Demographics

Overall, almost half of the study patients were male (47%) but these was some variation in gender composition across the treatment groups (range of 38% to 59% male). The treatment groups were reasonably well-balanced in terms of age, race, and ethnicity. The mean age across all groups was 13.8 years with 72% over the age of 12 years. Racially, the most common group was white (68%) followed by Black or African American (24%). About 88% were classified as not Hispanic or Latino in terms of ethnicity. U.S. patients made up 94% of the patient sample.

Most of the patients (58%) were in a mixed mood state at study entry, with 42% in a manic state. For the majority of the patients (61%), the current episode had lasted more than 4 weeks. Only 33% were naive to antipsychotic medication. About 12% were classified as rapid cyclers (≥4 mood episodes in the previous 12 months).

6.1.3 Subject Disposition

Patient disposition is displayed in the table below. About 87% of all patients completed the trial, with 80% continuing treatment in the extension trial. Completion rates were comparable across treatment groups. The most common reason for dropout overall was because of an adverse event, which occurred more frequently in the asenapine groups than in the placebo group. Kaplan-Meier plots of discontinuation over time were similar across the four treatment groups.

Table 3: Subject Disposition (P06107)

	Placebo		2.5 mg		5.0 mg		10.0 mg		Total	
Subject Disposition	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Randomized And Treated	101	(100.0)	104	(100.0)	99	(100.0)	99	(100.0)	403	(100.0)
Discontinued Treatment Phase	14	(13.9)	16	(15.4)	11	(11.1)	12	(12.1)	53	(13.2)
Adverse Event	4	(4.0)	7	(6.7)	5	(5.1)	5	(5.1)	21	(5.2)
AE/SAE Due To Disease Under Study	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Treatment Failure	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.0)	1	(0.2)
Lost To Follow-Up	3	(3.0)	2	(1.9)	3	(3.0)	2	(2.0)	10	(2.5)
Subject Withdrew Consent	0	(0.0)	2	(1.9)	0	(0.0)	3	(3.0)	5	(1.2)
Non-Compliance With Protocol	7	(6.9)	4	(3.8)	3	(3.0)	1	(1.0)	15	(3.7)
Did Not Meet Protocol Eligibility	0	(0.0)	1	(1.0)	0	(0.0)	0	(0.0)	1	(0.2)
Administrative	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Completed Treatment Phase	87	(86.1)	88	(84.6)	88	(88.9)	87	(87.9)	350	(86.8)
Continued In Extension Trial	81	(80.2)	80	(76.9)	84	(84.8)	77	(77.8)	322	(79.9)

The n and % of randomized and treated subjects are based on All-Patients-as-Treated, as a result entries represent n and % of subjects who were randomized and treated subjects.
The reasons for discontinuation and completers originate from the End of Treatment form.
All-Patients-as-Treated = All randomized subjects who received at least one dose of trial medication.
Data Source: [16.4]

The FAS consisted of 395 patients (or 98% of those randomized): 98 in the placebo group and 101, 98, and 98 in the 2.5mg, 5mg, and 10mg groups, respectively.

6.1.4 Analysis of the Primary Endpoint

Results on the primary efficacy endpoint are summarized in the following table.

Table 4: Change From Baseline to Day 21 in the Y-MRS (P06107)

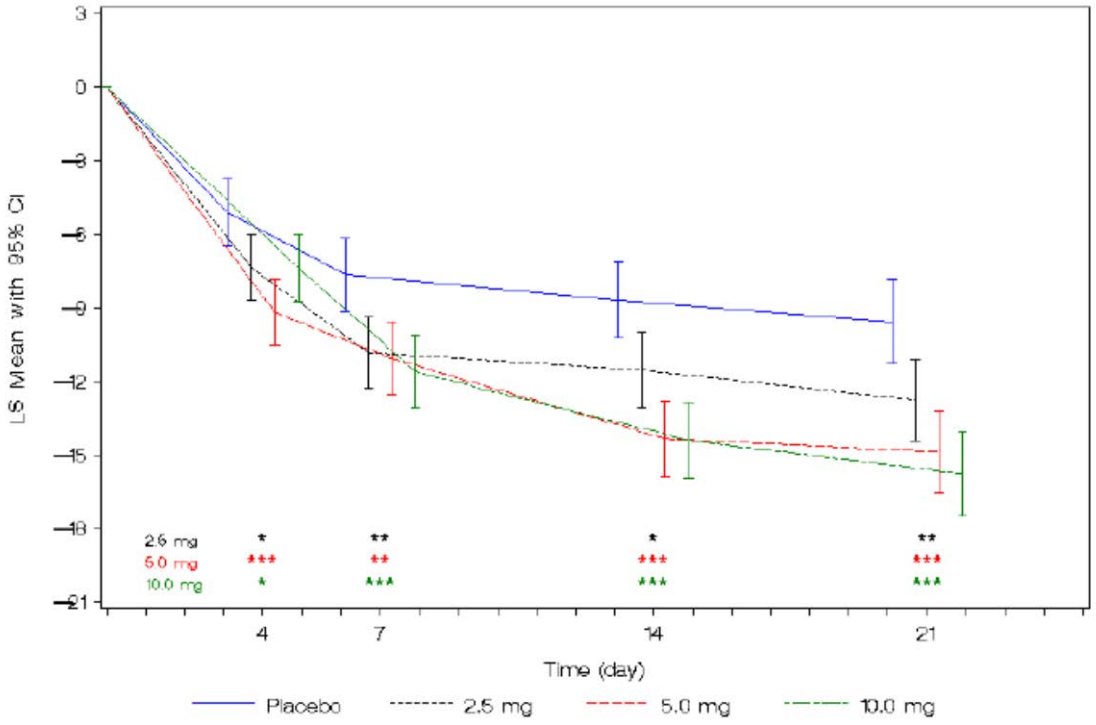
		Baseline		Day 21		Change from Baseline at Day 21			
Treatment	N	Mean	(SD)	Mean	(SD)	Mean	(SD)	LS Mean	(95% CI)[†]
Placebo	79	30.1	(5.7)	20.5	(8.4)	-9.6	(7.8)	-9.6	(-11.3, -7.9)
2.5 mg	88	29.5	(5.7)	17.2	(9.4)	-12.3	(9.0)	-12.8	(-14.4, -11.1)
5.0 mg	87	30.4	(5.9)	15.3	(8.4)	-15.1	(9.5)	-14.9	(-16.5, -13.2)
10.0 mg	81	30.1	(5.7)	14.2	(8.8)	-15.9	(9.1)	-15.8	(-17.5, -14.1)

Pairwise Comparison	Difference in LS Means (95% CI)	p-Value	Adjusted p-Value
2.5 mg vs. Placebo	-3.2 (-5.6, -0.8)	0.008	0.008
5.0 mg vs. Placebo	-5.3 (-7.7, -2.9)	<0.001	<0.001
10.0 mg vs. Placebo	-6.2 (-8.6, -3.8)	<0.001	<0.001

[†]Based on MMRM model with term of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit. The variance-covariance matrix over the repeated visits was taken unstructured. The adjusted p-Value at Day 21 is adjusted by Hochberg's method for testing three asenapine groups versus the placebo group.
N=Number of subjects with a Baseline and a Day 21 value. Y-MRS total score could range from 0 (all symptoms absent) to 60 (all symptoms extreme). Decreases from baseline within a treatment group were indicative of an improvement in symptoms. Full Analysis Set=All randomized subjects who received at least one dose of trial medication and had both baseline and at least one post-baseline in-treatment Y-MRS total score. Y-MRS=Young Mania Rating Scale; MMRM=Mixed Model for Repeated Measures; SD=Standard Deviation; LS=Least Squares; CI=Confidence Interval.
Data Source: [16.4]

The following figure depicts the mean change from baseline in the Y-MRS over time.

Figure 1: LS Mean Change from Baseline (95% CI) in the Y-MRS By Visit (P06107) (FAS)



Unadjusted p-Values for treatment comparisons with Placebo: ***p-Value <0.001, **p-Value <0.01, *p-Value<0.05; CI = Confidence Interval; Y-MRS = Young Mania Rating Scale; MMRM = Mixed Model for Repeated Measures; Full Analysis Set=All randomized subjects who received at least one dose of trial medication and had both baseline and at least one post-baseline in-treatment Y-MRS total score.

All three asenapine dose groups demonstrated statistically significant superiority over placebo on the primary efficacy endpoint after adjustment for multiple comparisons. The 5mg BID dose was numerically superior to the 2.5mg BID dose but roughly equal to the 10mg group.

6.1.5 Analysis of the Key Secondary Endpoints

The key secondary measure was the change from baseline to Day 21 in the CGI-BP overall score. Results on this endpoint are displayed in the table below.

Table 5: Change from Baseline to Day 21 in the CGI-BP Overall Score (P06107)

Treatment	N	Baseline Mean	Baseline (SD)	Day 21 Mean	Day 21 (SD)	Change from Baseline at Day 21 Mean	(SD)	LS Mean	(95% CI)†
Placebo	79	4.4	(0.5)	3.7	(0.9)	-0.7	(0.9)	-0.7	(-0.9, -0.5)
2.5 mg	88	4.5	(0.6)	3.2	(1.1)	-1.3	(1.1)	-1.3	(-1.5, -1.1)
5.0 mg	87	4.4	(0.6)	3.0	(1.0)	-1.4	(1.0)	-1.4	(-1.6, -1.2)
10.0 mg	81	4.4	(0.6)	3.0	(1.0)	-1.4	(1.0)	-1.4	(-1.6, -1.2)

Pairwise Comparison	Difference in LS Means (95% CI)	p-Value	Adjusted p-Value
2.5 mg vs. Placebo	-0.6 (-0.9, -0.3)	<0.001	<0.001
5.0 mg vs. Placebo	-0.7 (-0.9, -0.4)	<0.001	<0.001
10.0 mg vs. Placebo	-0.7 (-1.0, -0.4)	<0.001	<0.001

†Based on MMRM model with term of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit. The variance-covariance matrix over the repeated visits was taken unstructured. The adjusted p-Value at Day 21 is adjusted by Hochberg's method for testing three asenapine groups versus the placebo group.

N=Number of subjects with a Baseline and a Day 21 value. CGI-BP=Clinical Global Impression of Severity of Bipolar illness; Possible CGI-BP Score ranged from 1 (normal not at all ill) to 7 (among the most extremely ill subjects). Decreases from baseline within a treatment group were indicative of an improvement. Full Analysis Set=All randomized subjects who received at least one dose of trial medication and had both baseline and at least one post-baseline in-treatment Y-MRS total score. Y-MRS=Young Mania Rating Scale; MMRM=Mixed Model for Repeated Measures; SD=Standard Deviation; LS=Least Squares; CI=Confidence Interval.

Data Source: [16.4]

All three dose groups demonstrated statistically significant superiority over placebo after adjustment for multiplicity on the key secondary endpoint.

6.1.6 Other Endpoints

Other secondary endpoints included the Y-MRS responder rate and the Y-MRS remitter rate. A responder was defined as a patient who experienced at least a 50% decrease from baseline in the Y-MRS total score. At endpoint, the percentages of FAS patients who met the responder criterion were:

Placebo	28%	(27/98)
Asenapine 2.5mg	42%	(42/101)
Asenapine 5mg	54%	(53/98)
Asenapine 10mg	52%	(51/98)

A remitter was defined as a patient who had a Y-MRS total score ≤12. At endpoint, the percentages of FAS patients who met the remitter criterion were:

Placebo	18%	(18/98)
Asenapine 2.5mg	36%	(36/101)
Asenapine 5mg	42%	(41/98)
Asenapine 10mg	45%	(44/98)

These results follow the same pattern as the findings on the primary and key secondary endpoints.

6.1.7 Subpopulations

The sponsor conducted analyses of the potential effects of subgroup features (e.g., age, gender, race, region, cycling frequency, previous antipsychotic treatment) on the average treatment effect of asenapine versus placebo on the primary efficacy variable (change from baseline to day 21 in the Y-MRS total score). The results, shown in the following table, revealed no statistically significant differences between subgroups (alpha =0.10).

Table 6: Change From Baseline to Day 21 in the Y-MRS Score By Subgroup (Trial P06107)

Subgroup	Category	Pairwise comparison	Difference		p-Value interaction test Day 21*
			LS Means	(95% CI)	
Age Category	<= 12 years (N=111)	2.5 mg vs. Placebo	-4.9	(-9.3, -0.5)	0.301
		5.0 mg vs. Placebo	-6.6	(-11.1, -2.2)	
		10.0 mg vs. Placebo	-8.2	(-13.0, -3.4)	
	> 12 years (N=284)	2.5 mg vs. Placebo	-2.5	(-5.4, 0.3)	
		5.0 mg vs. Placebo	-4.8	(-7.6, -2.0)	
		10.0 mg vs. Placebo	-5.4	(-8.2, -2.6)	
Sex	Female (N=206)	2.5 mg vs. Placebo	-5.7	(-8.9, -2.5)	0.249
		5.0 mg vs. Placebo	-5.4	(-8.5, -2.3)	
		10.0 mg vs. Placebo	-6.3	(-9.7, -2.9)	
	Male (N=189)	2.5 mg vs. Placebo	-0.2	(-3.8, 3.3)	
		5.0 mg vs. Placebo	-4.8	(-8.5, -1.1)	
		10.0 mg vs. Placebo	-5.3	(-8.8, -1.8)	
Race	Caucasian (N=270)	2.5 mg vs. Placebo	-3.1	(-6.0, -0.3)	0.916
		5.0 mg vs. Placebo	-5.7	(-8.6, -2.8)	
		10.0 mg vs. Placebo	-6.0	(-9.0, -3.1)	
	Non-Caucasian (N=125)	2.5 mg vs. Placebo	-3.4	(-7.9, 1.0)	
		5.0 mg vs. Placebo	-4.4	(-8.7, -0.0)	
		10.0 mg vs. Placebo	-6.3	(-10.6, -2.0)	
Region	US (N=369)	2.5 mg vs. Placebo	-3.4	(-5.9, -0.9)	0.126
		5.0 mg vs. Placebo	-5.6	(-8.1, -3.1)	
		10.0 mg vs. Placebo	-6.4	(-8.9, -3.9)	
	Non-US (N=26)	2.5 mg vs. Placebo	0.6	(-8.2, 9.4)	
		5.0 mg vs. Placebo	1.3	(-8.2, 10.9)	
		10.0 mg vs. Placebo	1.2	(-9.0, 11.3)	
Ethnicity	Hispanic or Latino (N=50)	2.5 mg vs. Placebo	-0.4	(-7.4, 6.5)	0.344
		5.0 mg vs. Placebo	-4.2	(-10.8, 2.4)	
		10.0 mg vs. Placebo	-3.0	(-9.5, 3.4)	
	Not Hispanic or Latino (N=345)	2.5 mg vs. Placebo	-3.6	(-6.2, -1.1)	
		5.0 mg vs. Placebo	-5.5	(-8.1, -3.0)	
		10.0 mg vs. Placebo	-6.7	(-9.3, -4.1)	

Table 6: Change From Baseline to Day 21 in the Y-MRS Score By Subgroup (continued)

Subgroup	Category	Pairwise comparison	Difference		p-Value interaction test Day 21*
			LS Means	(95% CI)	
Age Category of Onset of Bipolar I Disorder	<= 11 years (N=219)	2.5 mg vs. Placebo	-3.7	(-6.9, -0.4)	0.255
		5.0 mg vs. Placebo	-7.3	(-10.7, -3.9)	
		10.0 mg vs. Placebo	-7.2	(-10.5, -3.8)	
	>11 years (N=176)	2.5 mg vs. Placebo	-2.8	(-6.5, 0.8)	
		5.0 mg vs. Placebo	-3.3	(-6.7, 0.0)	
		10.0 mg vs. Placebo	-5.1	(-8.7, -1.5)	
Concomitant Stimulant Use	Yes (N=95)	2.5 mg vs. Placebo	-4.6	(-9.4, 0.1)	0.135
		5.0 mg vs. Placebo	-9.3	(-14.4, -4.2)	
		10.0 mg vs. Placebo	-9.1	(-14.0, -4.1)	
	No (N=300)	2.5 mg vs. Placebo	-2.9	(-5.7, -0.2)	
		5.0 mg vs. Placebo	-4.1	(-6.8, -1.4)	
		10.0 mg vs. Placebo	-5.3	(-8.0, -2.5)	
Comorbid ADHD	Yes (N=216)	2.5 mg vs. Placebo	-3.4	(-6.6, -0.3)	0.680
		5.0 mg vs. Placebo	-5.4	(-8.9, -2.0)	
		10.0 mg vs. Placebo	-7.0	(-10.2, -3.8)	
	No (N=179)	2.5 mg vs. Placebo	-3.2	(-6.8, 0.5)	
		5.0 mg vs. Placebo	-4.9	(-8.3, -1.6)	
		10.0 mg vs. Placebo	-5.3	(-9.0, -1.6)	
Cycling Frequency	Rapid (N=38)	2.5 mg vs. Placebo	-6.3	(-14.0, 1.3)	0.219
		5.0 mg vs. Placebo	-11.3	(-20.5, -2.0)	
		10.0 mg vs. Placebo	-9.4	(-17.5, -1.2)	
	Not Rapid (N=281)	2.5 mg vs. Placebo	-3.3	(-6.1, -0.4)	
		5.0 mg vs. Placebo	-4.3	(-7.1, -1.5)	
		10.0 mg vs. Placebo	-5.7	(-8.6, -2.8)	
Naive to Antipsychotic Treatment	Yes (N=129)	2.5 mg vs. Placebo	-1.9	(-6.1, 2.2)	0.364
		5.0 mg vs. Placebo	-4.2	(-8.3, -0.2)	
		10.0 mg vs. Placebo	-5.0	(-9.3, -0.6)	
	No (N=266)	2.5 mg vs. Placebo	-4.0	(-6.9, -1.1)	
		5.0 mg vs. Placebo	-5.9	(-8.9, -3.0)	
		10.0 mg vs. Placebo	-7.0	(-9.9, -4.0)	

Table 6: Change From Baseline to Day 21 in the Y-MRS Score By Subgroup (continued)

Subgroup	Category	Pairwise comparison	Difference		p-Value interaction test Day 21*
			LS Means	(95% CI)	
Severe with Psychotic Features	Yes (N=31)	2.5 mg vs. Placebo	-2.2	(-11.0, 6.5)	0.562
		5.0 mg vs. Placebo	-12.2	(-23.7, -0.8)	
		10.0 mg vs. Placebo	-7.9	(-17.4, 1.5)	
	No (N=363)	2.5 mg vs. Placebo	-3.5	(-5.9, -1.0)	
		5.0 mg vs. Placebo	-5.2	(-7.6, -2.8)	
		10.0 mg vs. Placebo	-6.1	(-8.5, -3.6)	
Race (3 Categories)	White (N=270)	2.5 mg vs. Placebo	-3.1	(-6.0, -0.3)	0.815
		5.0 mg vs. Placebo	-5.7	(-8.6, -2.8)	
		10.0 mg vs. Placebo	-6.1	(-9.0, -3.1)	
	Black (N=94)	2.5 mg vs. Placebo	-4.7	(-10.0, 0.6)	
		5.0 mg vs. Placebo	-3.3	(-8.4, 1.8)	
		10.0 mg vs. Placebo	-7.7	(-12.8, -2.7)	
	Others (N=31)	2.5 mg vs. Placebo	0.0	(-8.0, 8.0)	
		5.0 mg vs. Placebo	-9.4	(-17.9, -0.9)	
		10.0 mg vs. Placebo	-1.4	(-10.0, 7.2)	

CI=Confidence Interval; MMRM=Mixed Model for Repeated Measures.
Full Analysis Set=All randomized subjects who received at least one dose of trial medication and had both baseline and at least one post-baseline in-treatment Y-MRS Total Score. Y-MRS=Young Mania Rating Scale.
Y-MRS Total Score could range from 0 (all symptoms absent) to 60 (all symptoms extreme). Decreases from baseline within a treatment group were indicative of an improvement in symptoms.
*The interaction test tests if the treatment effect of Asenapine versus placebo is equal between the defined categories of the subgroups.
Data Source: [16.4]

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The sponsor evaluated dose-response for efficacy by examining 7 possible dose response patterns across the four treatment groups based on adjusted p-values for the primary endpoint. The pattern that best fit the data was a sequential increase in response from placebo to 2.5mg BID to 5mg BID, with an equal response for 5mg BID and 10mg BID.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance of Effects

A trial to evaluate asenapine in the maintenance of efficacy in bipolar disorder in adults is ongoing in response to PMC #1496-5. It is expected that the study report will be forwarded to the Agency by October 31, 2015 (b) (4)

(b) (4)

[redacted]

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6.1.10 Additional Efficacy Issues/Analyses

I determined the frequency of concomitant mood stabilizer use in trial P06107 by searching the concomitant medication dataset (CRX.xpt) to identify patients who took such medication among patients who were randomized, treated, and took a concomitant medication during the interval from the first dose to the last dose of study drug (RANDOM=1, TREATED=1, and CONMFLG=1). Mood stabilizers were identified by any of the following parameters in this dataset:

- APSYCHCD=1 or 2 (any atypical or typical antipsychotic).
- MOODSFLG=1 (any prespecified mood stabilizer, such as lithium or valproate).
- CRXLIT (verbatim description of the concomitant agent) contained any of the following words: Saphris, asenapine, Tegretol, carbamazepine, Klonopin, or clonazepam (i.e., additional mood stabilizing agents not designated by MOODSFLG=1).

Use was very infrequent and equal across all treatment groups:

Placebo	1%	(1/101)
Asenapine 2.5mg	1%	(1/103)
Asenapine 5mg	1%	(1/99)
Asenapine 10mg	1%	(1/100)

This use was unlikely to have affected the efficacy conclusions from this trial.

7 Review of Safety

Safety Summary

Safety data in pediatric bipolar was derived primarily from an 3-week placebo-controlled trial (P06107) and, to a more limited extent, a 26-week open-label trial (P05898). As of the cutoff date for the original submission, the latter study was ongoing and, thus, data were incomplete. As of the cutoff date for the Four-Month Safety Update Report, the latter study had been completed but only limited safety data (serious adverse events and dropouts caused by adverse events) were submitted for review.

There were no deaths in the pediatric bipolar disorder studies.

Non-fatal serious adverse events were mostly related to exacerbation of the underlying illness in trial P06107. As of the cutoff for the Four-Month Safety Update Report, in the

50-week open label study (P05898), most of the serious adverse events were psychiatric in nature, the most commonly reported being suicidal ideation (8 patients), aggression, bipolar disorder, and depression (3 patients each); and agitation (2 patients).

The most common adverse events that led to dropout in trial P06107 were somnolence, abdominal pain, and nausea. As of the cutoff for the Four-Month Safety Update Report, adverse events that led to dropout in the open-label study P05898 (total N=321) were mostly psychiatric in nature: aggression and suicidal ideation (3 patients each) and anxiety, ADHD, bipolar disorder, depression, depressive symptom, irritability, and suicidal behavior (2 patients each).

Other significant safety findings were:

- hyperglycemia, new onset diabetes mellitus, and metabolic syndrome.
- dyslipidemia (increased cholesterol and triglycerides relative to placebo).
- increased body weight.
- hypersensitivity reactions.
- hyperprolactinemia.
- somnolence.
- extrapyramidal symptoms (akathisia and Parkinsonism).
- oral hypoesthesia.

The most common adverse events felt to be probably drug-related were oral paresthesia, nausea, fatigue, weight increased, increased appetite, somnolence, dizziness, and dysgeusia. Only fatigue and dysgeusia are considered possibly dose-related.

Remarkable laboratory test abnormalities associated with asenapine treatment were an increased mean change in platelet count and liver enzymes (SGPT, SGOT, and GGT) and a greater proportion of asenapine- versus placebo-treated patients with decreases in white blood cell and neutrophil counts and increased SGPT levels.

Vital sign changes associated with asenapine treatment were increased mean changes in standing diastolic blood pressure (about 2 mmHg) and increased supine pulse (2-4 bpm).

Most of these safety findings are already known to be associated with asenapine treatment and are labeled. There are no new findings that suggest a hazard which would preclude approval of this supplement or require a major labeling change.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data were derived primarily from studies P06107 and P05898.

7.1.2 Categorization of Adverse Events

Adverse event verbatim terms were coded to preferred terms using MedDRA version 16.0. Although an audit of this coding process revealed no major inaccuracies, the granularity of MedDRA does allow splitting of some adverse event terms to an extent that may not be clinically useful. Therefore, for purposes of this review, the following related adverse event preferred terms were subsumed under a common term for calculation of reporting rates in the following sections.

Common Term	Subsumed Preferred Terms
Somnolence	Somnolence, sedation, hypersomnia.
Abdominal pain	Abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort.
Bipolar disorder	Bipolar disorder, bipolar I disorder, mania, mood swings, tachyphrenia.
Hyperinsulinemia	Hyperinsulinemia, blood insulin increased.
Tachycardia	Tachycardia, heart rate increased.
Fatigue	Fatigue, lethargy.
Leukopenia	Leukopenia, neutropenia, white blood cell count decreased

Adverse events were also categorized as serious or non-serious. Serious adverse events (SAEs) were defined by one of the following criteria:

- results in death.
- life-threatening (at immediate risk of death at the time of the occurrence).
- requires inpatient hospitalization or prolongs inpatient hospitalization.
- results in persistent or significant disability or incapacity.
- congenital abnormality or birth defect.
- other important medical events, that is, events not meeting any of the above criteria but which may jeopardize the subject and may require medical or surgical intervention to prevent one of the above outcomes.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Because of the significant differences in study design between the 2 trials in the pediatric bipolar program, studies were not pooled.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

For purposes of evaluating exposure in the pediatric population, the 4 Phase 3 trials in pediatric patients were pooled, in accordance with the Written Request:

• P05896 - 8-week randomized, double-blind, placebo-controlled study in schizophrenic patients (ages 12-17).
• P05897 - 26-week open-label extension to P05896.
• P06107 - 3-week randomized, double blind, placebo-controlled study in patients with manic or mixed episodes associated with bipolar I disorder (ages 10-17).
• P05898 - 50-week ongoing open-label extension to P06107.

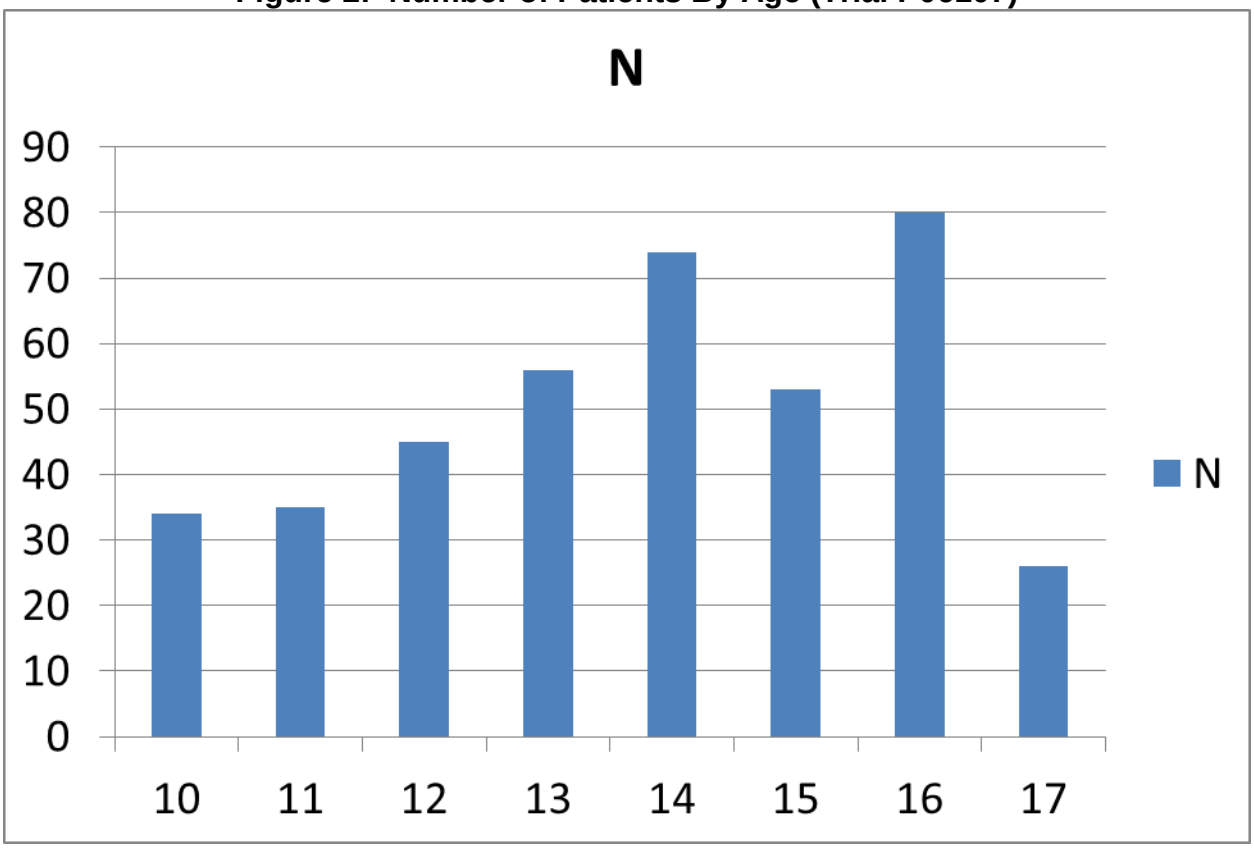
Across these 4 trials, patients were treated with sublingual asenapine in the dose range of 2.5mg BID to 10mg BID. As of October 31, 2014 (the cutoff date for the Four-Month Safety Update Report), a total of 651 patients received asenapine treatment for any duration, 352 received asenapine for 180 days or longer, and 58 received asenapine for 365 days or longer.

Demographic characteristics of patients in trial P06107 were generally consistent across the four treatment groups (placebo and asenapine 2.5mg, 5mg, and 10mg) with the exception of gender, which displayed moderate variability:

Dose Group	Percentage of Females
Placebo	62%
2.5mg	50%
5mg	57%
10mg	41%

Overall, the median age was 14.0 years, with 28% age 12 or younger. The most common racial groups were white (68%) and Black or African American (24%). Ethnically, most patients (88%) were classified as not Hispanic or Latino. Most of the patients were from U.S. sites (94%). The mean baseline weight and BMI percentiles adjusted for age and sex were 70% and 72%, respectively. In terms of height, the mean percentile adjusted for age and sex was 50%. So, although patients tended to be of average height, they were heavier for their age and sex. The distribution of patients by age is shown in the figure below.

Figure 2: Number of Patients By Age (Trial P06107)



There was a reasonable distribution of patients across ages in this trial.

7.2.2 Explorations for Dose Response

The fixed dose design of trial P06107 permitted an assessment of the dose-response relationship for safety findings.

7.2.4 Routine Clinical Testing

In addition to adverse event assessments, safety measurements in trial P06107 include the following:

• laboratory testing at screening and baseline and on day 21. Inpatients provided blood samples prior to breakfast and outpatients were instructed to fast overnight, if possible. Laboratory tests consist of hematology (including total WBC counts as well as neutrophil, monocyte, eosinophil, and lymphocyte counts), chemistry (including ALT, AST, alkaline phosphatase, total bilirubin, electrolytes, BUN, and creatinine), lipid and

endocrine parameters (including glucose, total cholesterol, LDL, HDL, triglycerides, HbA1c, and prolactin), and urinalysis.
• orthostatic pulse and blood pressure were measured at screening and baseline and on days 4, 7, 14, and 21.
• 12-lead ECGs were done at screening and on day 21.
• Columbia-Suicide Severity Rating Scale (C-SSRS) was assessed at screening and baseline and on days 1, 4, 7, 14, and 21.
• Extrapyramidal Symptom Rating Scale (ESRS) was conducted at baseline and on days 7, 14, and 21. The ESRS evaluates symptoms of parkinsonism, akathisia, dystonia, and dyskinesia.
• height (measured by stadiometer), weight, and girth were measured at screening and baseline and on days 4, 7, 14, and 21.
• Children's Depression Rating Scale-Revised (CDRS-R) was assessed at baseline and on days 7, 14, and 21 to monitor for the emergence of depression.
• Tanner stage was assessed at screening and on day 21.
• a cognitive battery was administered prior to randomized treatment and on day 21. This battery consisted of the following tests: Color Word Interference Task, Letter Fluency, Semantic Fluency, Auditory Number Sequencing, and the Strategic Target Detection Test. These assessments are described in more detail below.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The above assessments are expected to be adequate to detect potential adverse effects seen with similar drugs in this class, for example, metabolic changes, orthostatic hypotension, neutropenia, and tardive dyskinesia.

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred during the Phase 3 bipolar trials P06107 or P05898 or in the Phase 1 studies A7501022 and P06522 as of October 31, 2014, the cutoff for the Four-Month Safety Update Report.

7.3.2 Nonfatal Serious Adverse Events

There were no non-fatal SAEs in the Phase 1 studies A7501022 and P06522. In trial P06107, there were 7 patients with SAEs, 3 patients in the placebo group and 2 each in the 5mg and 10mg groups. All seven patients had events in the psychiatric System Organ Class which represented either probable worsening of bipolar illness or suicidal ideation or behavior. After combining similar terms, the numbers of patients with each type of serious adverse event were:

	Placebo	2.5mg	5mg	10mg
Suicidal Ideation/Behavior	1	0	0	1
Bipolar Disorder Worsening	2	0	2	1

As reported in the Four-Month Safety Update Report, in the open-label study P05898, 7% (22/321) of patients had experienced SAEs. Most of the SAEs were psychiatric in nature, the most commonly reported being suicidal ideation (8 patients), aggression, bipolar disorder, and depression (3 patients each); and agitation (2 patients). Other SAEs that were reported in one patient each were anxiety, disturbance in social behavior, exhibitionism, impulsive behavior, mania, self-injurious behavior, suicidal ideation, accidental overdose, intentional overdose, dystonia, loss of consciousness, somnolence, and drug hypersensitivity (swollen tongue). Tongue swelling is currently described in Saphris labeling. The case of loss of consciousness occurred in a 12 year old male (#67/100202) in the context of an accidental Ambien overdose

7.3.3 Dropouts and/or Discontinuations

In the Phase 1 studies A7501022 and P06522, there was only one dropout because of an adverse event (exacerbation of schizophrenia).

The percentages of patients who dropped out of trial P06107 because of adverse events are displayed in the following table. As mentioned above, certain closely related adverse event preferred terms were combined into common terms to enhance the clinical usefulness of event reporting rates. Common adverse events associated with dropout in trial P06107 and the corresponding proportions of patients who discontinued study treatment because of those events were:

Common Term	Placebo	2.5mg	5mg	10mg
Somnolence	0%	3%	1%	2%
Abdominal pain	0%	0%	0%	2%
Bipolar disorder	2%	0%	2%	0%

Adverse events, after combining terms, that led to dropout in at least 2% of patients in any asenapine arm (before rounding) at a rate at least twice the placebo rate were: somnolence, abdominal pain, and nausea.

As of the cutoff for the Four-Month Safety Update Report, adverse events that led to dropout in the open-label study P05898 (total N=321) were mostly psychiatric in nature: aggression and suicidal ideation (3 patients each) and anxiety, ADHD, bipolar disorder, depression, depressive symptom, irritability, and suicidal behavior (2 patients each). Agitation, anger, exhibitionism, mania, panic attack, and restlessness led to dropout in one patient each.

Non-psychiatric adverse events that resulted in dropout in more than one patient in study P05898 were somnolence/sedation/hypersomnia (12 patients) and fatigue (4 patients). Non-psychiatric events that led to discontinuation in only one patient each were as follows: akathisia, dizziness, dysgeusia, dyskinesia, dystonia, narcolepsy, drug ineffective, accidental overdose, intentional overdose, glossodynia, weight increased, back pain, and pregnancy.

Table 7: Adverse Events Leading to Dropout (Trial P06107)

System Organ Class (SOC)/ Preferred Term	Placebo N=101 n (%)	2.5 mg N=104 n (%)	5.0 mg N=99 n (%)	10.0 mg N=99 n (%)
Subjects reporting any adverse event	4 (4.0)	7 (6.7)	5 (5.1)	5 (5.1)
Psychiatric disorders	4 (4.0)	3 (2.9)	3 (3.0)	0 (0.0)
Anxiety	1 (1.0)	2 (1.9)	1 (1.0)	0 (0.0)
Bipolar 1 disorder	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mania	0 (0.0)	0 (0.0)	2 (2.0)	0 (0.0)
Depressive symptom	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Insomnia	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Suicidal behaviour	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Suicidal ideation	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	0 (0.0)	5 (4.8)	2 (2.0)	2 (2.0)
Somnolence	0 (0.0)	4 (3.8)	0 (0.0)	1 (1.0)
Akathisia	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Dizziness	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Dysgeusia	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Dystonia	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Oromandibular dystonia	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Paraesthesia	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Sedation	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Gastrointestinal disorders	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.0)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.0)
Abdominal discomfort	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Abdominal pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Infections and infestations	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Influenza	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)

Every subject is counted a single time for each applicable row and column.
MedDRA coding version 16.0
Presented in descending frequency based upon the counts for all treatments combined.
This includes treatment and non-treatment emergent adverse events.
Discontinued treatment: Study drug discontinued corresponding to AE eCRF.
All-Patients-as-Treated = All randomized subjects who received at least one dose of trial medication.
Data Source: [16.4]

7.3.4 Significant Adverse Events

There are several significant adverse effects of asenapine and other atypical antipsychotics. Observed effects in the placebo-controlled pediatric bipolar trial are discussed below.

Metabolic Changes
Hyperglycemia and Diabetes Mellitus

Mean changes from baseline to endpoint in fasting glucose levels in trial P06107 were higher in the asenapine groups:

Placebo	-2.2 mg/dl (N=56)
Asenapine 2.5mg	+1.4 mg/dl (N=51)
Asenapine 5mg	-0.5 mg/dl (N=57)
Asenapine 10mg	+0.3 mg/dl (N=52)

The proportions of patients who had a fasting glucose level ≥126 mg/dl at any point during trial P06107 were low across treatment groups:

Placebo	0% (0/59)
Asenapine 2.5mg	0% (0/52)
Asenapine 5mg	2% (1/60)
Asenapine 10mg	0% (053)

No patient in any treatment group had an HbA1c level ≥7.0% at any time point.

The fraction of patients with significant shifts from baseline in fasting glucose at any time during treatment are displayed in the following table. A greater proportion of patients in each asenapine group had a shift in fasting glucose from the normal range to borderline high compared to placebo.

Table 8: Proportion of Patients with Shifts in Fasting Glucose (Trial P06107)

Shift	Placebo	2.5mg	5mg	10mg
Normal to Low (>45 & <100) to ≤45 mg/dl	0% (0/56)	0% (0/51)	0% (0/57)	0% (0/52)
Normal to Borderline High (>45 & <100) to (≥100 & <126 mg/dl)	4% (2/56)	6% (3/51)	5% (3/57)	8% (4/52)
Normal to High (>45 & <100) to ≥126 mg/dl)	0% (0/56)	0% (0/51)	2% (1/57)	0% (0/52)

Adverse events in the hyperglycemia/new onset diabetes mellitus broad SMQ category were reported in a higher proportion of asenapine patients compared to placebo:

Placebo	3% (3/101)
Asenapine 2.5mg	14% (15/104)
Asenapine 5mg	13% (13/99)
Asenapine 10mg	9% (9/99)

New onset metabolic syndrome (MBS) criteria were met by 0% (0/101) of placebo patients and 4% (4/104), 5% (5/99), and 2% (2/99) of patients in the asenapine 2.5mg, 5mg, and 10mg groups, respectively. Criteria defined by the International Diabetes

Federation require obesity (waist circumference ≥90th percentile for children <16 years old or, for those 16 years and older, ≥94cm or ≥84cm for European males and females, respectively), ≥2 specific lab abnormalities, and/or abnormal blood pressure measurements at the same visit.

Patients with uncontrolled or unstable diabetes or a clinically significant abnormal blood glucose level were excluded from trial P06107.

Dyslipidemia
Mean changes from baseline to endpoint in lipid parameters in trial P06107 are displayed in the table below. Asenapine patients at all doses tended to have increases in serum lipid levels compared to placebo patients.

Table 9: Mean Change from Baseline to Endpoint in Lipid Measures (mg/dl) (Trial P06107)

	Placebo		2.5mg		5mg		10mg	
	N	**Δ**	**N**	**Δ**	**N**	**Δ**	**N**	**Δ**
Cholesterol	81	-3.6	89	+3.0	89	+6.2	86	+8.8
HDL	81	+0.2	88	+1.0	89	+1.7	86	+2.1
LDL	81	-3.5	89	-0.3	88	+1.5	85	+5.6
Fasting Triglycerides	57	-6.6	50	+8.7	57	+13.4	52	+14.7

The fraction of patients with significant shifts from baseline in lipid measurements during treatment are displayed in the following table. A small number of asenapine patients had shifts in fasting triglycerides from the normal range to high values compared to no placebo patients.

Table 10: Proportion of Patients with Significant Shifts in Lipid Parameters (Trial P06107)

	Placebo	2.5mg	5mg	10mg
Tot. Cholesterol Normal to High (<170 to ≥200 mg/dl)	1% (1/81)	1% (1/89)	1% (1/89)	0% (0/86)
HDL Normal to Low (≥40 to <40 mg/dl)	4% (3/81)	3% (3/88)	2% (2/89)	6% (5/86)
LDL Normal to High (<130 to ≥130 mg/dl)	3% (2/81)	5% (4/89)	2% (2/88)	5% (4/85)
Fasting TGs Normal to High (<150 to ≥200 mg/dl)	0% (0/57)	4% (2/50)	4% (2/57)	2% (1/52)

The proportion of patients with outlying values for cholesterol and triglyceride levels at any time during study drug treatment are shown in the table below. A much larger

fraction of asenapine patients at all doses had outlying cholesterol and fasting triglyceride levels compared to placebo.

Table 11: Proportion of Patients with Outlying Cholesterol or Triglyceride Levels (Trial P06107)

	Placebo	2.5mg	5mg	10mg
Total Cholesterol (≥200 mg/dl)	4% (3/81)	12% (11/89)	12% (11/89)	11% (9/86)
Fasted Triglycerides (≥200 mg/dl)	2% (1/60)	8% (4/52)	8% (5/60)	9% (5/53)

Weight Gain
Mean changes from baseline to endpoint in body weight in trial P06107 were:

Placebo	+0.5 kg	(N=89)
Asenapine 2.5mg	+1.7 kg	(N=92)
Asenapine 5mg	+1.6 kg	(N=90)
Asenapine 10mg	+1.4 kg	(N=87)

The percentages of subjects in this trial who experienced a 7% or greater increase in body weight from baseline to endpoint during the trial were much larger for each asenapine group versus placebo:

Placebo	1%	(1/89)
Asenapine 2.5mg	12%	(11/92)
Asenapine 5mg	9%	(8/90)
Asenapine 10mg	8%	(7/87)

Hypersensitivity Reactions
In trial P06107, drug hypersensitivity adverse events were reported in four patients: rash and pruritus each in one placebo patient, chelitis in one asenapine 2.5mg patient, and rash in one asenapine 5mg patient. None were rated as serious and none led to dropout. All were rated mild in severity.

There was one serious case of drug hypersensitivity that occurred in the open-label study P05898. A 14 year old male (#100212) experienced tongue swelling that was treated with oral diphenhydramine and resolved the same day. He continued in the study at a reduced asenapine dose. He had received placebo in the acute study P06107 and had received asenapine 10mg BID for 10 days in the open-label study prior to the event.

Hyperprolactinemia
Mean changes from baseline to endpoint in serum prolactin levels from trial P06107 reflected increases, with the largest increase in the 10mg dose group:

Placebo	+2.5 ng/ml	(N=72)
Asenapine 2.5mg	+3.2 ng/ml	(N=82)
Asenapine 5mg	+2.1 ng/ml	(N=84)
Asenapine 10mg	+6.4 ng/ml	(N=77)

The proportions of patients who had an elevated prolactin level (≥ULN) at endpoint in trial P06107 were higher for asenapine than placebo:

Placebo	6%	(5/79)
Asenapine 2.5mg	11%	(10/88)
Asenapine 5mg	11%	(10/90)
Asenapine 10mg	20%	(17/86)

There were 2 patients in the 5mg group and one patient in the placebo group of this trial who had an adverse event potentially related to prolactin (dysmenorrhea). In addition, one patient in the 10mg group experienced galactorrhea. Thus, the incidence rates of prolactin-related events were:

Placebo	1%	(1/101)
Asenapine 2.5mg	0%	(0/104)
Asenapine 5mg	2%	(2/99)
Asenapine 10mg	1%	(1/99)

Each event was rated as mild in severity. None of these events were serious and none led to dropout.

I searched the ae.xpt files of trial P06107 to locate reports of breast enlargement associated with asenapine. The search terms were “gynecomastia” and “breast,” with the objective of identifying adverse event occurrences with a preferred term (AEDECOD) or a verbatim term (AELIT) containing either of the search terms. No such events were found.

Seizures

I searched the ae.xpt files of trials P06107 to locate reports of seizures associated with asenapine. The search terms were “seiz” and “convuls,” with the objective of identifying adverse event occurrences with a preferred term (AEDECOD) or a verbatim term (AELIT) containing either of the search terms. No occurrences were located.

Patients with any known or suspected seizure disorders were excluded from the trials.

Somnolence

The preferred terms somnolence, sedation, and hypersomnia were combined by the sponsor to gauge the incidence of adverse events related to somnolence in trial P05896. The reporting rates for the combined term by treatment group were:

Placebo	12%	(12/101)
Asenapine 2.5mg	46%	(48/104)
Asenapine 5mg	53%	(52/99)
Asenapine 10mg	49%	(49/99)

None of these events were classified as serious and most were rated as mild or moderate in severity. Six patients dropped out because of one of these experiences (3 in the 2.5mg group, one in the 5mg group, and 2 in the 10mg group). Clearly, somnolence was very common and related to asenapine treatment but infrequently led to dropout.

Extrapyramidal Symptoms (EPS)

The reporting rates for EPS-related events (based on SMQ broad definitions) in trial P06107 are shown in the table below.

Table 12: Treatment-Emergent EPS-Related Adverse Events (Trial P05896)

	Placebo N=101 n (%)	2.5 mg N=104 n (%)	5.0 mg N=99 n (%)	10.0 mg N=99 n (%)
SMQ EPS (broad)	3 (3.0)	6 (5.8)	5 (5.1)	6 (6.1)
SMQ Parkinson-Like Events (broad)	0 (0.0)	4 (3.8)	1 (1.0)	4 (4.0)
Parkinsonism	0 (0.0)	1 (1.0)	0 (0.0)	2 (2.0)
Musculoskeletal stiffness	0 (0.0)	1 (1.0)	1 (1.0)	0 (0.0)
Tremor	0 (0.0)	2 (1.9)	0 (0.0)	0 (0.0)
Bradykinesia	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Resting tremor	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
SMQ Akathisia (broad)	0 (0.0)	3 (2.9)	2 (2.0)	2 (2.0)
Akathisia	0 (0.0)	2 (1.9)	2 (2.0)	1 (1.0)
Psychomotor hyperactivity	0 (0.0)	1 (1.0)	0 (0.0)	1 (1.0)
SMQ Dystonia (broad)	2 (2.0)	1 (1.0)	2 (2.0)	0 (0.0)
Dystonia	0 (0.0)	1 (1.0)	1 (1.0)	0 (0.0)
Musculoskeletal stiffness	0 (0.0)	1 (1.0)	1 (1.0)	0 (0.0)
Oromandibular dystonia	1 (1.0)	0 (0.0)	1 (1.0)	0 (0.0)
Muscle contractions involuntary	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Muscle twitching	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
SMQ Dyskinesia (broad)	2 (2.0)	0 (0.0)	1 (1.0)	1 (1.0)
Dyskinesia	1 (1.0)	0 (0.0)	0 (0.0)	1 (1.0)
Muscle twitching	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protrusion tongue	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)

Every subject is counted a single time for each applicable row and column.
MedDRA coding version 16.0
An SMQ was defined as a Tier 2 event if the incidence >= 4 subjects in one or more treatment groups.
Presented in descending frequency based upon the counts for all treatments combined.
All-Patients-as-Treated = All randomized subjects who received at least one dose of trial medication.
Data Source: [16.4]

Rates of Parkinson-like events and akathisias were higher in all asenapine dose groups compared to placebo but were not dose-related. Dystonias and dyskinesias were not more frequent in asenapine versus placebo patients.

The reporting rates of all non-akathisia EPS (broadly defined) were similar across treatment groups:

Placebo	3%	(3/101)
Asenapine 2.5mg	4%	(4/104)
Asenapine 5mg	3%	(3/99)
Asenapine 10mg	5%	(5/99)

Changes from baseline to endpoint in the Extrapyramidal Symptom Rating Scale (ESRS) III (dystonia) and IV (dyskinesia) scores in trial P06107 were comparable across treatment groups.

Patients with a history of NMS, tardive dyskinesia, or tardive dystonia were excluded from the trials.

Suicidal Ideation and Behavior

Suicidal ideation and behavior was assessed during trial P06107 using the C-SSRS at each visit. The percentage of patients who endorsed items on this scale are displayed in the table below. In this table, patients were enumerated only once in each cell. However, a patient who endorsed different items at different visits was counted in the cell for each item endorsed.

Table 13: Number (%) of Patients with Positive Responses on the C-SSRS (Trial P06107)

Subjects with†	Placebo N=101	2.5 mg N=104	5.0 mg N=99	10.0 mg N=99
No events	94 (93.1)	95 (91.3)	91 (91.9)	89 (89.9)
Suicidal ideation	5 (5.0)	5 (4.8)	6 (6.1)	8 (8.1)
Passive	4 (4.0)	5 (4.8)	5 (5.1)	7 (7.1)
Active - nonspecific (no method, intent, or plan)	4 (4.0)	0 (0.0)	3 (3.0)	2 (2.0)
Active - method, but no intent or plan	1 (1.0)	0 (0.0)	1 (1.0)	1 (1.0)
Active - intent, with or without a method, but no plan	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Active - method, intent and plan	1 (1.0)	0 (0.0)	0 (0.0)	1 (1.0)
Suicidal behavior	1 (1.0)	0 (0.0)	0 (0.0)	1 (1.0)
Preparatory actions toward imminent suicidal behaviors	1 (1.0)	0 (0.0)	0 (0.0)	1 (1.0)
Aborted attempt	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Interrupted attempt	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Suicide attempt	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Completed suicide	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Suicidal ideation and/or suicidal behavior	5 (5.0)	5 (4.8)	6 (6.1)	8 (8.1)
Self-injurious behavior, no suicidal intent	3 (3.0)	1 (1.0)	3 (3.0)	1 (1.0)

† Columbia Suicide Severity Rating Scale (C-SSRS) questions map to suicidal ideation and behavior categories; positive responses (ie, 'Yes') to C-SSRS questions correspond to events in these categories with the exception of the category 'No events'.
Suicidal ideation: Subjects with positive responses in at least one of the presented subcategories. Suicidal behavior: Subjects with positive responses in at least one of the presented subcategories. Suicidal ideation and/or suidical behavior: Subjects with positive reponses in the category suicidal ideation and/or suicidal behavior.
Every subject is counted a single time for each applicable row and column.
All-Patients-as-Treated = All randomized subjects who received at least one dose of trial medication.
Data Source: [16.4]

About 90% of patients in each treatment group reported no events on the C-SSRS during the trial. A higher proportion of patients in the 10mg group experienced suicidal ideation compared to placebo (8% vs. 5%) but this difference was not statistically significant (p= 0.4, 2-tailed Fishers exact test). One patient in the placebo group and another in the 10mg group had active ideation with a method, intent, and plan. There were no completed suicides in this trial. There was one aborted attempt in the placebo group and one suicide attempt in the 10mg group. Overall, there was no clear evidence that asenapine treatment was causally associated with suicidal thoughts or behavior.

Patients at imminent risk of self-harm, suicidal ideation with intent in the prior 2 months, or suicidal behavior in the prior 6 months were excluded from this trial.

Depression

Treatment-emergent depression was assessed in trial P06107 using the CDRS-R. CDRS-R total scores were roughly comparable across treatment groups at baseline (range of 33.5 to 35.4). Mean changes from baseline at Day 21 reflected numeric improvement for the asenapine groups (especially the 5mg group) versus placebo:

Placebo	-6.1	(N=78)
Asenapine 2.5mg	-6.9	(N=87)
Asenapine 5mg	-8.7	(N=87)
Asenapine 10mg	-6.8	(N=81)

Likewise, the percentages of CDRS-R responders (defined as a ≥50% decrease from baseline in the total score) were greater for the asenapine-treated patients compared to placebo:

Placebo	31%	(29/95)
Asenapine 2.5mg	42%	(41/97)
Asenapine 5mg	46%	(44/95)
Asenapine 10mg	41%	(39/95)

These data suggest that asenapine treatment of pediatric patients with bipolar disorder in a manic or mixed state is not associated with an increase in depression.

Oral Hypoesthesia

Oral hypoesthesia is an event somewhat unique to asenapine caused by its anesthetic properties when administered sublingually. In trial P06107, oral hypoesthesia was reported much more frequently in the asenapine treatment arms compared to placebo:

Placebo	2%	(2/101)
Asenapine 2.5mg	17%	(18/104)
Asenapine 5mg	18%	(18/99)
Asenapine 10mg	20%	(20/99)

None of these events were serious or led to dropout. All were rated as mild or moderate in severity.

Oral paresthesia and oral dysesthesia (such as a tingling sensation in the mouth), related adverse events, were reported by several patients in this trial. The percentages of patients who reported either oral hypoesthesia, paresthesia, or dysesthesia followed a similar pattern of reporting rates:

Placebo	4%	(4/101)
Asenapine 2.5mg	25%	(26/104)
Asenapine 5mg	25%	(25/99)
Asenapine 10mg	30%	(30/99)

Dysphagia
There was one report of dysphagia in trial P06107 that occurred in the asenapine 2.5mg group (1% or 1/104). The adverse event dataset (ae.xpt) for this trial was searched for reports of choking by searching all verbatim terms (AELIT) for any that contained any of the following: "chok," "aspiration," or "gag." No such adverse events were identified.

7.3.5 Submission Specific Primary Safety Concerns

The assessment of the potential effects of asenapine on learning and memory in pediatric patients with bipolar disorder consisted of the following tests in trial P06107:

• Color Word Interference Task (CWIT) - words describing a color are presented in colored font under one of two conditions: in the congruent condition (in which the color word and the color of the word are the same, e.g., the word red is printed in red color) and the incongruent condition (in which the color word and the color of the word are different). Performance is measured by response latencies, that is, lower numbers represent better performance. Interference in the incongruent condition typically yields longer latencies than for the congruent condition. Thus, performance is assessed by the key metric "net score" which equals incongruent latency minus congruent latency. Latency of response is impacted by the speed/accuracy trade-off employed by each participant.
• Letter Fluency Test (LFT) - a measure of language and executive function, such as planning and strategic thinking. The key measure is the "number of correct words," with higher numbers representing better performance.
• Semantic Fluency Test (SFT) - this is also a measure of language and executive function, such as planning and strategic thinking. The key measure is the "number of correct words," with higher numbers representing better performance.
• Auditory Number Sequencing (ANS) - a measure of working memory. The key metric is the "number correct." Higher number reflect better performance.
• Strategic Target Detection Test (STDT) - a visual search task that indexes attention span. Accuracy is intended to reflect interference with attention, especially by performance at the four shape level. The key metric is "total correct," with higher numbers reflecting better performance (total correct at the four shape level is taken as the key metric).

These assessments were added to the conduct of trial P06107 with a protocol amendment which was implemented more than a year after enrollment started. Thus,

the sample size for cognitive data is much smaller than the total number of randomized patients in this trial.

Results on the key metrics are summarized in the following table. The mean changes from baseline to endpoint generally reflected improvement, with differences among treatment groups not felt to be clinically significant.

Table 14: Summary of Results of Cognitive Testing (Trial P06107)
Mean Change from Baseline to Endpoint in Key Metrics

Test/Units	Placebo		2.5mg		5mg		10mg	
	N	Mean Δ	N	Mean Δ	N	Mean Δ	N	Mean Δ
CWIT (msec)	17	+48.5	9	-19.5	19	-71.0	17	+24.3
LFT (# correct)	34	+1.7	27	+1.5	28	+0.6	32	+1.0
SFT (# correct)	33	+0.7	28	+2.3	25	+0.8	30	-1.6
ANS (# correct)	33	+0.4	28	+1.3	27	-0.2	31	+0.6
STDT (total correct)	26	+3.9	24	-1.6	28	+4.5	27	+0.4

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The incidence of treatment-emergent adverse events in trial P06107 that were reported in at least one of the three asenapine arms at a rate ≥2% (before rounding) and at a rate that was higher than the placebo rate are displayed in the table below.

Table 15: Reporting Rates (%) of Adverse Reactions (Trial P06107)				
System Organ Class/ AE Preferred Term	**Placebo N=101**	**2.5mg N=104**	**5mg N=99**	**10mg N=99**
Cardiac Disorders				
Tachycardia[1]	0%	3%	0%	1%
Gastrointestinal Disorders				
Oral paraesthesia[2]	4%	25%	25%	30%
Nausea	3%	6%	6%	6%
Abdominal pain[3]	7%	9%	3%	5%
Glossodynia	0%	0%	2%	0%
General Disorders and Administrative Site Disorders				
Fatigue[4]	5%	4%	8%	14%
Irritability	1%	1%	1%	2%
Immune System Disorders				
Seasonal allergy	0%	0%	1%	2%
Injury, Poisoning, and Procedural Complications				
Muscle strain	0%	0%	0%	2%
Investigations				
Weight increased	0%	6%	2%	2%
Hyperinsulinemia[5]	0%	1%	3%	1%
ALT increased	0%	0%	0%	2%
AST increased	0%	0%	0%	2%
Metabolism and Nutrition Disorders				
Increased appetite	2%	10%	9%	6%
Dehydration	1%	0%	2%	0%
Musculoskeletal and Connective Tissue Disorders				
Myalgia	0%	0%	2%	1%
Nervous System Disorders				
Somnolence[6]	12%	46%	53%	49%
Headache	6%	8%	11%	9%
Dizziness	3%	6%	10%	5%
Dysgeusia	2%	4%	5%	9%
Akathisia	0%	2%	2%	1%
Parkinsonism	0%	1%	0%	2%
Psychiatric Disorders				

[1] Includes the preferred terms tachycardia and heart rate increased.
[2] Includes the preferred terms oral hypoesthesia, oral paresthesia, and oral dysesthesia.
[3] Includes the preferred terms abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal discomfort.
[4] Includes the preferred terms fatigue and lethargy.
[5] Includes the preferred terms hyperinsulinemia and blood insulin increased.
[6] Includes the preferred terms somnolence, sedation, and hypersomnia.

Table 15: Reporting Rates (%) of Adverse Reactions (Trial P06107)				
System Organ Class/ AE Preferred Term	**Placebo N=101**	**2.5mg N=104**	**5mg N=99**	**10mg N=99**
Insomnia	3%	3%	4%	3%
Suicidal ideation	1%	4%	1%	3%
Bipolar Disorder[7]	4%	0%	5%	4%
Anger	0%	0%	0%	2%
Reproductive System and Breast Disorders				
Dysmenorrhea	1%	0%	2%	0%
Respiratory, Thoracic, and Mediastinal Disorders				
Oropharyngeal pain	2%	0%	3%	1%
Nasal congestion	1%	0%	2%	0%
Dyspnea	0%	0%	2%	0%
Skin and Subcutaneous Tissue Disorders				
Rash	1%	0%	1%	2%

Common, probably drug-related adverse reactions (reported by at least 5% of patients in at least one asenapine arm and at a rate at least twice the placebo rate) were: oral paresthesia, nausea, fatigue, weight increased, increased appetite, somnolence, dizziness, and dysgeusia.

7.4.2 Laboratory Findings

Hematology

In trial P06107, mean changes from baseline to endpoint in hematology parameters were similar across treatment groups except for platelet counts, for which there was a trend for increases with increasing asenapine dose:

Placebo	+1.5 $x10^3$/µL (N=79)
Asenapine 2.5mg	+4.4 $x10^3$/µL (N=85)
Asenapine 5mg	+8.7 $x10^3$/µL (N=86)
Asenapine 10mg	+13.5 $x10^3$/µL (N=84)

Median changes in platelet count were larger in the asenapine groups (+8 to +10 $x10^3$/µL) compared to placebo (-1.0 $x10^3$/µL).

The proportions of patients who met Predefined Limits of Change (PDLC) for hematology measures in trial P06107 are presented in the table below.

[7] Includes the preferred terms bipolar disorder, bipolar I disorder, mania, mood swings, and tachyphrenia.

Table 16: Percentage of Patients With Hematology Values That Met PDLC During Treatment (Trial P06107)

Parameter	PDLC	Placebo N=101		2.5 mg N=104		5.0 mg N=99		10.0 mg N=99	
		n	%	n	%	n	%	n	%
Hemoglobin (g/dL)	Number of subjects	79		86		88		85	
	<= 0.9 LLN	0		1	(1.2)	0		0	
	>= 1.1 ULN	8	(10.1)	7	(8.1)	6	(6.8)	7	(8.2)
Hematocrit (%)	Number of subjects	79		86		88		85	
	<= 0.9 LLN	0		0		0		0	
	>= 1.1 ULN	7	(8.9)	5	(5.8)	5	(5.7)	6	(7.1)
Erythrocyte count ($10^6/\mu L$)	Number of subjects	79		86		88		85	
	<= 0.8 LLN	0		0		0		0	
	>= 1.2 ULN	0		1	(1.2)	0		0	
Leukocyte count ($10^3/\mu L$)	Number of subjects	79		86		88		85	
	<= 0.8 LLN	0		1	(1.2)	1	(1.1)	1	(1.2)
	>= 1.2 ULN	0		1	(1.2)	1	(1.1)	0	
Platelet count ($10^3/\mu L$)	Number of subjects	79		85		86		85	
	<= 100	0		0		0		0	
	>= 600	0		0		0		0	
Neutrophils ($10^3/\mu L$)	Number of subjects	79		86		88		85	
	<= 1.5 (Mild)	1	(1.3)	3	(3.5)	3	(3.4)	3	(3.5)
	<= 1.0 (Moderate)	0		0		1	(1.1)	0	
	<= 0.5 (Severe)	0		1	(1.2)	0		0	
	>= 10.0	1	(1.3)	1	(1.2)	0		0	
Lymphocytes ($10^3/\mu L$)	Number of subjects	79		86		88		85	
	<= 0.8 LLN	3	(3.8)	1	(1.2)	1	(1.1)	0	
	>= 1.2 ULN	0		0		0		0	
Monocytes ($10^3/\mu L$)	Number of subjects	79		86		88		85	
	>= 1.2 ULN	0		0		0		1	(1.2)
Eosinophils ($10^3/\mu L$)	Number of subjects	80		86		88		85	
	>= 1.0	1	(1.3)	0		0		0	
Basophils ($10^3/\mu L$)	Number of subjects	79		86		88		85	
	>= 1.2 ULN	0		0		0		0	

LLN = Lower Limit Normal; ULN = Upper Limit Normal; PDLC = Predefined Limit of Change.
Number of Subjects with post-baseline value of the parameter during the treatment phase.
n = number of subjects meeting the PDLC of the parameter during the treatment phase.
All-Patients-as-Treated = All randomized subjects who received at least one dose of trial medication.
Data Source: [16.4]

The proportion of PLDC outliers for indices of low white blood cell (WBC) counts was larger for asenapine than placebo for the following measures:

• leukocyte count ≤0.8 xLLN.
• mild reduction in neutrophil count ≤1,500/μL.

One patient, a 14 year old Black female in the asenapine 2.5mg group (#100422), had severe neutropenia (i.e., a neutrophil count ≤500/μL) on Day 21 of trial P06107. Despite this finding, this patient continued treatment in study P05898; on Day 27 of this study, her neutrophil count improved and, on Day 131, returned to baseline. Her WBC and neutrophil counts are summarized below.

	WBC (total)	Neutrophil Count
Screening	3,600/μL	1,400/μL
Trial P06107		
Baseline	3,300/μL	1,200/μL
Day 21	3,100/μL	400/μL
Study P05898		
Day 27	2,800/μL	900/μL
Day 131	3,800/μL	1,600/μL

This patient experienced a possible urinary tract infection with proteinuria that was detected on Day 1 of trial P06107 and reportedly ended on Day 21 of that trial. Otherwise, no adverse events likely to be related to neutropenia were reported during either study.

I searched the lab results dataset (labrslt.xpt) for each of the two Phase 3 pediatric bipolar disorder trials for other patients who had significant leukopenia (≤1,000/μL) or neutropenia (≤500/μL) at non-baseline visits. The following cases were identified from this search.

In the 50-week, open-label bipolar disorder study P05898 (as of the interim safety cutoff date July 12, 2013), a 16 year old male (#100261) had severe neutropenia on Day 177:[8]

Baseline	4,300/μL
Day 28	3,900/μL
Day 132	3,500/μL
Day 177	400/μL

This patient reportedly completed the trial without interruption of study medication. No subsequent laboratory data was captured. According to information from the sponsor submitted on February 3, 2015, the patient was asymptomatic and continued to be

[8] Complete safety datasets for study P05898 were not available at the time of this review.

followed by the investigator for over 2 years after completing study P05898. During this time, the investigator reports that the patient has been physically healthy.

In trial P06107, the proportions of patients who had a treatment-emergent adverse event coded as either leukopenia, neutropenia, or "white blood cell count decreased" were small:

Placebo	0%	(0/101)
Asenapine 2.5mg	1%	(1/104)
Asenapine 5mg	0%	(0/99)
Asenapine 10mg	1%	(1/99)

No patient dropped out of trial P06107 because of an adverse event related to a hematology lab test abnormality.

Chemistry

Mean changes from baseline to endpoint in chemistry variables were comparable to placebo with the exception of the liver transaminases aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma glutamyl transferase (GGT). There were small increases relative to placebo in the 2.5mg and 5mg groups and larger increases in the 10mg group, as shown in the table below.

Table 17: Mean Change from Baseline to Endpoint in Liver Transaminase Concentrations (U/L)

	Placebo		Asenapine 2.5mg		Asenapine 5mg		Asenapine 10mg	
	N	Δ	N	Δ	N	Δ	N	Δ
AST	80	-1.2	90	+0.6	90	+0.4	85	+3.4
ALT	80	-1.0	90	+1.3	90	+3.9	85	+8.8
GGT	80	-1.2	90	+0.4	90	+1.2	85	+2.2

Mean changes from baseline in alkaline phosphatase and total bilirubin were unremarkable.

With respect to hormone parameters, there were increases in serum prolactin levels in all groups, including placebo, with the largest mean change from baseline in the asenapine 10mg group:

Placebo	+2.5 µg/L	(N=72)
Asenapine 2.5mg	+3.3 µg/L	(N=82)
Asenapine 5mg	+2.1 µg/L	(N=84)
Asenapine 10mg	+6.4 µg/L	(N=77)

The proportions of patients who met Predefined Limits of Change (PDLC) for chemistry measures in trial P06107 are presented in the table below. There were appreciable differences between asenapine and placebo for the following variables:

- BUN increased (all asenapine dose groups).
- phosphorus increased (all asenapine dose groups).
- ALT elevated (10mg).
- total bilirubin increased (2.5 and 5mg).

The increase in BUN is less concerning given 1) decreases from baseline to endpoint in mean serum creatinine for asenapine versus placebo and 2) an absence of asenapine patients meeting the PDLC criterion for elevated serum creatinine levels.

The clinical relevance of the increased proportion of asenapine patients with elevated phosphorus levels is not clear.

Two patients in trial P6107 met the PDLC criterion for SGPT. One patient (#100641) had a baseline SGPT of 30 U/L, an increase to 190 U/L after about 3 weeks of asenapine in the 10mg group, and a decrease to 78 U/L 5 days after stopping drug.

The other patient (#101070), a 16 year old female, had a baseline SGPT of 32 U/L and an increase to 115 U/L after 3 weeks of treatment in the asenapine 10mg group. The AST also slightly increased (62 U/L). These findings were attributed by the investigator to ibuprofen use, which the patient had been taking prophylactically for pain and the dose of which was increased during the trial to treat headaches. The patient was continued on asenapine in study P05898 and subsequent laboratory testing revealed a gradual return of both SGPT and SGOT levels to normal range over the next month.

To further evaluate the findings regarding increased ALT and total bilirubin levels, I searched the laboratory results datasets (labrslt.xpt) for trials P06107 and P05898 (as of the interim safety cutoff date July 12, 2013) to identify patients who met Hy's Law criteria (ALT or AST ≥3 xULN, total bilirubin ≥2 xULN, and alkaline phosphatase <2 xULN). I found no case that met these criteria.

There were no dropouts in studies P06107 or P05898 because of adverse events related to chemistry laboratory abnormalities.

Table 18: Percentage of Patients With Chemistry Values That Met PDLC During Treatment (Trial P06107)

Parameter	PDLC	Placebo N=101		2.5 mg N=104		5.0 mg N=99		10.0 mg N=99	
		n	%	n	%	n	%	n	%
Sodium (mEq/L)	Number of subjects	80		89		88		85	
	<= 0.8 LLN	0		0		0		0	
	>= 1.2 ULN	0		0		0		0	
Potassium (mEq/L)	Number of subjects	79		89		88		84	
	<= 0.9 LLN	0		0		0		0	
	>= 1.1 ULN	0		0		0		0	
Chloride (mEq/L)	Number of subjects	80		89		88		85	
	<= 0.8 LLN	0		0		0		0	
	>= 1.2 ULN	0		0		0		0	
Bicarbonate (mEq/L)	Number of subjects	80		90		89		86	
	<= 0.8 LLN	0		1	(1.1)	0		1	(1.2)
	>= 1.5 ULN	0		0		0		0	
Blood urea nitrogen (mg/dL)	Number of subjects	80		90		90		85	
	>= 1.1 ULN	4	(5.0)	8	(8.9)	6	(6.7)	6	(7.1)
Creatinine (mg/dL)	Number of subjects	80		90		90		85	

Table 18: Percentage of Patients With Chemistry Values That Met PDLC During Treatment (continued)

Parameter	PDLC	Placebo N=101		2.5 mg N=104		5.0 mg N=99		10.0 mg N=99	
		n	%	n	%	n	%	n	%
	>= 1.1 ULN	0		0		0		0	
Calcium (mg/dL)	Number of subjects	79		89		88		85	
	<= 0.9 LLN	0		0		0		1	(1.2)
	>= 1.1 ULN	0		0		1	(1.1)	0	
Phosphorus (mg/dL)	Number of subjects	80		89		90		84	
	<= 0.9 LLN	0		0		0		0	
	>= 1.1 ULN	11	(13.8)	31	(34.8)	26	(28.9)	22	(26.2)
Magnesium (mg/dL)	Number of subjects	79		89		88		85	
	<= 0.9 LLN	0		0		0		1	(1.2)
	>= 1.1 ULN	0		0		0		0	
Aspartate aminotransferase(AST) (U/L)	Number of subjects	80		90		90		85	
	>= 3 ULN	0		0		0		0	
Alanine aminotransferase(ALT) (U/L)	Number of subjects	80		90		90		85	
	>= 3 ULN	0		0		0		2	(2.4)
Alkaline phosphatase (U/L)	Number of subjects	79		89		88		85	

Table 18: Percentage of Patients With Chemistry Values That Met PDLC During Treatment (continued)

Parameter	PDLC	Placebo N=101		2.5 mg N=104		5.0 mg N=99		10.0 mg N=99	
		n	%	n	%	n	%	n	%
	>= 3 ULN	0		0		0		0	
Total bilirubin (mg/dL)	Number of subjects	80		90		90		85	
	>= 1.5 ULN	0		1	(1.1)	1	(1.1)	0	
Protein, total (g/dL)	Number of subjects	80		90		90		85	
	<= 0.8 LLN	0		0		0		0	
	>= 1.2 ULN	0		0		0		0	
Albumin (g/dL)	Number of subjects	80		90		90		85	
	<= 0.8 LLN	0		0		0		0	
	>= 1.2 ULN	0		0		0		0	
Gamma glutamyl transferase (U/L)	Number of subjects	80		90		90		85	
	>= 3 ULN	0		0		0		0	
Lactate dehydrogenase (U/L)	Number of subjects	80		90		90		84	
	>= 3 ULN	0		0		0		0	
Creatine kinase (U/L)	Number of subjects	80		90		90		85	
	>= 3 ULN	2	(2.5)	1	(1.1)	0		1	(1.2)

LLN = Lower Limit Normal; ULN = Upper Limit Normal; PDLC = Predefined Limit of Change.
Number of Subjects with post-baseline value of the parameter during the treatment phase.
n = number of subjects meeting the PDLC of the parameter during the treatment phase.
All-Patients-as-Treated = All randomized subjects who received at least one dose of trial medication.
Data Source: [16.4]

Urinalysis
Mean changes from baseline to endpoint in urine specific gravity and urine pH were small in all treatment groups in trial P06107.

The proportion of asenapine patients meeting PDLC criteria for any urinalysis parameter was higher than that in the placebo group for only glucosuria (non-negative finding) in the 5mg group:

Placebo	0%	(0/79)
Asenapine 2.5mg	0%	(0/87)
Asenapine 5mg	2%	(2/87)
Asenapine 10mg	0%	(0/85)

The difference between placebo and the 5mg group was not statistically significant (p =0.50, 2-tailed Fishers exact test).

No patient in this trial dropped out because of an adverse event related to a urinalysis abnormality.

7.4.3 Vital Signs

Mean changes from baseline to endpoint in supine and standing systolic and diastolic blood pressure and pulse in trial P06107 are shown in the table below.

Appreciable differences between asenapine and placebo are present for the following measures:

• increased standing DBP (about 2 mmHg across all asenapine doses).
• increased supine pulse (2-4 bpm across all asenapine doses).

The mean increase in supine pulse relative to placebo was especially noticeable in the 10mg dose group (+4.3 bpm). The median changes were +4.5 bpm for asenapine 10mg versus 0.0 bpm for placebo.

Table 19: Mean Changes From Baseline To Endpoint in Blood Pressure and Pulse (Trial P06107)

Parameter		Placebo N=101			2.5 mg N=104			5.0 mg N=99			10.0 mg N=99		
		n	Mean (SD)	Media n	n	Mean (SD)	Media n	n	Mean (SD)	Media n	n	Mean (SD)	Media n
Supine SBP (mmHg)	Baseline	99	111.2 (12.4)	111.0	99	112.0 (9.9)	112.0	99	113.7 (9.8)	114.0	96	113.5 (11.6)	112.5
	Endpoint	99	112.2 (12.7)	111.0	99	111.8 (9.9)	112.0	99	113.2 (10.7)	115.0	96	112.9 (12.2)	113.0
	Change	99	1.0 (10.8)	0.0	99	-0.2 (10.1)	0.0	99	-0.6 (8.7)	-1.0	96	-0.6 (11.6)	-1.0
Standing SBP (mmHg)	Baseline	100	111.6 (11.7)	110.0	100	112.1 (11.7)	111.0	98	114.7 (10.7)	116.0	98	113.8 (11.0)	112.0
	Endpoint	100	110.8 (13.5)	110.0	100	112.6 (12.6)	112.0	98	114.1 (13.1)	115.5	98	114.4 (12.1)	116.0
	Change	100	-0.8 (12.1)	0.0	100	0.4 (12.5)	1.5	98	-0.6 (11.3)	0.0	98	0.6 (9.5)	0.0
Supine DBP (mmHg)	Baseline	99	68.6 (9.0)	70.0	99	69.1 (9.5)	69.0	99	68.5 (8.7)	69.0	96	68.6 (9.7)	67.5
	Endpoint	99	68.1 (8.1)	67.0	99	68.8 (8.5)	68.0	99	69.2 (9.1)	68.0	96	68.3 (8.5)	68.0
	Change	99	-0.5 (9.5)	0.0	99	-0.2 (9.0)	0.0	99	0.8 (9.0)	0.0	96	-0.2 (10.9)	0.0
Standing DBP (mmHg)	Baseline	100	72.3 (7.8)	71.0	100	71.6 (8.7)	70.5	98	71.8 (8.9)	72.5	98	72.5 (8.0)	71.0
	Endpoint	100	70.9 (9.2)	71.0	100	72.2 (9.1)	72.0	98	72.6 (9.0)	72.0	98	73.1 (8.0)	72.5
	Change	100	-1.4 (9.7)	-1.0	100	0.6 (9.2)	0.5	98	0.8 (9.6)	1.0	98	0.6 (9.1)	0.0
Supine pulse (bpm)	Baseline	99	76.2 (12.3)	76.0	99	76.5 (11.4)	77.0	99	75.7 (13.8)	75.0	96	74.2 (12.2)	75.0
	Endpoint	99	75.7 (12.9)	76.0	99	78.6 (11.1)	79.0	99	77.1 (13.1)	77.0	96	78.0 (12.9)	78.0
	Change	99	-0.5 (11.5)	0.0	99	2.1 (12.7)	2.0	99	1.5 (10.5)	0.0	96	3.8 (12.3)	4.5
Standing pulse (bpm)	Baseline	100	84.1 (13.7)	82.0	100	87.3 (13.6)	86.0	98	85.9 (14.1)	86.0	98	84.7 (13.3)	84.0
	Endpoint	100	86.2 (14.4)	85.0	100	88.2 (13.3)	89.0	98	87.9 (14.5)	86.0	98	87.3 (13.8)	87.5
	Change	100	2.2 (10.8)	2.0	100	0.9 (14.3)	0.0	98	2.1 (12.8)	0.5	98	2.6 (15.2)	3.5

SD = Standard Deviation; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure.
Change = Change from Baseline to Endpoint.
For each vital signs test, only subjects with baseline and at least one value during treatment phase are included.
All-Patients-as-Treated = All randomized subjects who received at least one dose of trial medication.
Data Source: [16.4]

Mean changes in standing diastolic blood pressure over time, adjusted for placebo, were not substantially different across dose groups and tended to be largest at the final visit (an increase of about 3 mmHg on Day 21), as shown in the following table.

Table 20: Placebo-Adjusted Changes From Baseline in Standing Diastolic Blood Pressure (mmHg) By Visit (Trial P06107)

Visit	2.5mg	5mg	10mg
Day 4	+1.6	+2.3	+1.9
Day 7	+1.9	+2.5	+1.8
Day 14	+0.9	+2.1	+2.3
Day 21	+3.4	+3.1	+2.7

Examination of the mean changes in supine pulse relative to placebo by visit reveals that, in all dose groups, increases relative to placebo began in the first few days of treatment but did not persist in the two lower dose groups. Increases were greater in the 10mg dose group, as shown in the table below:

Table 21: Placebo-Adjusted Changes From Baseline in Supine Pulse (bpm) By Visit (Trial P06107)

Visit	2.5mg	5mg	10mg
Day 4	+3.4	+2.0	+4.8
Day 7	+0.1	+1.0	+4.2
Day 14	+2.1	+2.8	+6.4
Day 21	+1.9	+1.0	+2.1

In sum, vital sign changes associated with asenapine treatment were increases in supine pulse (2-3 bpm in the 2.5mg and 5mg groups and 4-6 bpm in the 10mg group after adjustment for the placebo change) and increases in standing diastolic blood pressure of 2-3 mmHg in all asenapine dose groups compared to placebo.

PDLC criteria for vital signs are displayed in the table below.

Table 22: Pre-Defined Limits of Change Criteria for Vital Signs

Parameter	Clinically Important at Any Time[a]	
	Value	Change
Supine Pulse (bpm)	***>120 bpm***	≥15 bpm increase from baseline
	<50 bpm	≥15 bpm decrease from baseline
Standing Pulse (bpm)	***>120 bpm***	≥15 bpm increase from baseline
	<50 bpm	≥15 bpm decrease from baseline
Supine Systolic Blood Pressure (mmHg)	>mmHg[b] 10-12 years: boys >123, girls >121; 13-18 years: boys >136, girls >128	≥20 mmHg increase from baseline
	≤mmHg[b] 10-12 years ≤89, 13-18 years ≤99	≥20 mmHg decrease from baseline
Standing Systolic Blood Pressure (mmHg)	>mmHg[b] 10-12 years: boys >123, girls >121; 13-18 years: boys >136, girls >128	≥20 mmHg increase from baseline
	≤mmHg[b] 10-12 years ≤89, 13-18 years ≤99	≥20 mmHg decrease from baseline
Supine Diastolic Blood Pressure (mmHg)	≥mmHg[b] 10-12 years ≥78; 13-18 years: boys ≥85, girls ≥82	≥10 mmHg increase from baseline
	≤mmHg[b] 10-12 years ≤52, 13-18 years ≤56	≥10 mmHg decrease from baseline
Standing Diastolic Blood Pressure (mmHg)	≥mmHg[b] 10-12 years ≥78; 13-18 years: boys ≥85, girls ≥82	≥10 mmHg increase from baseline
	≤mmHg[b] 10-12 years ≤52, 13-18 years ≤56	≥10 mmHg decrease from baseline

bpm = beats per minute; mmHg = millimeters of mercury

[a] ***Clinically important at any time: if Value and Change in the same row both hold.***

[b] Definitions used for cut-offs differ by gender and/or age.

The proportions of patients who met any of these criteria during trial P06107 are presented in the following table.

Table 23: Percentage of Patients With Vital Sign Measurements That Met PDLC During Treatment (Trial P06107)

Parameter	PDLC	Placebo N=101 n (%)	2.5 mg N=104 n (%)	5.0 mg N=99 n (%)	10.0 mg N=99 n (%)
Supine SBP (mmHg)	Number of Subjects	99	99	99	96
	Upper limit	4 (4.0)	7 (7.1)	3 (3.0)	4 (4.2)
	Lower limit	5 (5.1)	2 (2.0)	1 (1.0)	3 (3.1)
Standing SBP (mmHg)	Number of Subjects	100	100	98	98
	Upper limit	6 (6.0)	6 (6.0)	4 (4.1)	4 (4.1)
	Lower limit	7 (7.0)	3 (3.0)	3 (3.1)	2 (2.0)
Supine DBP (mmHg)	Number of Subjects	99	99	99	96
	Upper limit	11 (11.1)	10 (10.1)	10 (10.1)	10 (10.4)
	Lower limit	6 (6.1)	12 (12.1)	2 (2.0)	10 (10.4)
Standing DBP (mmHg)	Number of Subjects	100	100	98	98
	Upper limit	13 (13.0)	16 (16.0)	16 (16.3)	18 (18.4)
	Lower limit	11 (11.0)	7 (7.0)	7 (7.1)	3 (3.1)
Supine pulse (bpm)	Number of Subjects	99	99	99	96
	Upper limit	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
	Lower limit	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Standing pulse (bpm)	Number of Subjects	100	100	98	98
	Upper limit	1 (1.0)	1 (1.0)	6 (6.1)	4 (4.1)
	Lower limit	1 (1.0)	1 (1.0)	1 (1.0)	0 (0.0)

PDLC = Predefined Limit of Change.
SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure.
Number of subjects with baseline and post-baseline value of the parameter during the treatment phase.
n = number of subjects meeting the PDLC of the parameter during the treatment phase.
All-Patients-as-Treated = All randomized subjects who received at least one dose of trial medication.
Data Source: [16.4]

Differences between asenapine and placebo were noted for the following measures:

- low supine DBP (2.5mg and 10mg).
- high standing DBP (all asenapine dose groups).
- high standing pulse (5mg and 10mg).

These data exhibit considerable variability across dose groups and among related variables. The larger proportions of asenapine patients with high standing diastolic blood pressure compared to placebo is consistent with the higher mean changes in this variable noted above. Nonetheless, these differences in the proportions meeting PDLC criteria from placebo were not statistically significant (alpha=0.10).

Orthostatic hypotension was defined as >20 mmHg drop in systolic blood pressure or >10 mmHg drop in diastolic blood pressure (with a change in position from supine to standing) at any visit. The percentages of patients who met this criterion in trial P06107 are presented below (denominators represent only those patients with both supine and standing measurements taken in the order supine to standing with ≤3 minutes between positions):

Placebo	9%	(8/94)
Asenapine 2.5mg	10%	(9/94)
Asenapine 5mg	10%	(9/94)
Asenapine 10mg	9%	(8/93)

The frequency of orthostatic hypotension was comparable across all treatment groups.

There were two cases of treatment-emergent syncope in trial P06107, both on asenapine:

• one patient was a 12 year old female (#101263) in the 2.5mg group who experienced syncope immediately after visiting a family member in the intensive care unit of a hospital. She was reportedly emotionally upset by the visit and had a history of fainting under emotionally disturbing circumstances. The episode lasted several minutes. She was taken to the emergency room of the hospital, given intravenous fluids, and discharged to home. She was discontinued from the study because of non-compliance, having taken her last dose of asenapine the day prior to the syncopal episode.
• the other patient was a 12 year old female (#100821) in the 5mg group who fainted during attempted venipuncture at the study site. She quickly regained consciousness and completed the trial.

A causal link to asenapine seems unlikely in both cases.

There were no dropouts in trial P06107 because of a vital sign abnormality.

7.4.4 Electrocardiograms (ECGs)

Mean changes from baseline to endpoint in ECG measures for patients in trial P06107 are displayed in the following table.

The only remarkable differences relative to placebo were increases in heart rate (about 3 bpm in the 10mg group), consistent with the vital sign changes described above, and decreases in the RR interval, corresponding to the increases in heart rate.

The increases in QTcB relative to placebo (about +4 msec in the 2.5mg group and +3 msec in the 10mg group) are not considered clinically significant and are greater than the changes in QTcF (+1.8 msec in the 2.5mg group and 0.0 msec in the 10mg group).

Table 24: Changes From Baseline To Endpoint in ECG Parameters (Trial P06107)

Parameter		Placebo N=101			2.5 mg N=104			5.0 mg N=99			10.0 mg N=99		
		n	Mean (SD)	Media n	n	Mean (SD)	Media n	n	Mean (SD)	Media n	n	Mean (SD)	Media n
Heart rate (bpm)	Baseline	76	71.4 (12.9)	72.0	82	72.3 (11.8)	70.5	84	71.5 (13.4)	70.0	76	69.9 (12.8)	67.5
	Endpoint	76	72.6 (13.0)	70.0	82	75.9 (12.1)	74.5	84	74.0 (15.3)	73.0	76	74.2 (14.3)	73.0
	Change	76	1.2 (11.7)	0.0	82	3.6 (11.3)	4.0	84	2.5 (11.9)	1.0	76	4.3 (12.9)	4.0
RR interval (msec)	Baseline	76	867.7 (160.6)	836.5	82	851.1 (136.5)	850.5	84	869.5 (166.8)	853.5	76	886.7 (166.8)	888.5
	Endpoint	76	851.3 (151.2)	854.5	82	810.8 (127.8)	806.0	84	846.2 (175.9)	821.5	76	839.4 (167.9)	821.5
	Change	76	-16.3 (134.5)	-3.0	82	-40.3 (117.5)	-38.5	84	-23.3 (137.9)	-13.5	76	-47.3 (143.1)	-55.0
PR interval (msec)	Baseline	76	144.9 (17.9)	143.0	82	143.0 (17.4)	142.0	84	147.3 (18.8)	145.5	76	147.6 (19.2)	147.5
	Endpoint	76	145.9 (17.5)	144.0	82	144.5 (17.0)	143.0	84	147.0 (17.4)	143.5	76	146.8 (18.5)	149.0
	Change	76	1.1 (11.2)	1.0	82	1.5 (13.8)	1.5	84	-0.3 (11.7)	-1.0	76	-0.9 (12.6)	0.0
QRS complex (msec)	Baseline	76	88.9 (7.1)	88.0	82	90.4 (6.7)	90.0	84	89.2 (7.0)	89.0	76	88.8 (7.6)	89.0
	Endpoint	76	89.0 (7.5)	89.5	82	91.9 (10.5)	90.0	84	89.0 (7.7)	89.0	76	89.9 (8.2)	89.0
	Change	76	0.2 (6.4)	0.0	82	1.5 (10.2)	1.0	84	-0.1 (6.3)	0.5	76	1.1 (6.5)	1.0
QT interval (msec)	Baseline	76	381.7 (26.4)	380.5	82	376.0 (25.0)	378.0	84	384.0 (33.1)	384.0	76	380.9 (29.1)	384.0
	Endpoint	76	378.4 (25.2)	378.0	82	370.7 (24.7)	374.0	84	378.4 (33.9)	380.0	76	372.9 (29.8)	374.5
	Change	76	-3.3 (23.3)	-2.0	82	-5.3 (20.4)	-4.5	84	-5.6 (23.8)	-5.5	76	-8.0 (25.9)	-8.0
QTc Bazett (msec)	Baseline	76	412.9 (23.5)	411.5	82	409.8 (22.0)	413.0	84	414.5 (23.3)	412.0	76	407.6 (24.8)	408.0
	Endpoint	76	413.0 (21.8)	411.5	82	413.8 (21.1)	415.0	84	414.7 (23.0)	415.5	76	410.4 (24.6)	415.5
	Change	76	0.1 (20.1)	1.0	82	4.0 (20.1)	1.0	84	0.2 (19.6)	1.5	76	2.8 (22.0)	5.5

Table 24: Changes From Baseline To Endpoint in ECG Parameters (continued)

Parameter		Placebo N=101			2.5 mg N=104			5.0 mg N=99			10.0 mg N=99		
		n	Mean (SD)	Median	n	Mean (SD)	Median	n	Mean (SD)	Median	n	Mean (SD)	Median
QTc Fridericia (msec)	Baseline	76	401.9 (17.6)	400.5	82	398.0 (17.8)	401.0	84	403.7 (20.7)	402.5	76	398.1 (20.2)	398.5
	Endpoint	76	400.8 (16.0)	403.0	82	398.6 (17.3)	399.0	84	401.8 (19.4)	403.0	76	397.0 (19.7)	398.5
	Change	76	-1.1 (15.2)	-0.5	82	0.7 (15.2)	-1.0	84	-1.9 (14.9)	-2.0	76	-1.1 (17.4)	-1.0

SD = Standard Deviation; Bpm = beats per minute; QT = Time from beginning of the QRS complex to the end of the T-wave;
QTc = QT interval corrected for heart rate; QTc Fridericia = QTc calculated using the Fridericia formula; QTc Bazett = QTc calculated using the Bazett formula.
Change = Change from Baseline to Endpoint.
For each ECG test, only subjects with baseline and at least one value during treatment phase are included.
All-Patients-as-Treated = All randomized subjects who received at least one dose of trial medication.
Data Source: [16.4]

The criteria for PDLC for ECG measures in trial P06107 are provided in the table below.

Table 25: Pre-Defined Limits of Change for ECG Parameters

Parameter	Clinically important at any time[a]	
	Value	Change
Heart rate (bpm)	>120 bpm	≥ 15 bpm increase from Baseline
	<50 bpm	≥ 15 bpm decrease from Baseline
RR interval (msec)	>1200 msec	≥ 400 msec increase from baseline
	<500 msec	≥ 400 msec decrease from baseline
	>1200 msec	No requirement
	<500 msec	No requirement
PR interval (msec)	≥200 msec	≥ 30 msec increase from Baseline
QRS complex (msec)	≥120 msec	≥ 20 msec increase from Baseline
QT interval (msec)	No requirement	No requirement
QTc Bazett[b] (msec)	≥ 450 msec	No requirement
	≥ 480 msec	No requirement
	≥ 500 msec	No requirement
	No requirement	≥30 msec increase from Baseline
	No requirement	≥60 msec increase from Baseline
QTc Fridericia[c] (msec)	≥ 450 msec	No requirement
	≥ 480 msec	No requirement
	≥ 500 msec	No requirement
	No requirement	≥ 30 msec increase from Baseline
	No requirement	≥ 60 msec increase from Baseline

nnn. bpm = beats per minute; QT = Time from the beginning of the QRS complex to the end of the T wave; QTc = QT interval corrected for heart rate; RR = RR interval

ooo. [a] Clinically important at any time: if Value and Change in the same row both hold.

ppp. [b] $QTc = QT/(RR)^{1/2}$ for Bazett's correction

qqq. [c] $QTc = QT/(RR)^{1/3}$ for Fridericia's correction where RR = 60/HR.

The proportion of patients who met any of these criteria during treatment in trial P06107 are shown in the following table. The only remarkable finding from these data are increased proportions of asenapine patients, compared to placebo, with a change in QTcB ≥30msec. However, the decreasing frequency of this finding with increasing dose (inverse dose-response), which was also observed for the proportions of patients with a change in QTcF ≥30msec, casts doubt on whether this is attributable to asenapine exposure.

No patient in any treatment group had a QTcB or QTcF value of 500 msec or greater.

Table 26: Proportion of Patients With PDLC Changes in ECG Parameters (Trial P06107)

Parameter	PDLC	Placebo N=101 n (%)	2.5 mg N=104 n (%)	5.0 mg N=99 n (%)	10.0 mg N=99 n (%)
Heart rate (bpm)	Number of Subjects	76	82	84	76
	Upper limit	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Lower limit	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
RR interval (msec)	Number of Subjects	76	82	84	76
	Upper limit	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Lower limit	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
RR interval (msec)	Number of Subjects	83	90	90	86
	Value <500 msec	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Value >1200 msec	2 (2.4)	0 (0.0)	1 (1.1)	3 (3.5)
PR interval (msec)	Number of Subjects	76	82	84	76
	Upper limit	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
QRS complex (msec)	Number of Subjects	76	82	84	76
	Upper limit	0 (0.0)	2 (2.4)	0 (0.0)	0 (0.0)
QTc Bazett (msec)	Number of Subjects	83	90	90	86
	Value >=450 msec	4 (4.8)	3 (3.3)	8 (8.9)	4 (4.7)
	Value >=480 msec	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)
	Value >=500 msec	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
QTc Bazett (msec)	Number of Subjects	76	82	84	76
	Increase >=30 msec	3 (3.9)	10 (12.2)	5 (6.0)	4 (5.3)
	Increase >=60 msec	0 (0.0)	1 (1.2)	0 (0.0)	1 (1.3)
QTc Fridericia (msec)	Number of Subjects	83	90	90	86
	Value >=450 msec	0 (0.0)	1 (1.1)	2 (2.2)	0 (0.0)
	Value >=480 msec	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Value >=500 msec	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
QTc Fridericia (msec)	Number of Subjects	76	82	84	76
	Increase >=30 msec	1 (1.3)	3 (3.7)	0 (0.0)	1 (1.3)
	Increase >=60 msec	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)

PDLC = Predefined Limit of Change.
Bpm = beats per minute; QT = Time from beginning of the QRS complex to the end of the T-wave;
QTc = QT interval corrected for heart rate; QTc Fridericia = QTc calculated using the Fridericia formula;
QTc Bazett = QTc calculated using the Bazett formula.
Increase = Increase from Baseline.
For the PDLCs using parameter value for RR interval, QTc Bazett, and QTc Fridericia, number of subjects with post-baseline value of the parameter during the treatment phase. For all other PDLCs, number of subjects with baseline and post-baseline value of the parameter during the treatment phase.
n = number of subjects meeting the PDLC of the parameter during the treatment phase.
All-Patients-as-Treated = All randomized subjects who received at least one dose of trial medication.
Data Source: [16.4]

There were no dropouts in trial P06107 because of an adverse event related to an ECG abnormality.

There were 2 events within the torsades de pointe/QT prolongation broad SMQ in this trial. Both were reports of syncope and are discussed under section 7.4.3 above.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Among the common and probably drug-related adverse reactions in trial P06107 (somnolence, fatigue, dizziness, oral paresthesia, nausea, weight increased, increased appetite, and dysgeusia), only fatigue and dysgeusia showed some evidence of being dose-related:

	2.5mg	5mg	10mg
Fatigue	4%	8%	14%
Dysgeusia	4%	5%	9%

7.5.3 Drug-Demographic Interactions

The sponsor conducted analyses of the effect of gender and race for treatment-emergent adverse events, by MedDRA preferred terms, in trial P06107 that were reported by at least 5% of asenapine-treated patients in a demographic/dose subgroup and at a rate at least twice the corresponding placebo rate. Statistical testing of the odds ratios using the Breslow-Day test was conducted using a nominal alpha level of 0.10.

Significant differences with respect to gender were observed for sedation in the 2.5mg and 5mg groups. Significant differences by racial subgroup were seen for increased appetite in the 2.5mg and 5mg groups and for oral paresthesia in the 10mg group. These findings are summarized in the following table.

For sedation in the 10mg group versus placebo, the odds ratios for the gender subgroups followed the pattern for the lower groups (i.e., much larger OR in females) and approached the nominal significance level (p= 0.119). But for all three dose groups, the asenapine rates were comparable for females and males, the significant differences being explained by a large difference in the placebo rate (much larger in males). The reason for placebo-treated males to report sedation much more commonly than females is not known.

The differences regarding increased appetite by racial subgroups cannot be so consistently explained. For example, in the Black subgroup, the odds ratio in the 2.5mg group is 1.8 but in the 5mg group, it is 0.4 (more common in placebo) and in the 10mg group, it is 1.8 again. Likewise, the odds ratios in the White subgroup are much higher in the two lower dose groups than in the high dose group. Such inconsistencies across dose groups are difficult to explain and suggest that this may be a spurious finding.

Similarly, inconsistent odds ratios across the three dose groups for oral paresthesia, particularly within the Black and Others subgroups, make it hard to draw a firm conclusion regarding an effect of race on the incidence of this adverse event.

Table 27: Treatment-Emergent Adverse Event Incidence (%) By Demographic Subgroups (Trial P06107)

Sedation	**Subgroup**	**Placebo**	**2.5mg**	**Odds Ratio**	**p-Value**
	Female	2%	17%	13.0	0.051
	Male	11%	14%	1.3	
Sedation	**Subgroup**	**Placebo**	**5mg**	**Odds Ratio**	**p-Value**
	Female	2%	21%	16.9	0.044
	Male	11%	16%	1.7	
Increased Appetite	**Subgroup**	**Placebo**	**2.5mg**	**Odds Ratio**	**p-Value**
	White	0%	9%	15.0	0.089
	Black	9%	14%	1.8	
	Others	0%	0%	N/A	
Increased Appetite	**Subgroup**	**Placebo**	**5mg**	**Odds Ratio**	**p-Value**
	White	0%	12%	19.6	0.008
	Black	9%	4%	0.4	
	Others	0%	0%	N/A	
Oral Paresthesia	**Subgroup**	**Placebo**	**10mg**	**Odds Ratio**	**p-Value**
	White	0%	11%	17.6	0.006
	Black	4%	0%	0.3	
	Others	10%	57%	12.0	

7.6 Additional Safety Evaluations

7.6.2 Human Reproduction and Pregnancy Data

There was one pregnancy in trial P06107. A 16 year old female (#100488) in the asenapine 10mg group had a positive serum pregnancy test on Day 21 of the trial (screening and baseline pregnancy tests were negative). This patient had a miscarriage during the safety follow-up period (Day 42).

Two pregnancies occurred during the 50-week open-label extension trial (P05898) as of October 31, 2014:

• a 15 year old female (#100484) taking asenapine 10mg BID had positive urine and serum pregnancy tests on Day 29 of the study. The outcome of the pregnancy is unknown.

• a 17 year old female (#100803) had a positive serum pregnancy test on Day 30 of the study. The patient stopped the study drug (asenapine 10mg BID). The pregnancy was terminated about 2 weeks later.

No other new data on the reproductive effects of asenapine are presented in this supplement.

7.6.3 Pediatrics and Assessment of Effects on Growth

Age- and sex-adjusted growth percentile rankings were determined for patients in trial P06107. At baseline, mean percentiles indicated that the patient sample was of roughly average height (mean percentiles 46-53%). Changes from baseline to endpoint in height percentile ranking among all treatment groups were small (<1%) and asenapine patients tended to fall slightly behind the placebo group:

Placebo	+0.53%	(N=89)
Asenapine 2.5mg	+0.03%	(N=92)
Asenapine 5mg	-0.08%	(N=90)
Asenapine 10mg	-0.33%	(N=87)

In terms of z-score changes from baseline to endpoint for height, there was not much difference among the groups:

Placebo	+0.02 SD	(N=89)
Asenapine 2.5mg	-0.00 SD	(N=92)
Asenapine 5mg	-0.01 SD	(N=90)
Asenapine 10mg	-0.01 SD	(N=87)

In the 50-week, open-label bipolar disorder study P05898 (as of the interim safety cutoff date July 12, 2013), the changes from the baseline for this study in percentile rankings and z-scores for height (based on all patients treated with placebo in the preceding short-term trial) were +0.27% (N=65) and -0.00 SD (N=65).

To evaluate the potential effects of asenapine on sexual maturation, Tanner staging in patients of both sexes was performed. Tanner staging consisted of breast staging for females, genital growth staging for males, and pubic hair staging for females and males. Shifts from baseline to endpoint in Tanner stage are displayed for females and males in the following two tables.

Among females, there were relatively small numbers of asenapine-treated patients who experienced a negative change in Tanner stage across all dose groups compared to no placebo patients with a negative change. On the other hand, a number of asenapine patients had an increase of at least one stage, comparable to or greater than the number of such placebo patients.

For males, over 90% in each treatment group had no change in Tanner stage. One patient had a negative change for each measure and a small number had an increase of one level or greater.

Given the brief duration of this trial and missing data for a number of patients, it is difficult to make a precise assessment of the effect of asenapine on sexual maturation.

Table 28: Shifts in Tanner Stage Among Females (Trial P06107)

Parameter	Shift	Placebo N=63 n (%)	2.5 mg N=52 n (%)	5.0 mg N=56 n (%)	10.0 mg N=41 n (%)
Breast	Number of Subjects	48	40	45	31
	<0	0 (0.0)	2 (5.0)	1 (2.2)	2 (6.5)
	0	44 (91.7)	35 (87.5)	43 (95.6)	26 (83.9)
	1	4 (8.3)	3 (7.5)	1 (2.2)	1 (3.2)
	2	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.2)
	3	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.2)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pubic Hair	Number of Subjects	48	40	45	31
	<0	0 (0.0)	2 (5.0)	0 (0.0)	2 (6.5)
	0	46 (95.8)	34 (85.0)	37 (82.2)	27 (87.1)
	1	1 (2.1)	4 (10.0)	8 (17.8)	2 (6.5)
	2	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Shift from Baseline to Endpoint: <0 = negative change, 0 = no stage change, 1 = 1 stage up, 2 = 2 stages up, 3 = 3 stages up, 4 = 4 stages up.
For each tanner question, only subjects with baseline and at least one value during treatment phase are included.
All-Patients-as-Treated= All randomized subjects who received at least one dose of trial medication.
Data Source [16.4]

Table 29: Shifts in Tanner Stage Among Males (Trial P06107)

Parameter	Shift	Placebo N=38 n (%)	2.5 mg N=52 n (%)	5.0 mg N=43 n (%)	10.0 mg N=58 n (%)
Genital Growth	Number of Subjects	28	44	39	45
	<0	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)
	0	27 (96.4)	41 (93.2)	36 (92.3)	45 (100.0)
	1	1 (3.6)	2 (4.5)	3 (7.7)	0 (0.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pubic Hair	Number of Subjects	28	43	38	45
	<0	1 (3.6)	1 (2.3)	0 (0.0)	0 (0.0)
	0	27 (96.4)	39 (90.7)	37 (97.4)	45 (100.0)
	1	0 (0.0)	3 (7.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	0 (0.0)	1 (2.6)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Shift from Baseline to Endpoint: <0 = negative change, 0 = no stage change, 1 = 1 stage up, 2 = 2 stages up, 3 = 3 stages up, 4 = 4 stages up.
For each tanner question, only subjects with baseline and at least one value during treatment phase are included.
All-Patienst-as-Treated= All randomized subjects who received at least one dose of trial medication.
Data Source [16.4]

Among placebo/asenapine patients in the long-term study P05898 (as of the interim cutoff date), shifts in Tanner stage from baseline to endpoint are displayed in the following table. An appreciable number of males and females progressed in Tanner stage during this study but these figures cannot be interpreted without a control group.

Table 30: Enumeration of Patients (N(%)) with Tanner Stage Shifts Study P05898 (Placebo/Asenapine-Treated Patients)

Sex	Stage Shift	Genital Growth/Breast	Pubic Hair
Males (M=14)	0	10 (71%)	10 (71%)
	+1	3 (21%)	3 (21%)
	+2	1 (7%)	1 (7%)
Females (N=20)	Negative	0	1 (5%)
	0	14 (70%)	13 (65%)
	+1	6 (30%)	5 (25%)
	+3	0	1 (5%)

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

One patient (#101081) in the placebo group of trial P06107 took an accidental overdose of study medication: 2 placebo tablets BID (instead of one tablet BID) for 4 consecutive days. Another patient (#100981) in the 10mg group took an overdose of acetaminophen (20 extra strength tablets) in a suicide attempt. Two patients in the 50-week open label study P05898 took overdoses classified as serious adverse events as of October 31, 2014: one (#100202) took an accidental overdose of Ambien and the other (#100602) took an intentional overdose of melatonin. Both had been treated with asenapine in the preceding short-term trial.

There were no studies to assess drug abuse potential, rebound, or withdrawal in pediatric patients with bipolar I disorder

Patients with a history of substance abuse or dependence (except nicotine and caffeine) within the previous 6 months were excluded from the bipolar disorder studies.

8 Postmarket Experience

The sponsor provided an assessment of postmarketing exposure and safety in pediatric patients ages 10-17 years. According to (b) (4), distribution data from U.S. drug stores indicates that (b) (4)% of all prescribed doses were for patients ages 10-17 years. If this is extrapolated to worldwide exposure, exposure to asenapine in this age range would be (b) (4) patient-years from August 13, 2009, through October 31, 2013. The Four-Month Safety Update Report provides data for the interval from November 1, 2013, to October 31, 2014. During this timeframe, it is estimated there was (b) (4) patient-years of exposure in the 10 to 17 year age range.

Merck searched their safety database (MARRS) for all spontaneous and literature reports where asenapine was used in patients 10-17 years from product launch (October 2009) to October 31, 2013. A total of 100 postmarketing safety reports had been received that involved 342 events. No events were fatal. The sponsor's examination of the events revealed that 44 were unlisted in the current labeling. Of these, 19 contained insufficient information for analysis and 17 represented events closely related or the consequence of labeled events. Of the remaining 8 cases, I found that the only remarkable event was oropharyngeal blistering in a 13 year old female patient, who had a positive dechallenge after stopping asenapine. This event is labeled as a postmarketing report. The most common event reported was oral hypoesthesia (1.9 cases/1,000 patient-years). This event is labeled.

My own examination of the listing of these 342 adverse events revealed that none represented a previously unrecognized hazard associated with asenapine treatment.

The Four-Month Safety Update Report contains an updated (b) (4) search covering the period from November 1, 2013, to October 31, 2014. During this time, 13 postmarketing safety reports describing 43 adverse events in patients in the age range 10 to 17 years were received. No case had a fatal outcome. Three reports were prompted by events consistent with lack of efficacy, two described medication errors, prescribed overdoses, or off-label use; and five were for adverse events either labeled or related to labeled reactions. The other three cases are summarized below:

• a 14 year old male experienced non-food vomiting, mouth foaming, white tongue, and mild cyanosis the day he started asenapine 10mg qday for a "manic state in congenital dementia." Asenapine was stopped the next day and he recovered that same day. Concomitant medications were fluoxetine, quetiapine, clothiapine.
• a 14 year old female experienced pain under the rib cage and shortness of breath within 3 months of starting asenapine 5mg qhs for schizophrenia. She was medically evaluated and no treatment was administered. Other events included tongue numbness (date unknown) and a ruptured ovarian cyst with vasovagal reaction (about 3 years after starting asenapine). She recovered from the latter events and asenapine was stopped. At some time after discontinuation, she had multiple episodes of dizziness, pain behind her head, chest discomfort, and trouble breathing. These events resolved 2 months later.
• an adolescent female (age not specified) started asenapine 2.5mg for 2-3 days to treat borderline personality disorder. On an unknown date, she experienced projectile vomiting, nausea, and lack of appetite. Asenapine was stopped and not restarted. The outcome of the events was reported as resolved. The physician suspected a problem with the batch of drug.

I examined the listing of these 43 adverse events and found that none represented a previously unrecognized hazard likely to be caused by asenapine treatment.

Overall, the sponsor concluded that the postmarketing safety data for patients age 10-17 years was consistent with the U.S. labeling.

9 Appendices

9.1 Literature Review/References

Merck staff reviewed the published literature from January 1, 2009, through October 31, 2013, and provided the search results in the original submission of this application. The Clinical Literature Information Center (CLIC) is located within Merck Research Laboratories Information Technology division and maintains a database of abstracts of published literature related to Merck products. This database encompasses over 400,000 CLIC-authored abstracts as well as author abstracts. These abstracts were searched by the CLIC screening staff using the terms "asenapine," "pediatric,", "case reports," and "published articles" to identify relevant abstracts. Full articles were

requested when abstracts of interest were found. Ronald Landbloom, M.D., the Clinical Director of Neuroscience at Merck, provided a signed warrant on January 21, 2015, that he evaluated the results of this literature search and confirmed that there were no unexpected safety findings with asenapine use in pediatrics.

The Four-Month Safety Update Report contained an updated literature review covering the interval from November 1, 2013, to October 31, 2014. This search was conducted using MedLine, Embase, and Biosis using the search string "(asenapine OR saphris) AND (human) AND (20131101-20141031) AND (pediatric or child or adolescent)." (b) (4), conducted the search at the abstract level. Darren Weissman, M.D., the Director of Pharmacovigilance and Risk Management at Forest Research Institute, provided a signed warrant on January 20, 2015, that he evaluated the results of this literature search and confirmed that there were no unexpected safety findings with asenapine use in pediatrics found in the literature.

9.2 Labeling Recommendations

Adverse reaction information in Section 6 of Saphris labeling should be revised to describe the reporting rates of combined event terms, i.e., terms which encompass a number of closely related preferred terms, as discussed in section 7.1.2 above.

9.3 Advisory Committee Meeting

This supplement was not taken to an Advisory Committee.

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

/s/

GREGORY M DUBITSKY
02/17/2015

JING ZHANG
02/18/2015