CLINICAL REVIEW

Application Type	sNDA
Application Number	22-117 S-018
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 19, 2015
Established Name	Asenapine
Trade Name	Saphris
Therapeutic Class	Antipsychotic
Applicant	Forest Laboratories
Formulation	Sublingual Tablets
Dosing Regimen	2.5mg BID or 5mg BID
Indication	Schizophrenia
Intended Population	(b) (4)

Template Version: March 6, 2009

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(b) (4)

1 Recommendations/Risk Benefit Assessment

(b) (4)

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 (b) (4)

Currently approved treatments for schizophrenia in adolescent patients are: Risperdal (risperidone), Abilify (aripiprazole), Seroquel (quetiapine), Zyprexa (olanzapine), and Invega (paliperidone).

2.3 Availability of Proposed Active Ingredient in the United States

Asenapine has been available in the U.S. as Saphris 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.

PMRs 1496-3 and 1496-4 are the corresponding requirements for deferred studies in pediatric patients (ages 10-17) 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 1496-1 and PMR 1496-2 as well as the requirements of the WR with respect to schizophrenia were conducted under IND 51,641.

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 trials relevant to schizophrenia.

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 within this application was assessed by comparing information across the following documents for a sample of 5 patients: Case Report Forms (CRFs), Narrative Summaries, and adverse event data listings (ae.xpt files). The 5 patients audited were:

- P05896-0128-100113
- P05896-8102-100211
- P05896-8103-100027
- P05897-0103-100134
- P05897-0714-100083

Adverse event information was consistently documented for all 5 patients.

Additionally, the sponsor's coding of adverse event verbatim terms (AELIT) to MedDRA preferred terms (AEDECOD), as documented in the adverse event data files (ae.xpt) for trials P05896 and P05897, was audited. No inaccuracies in adverse event coding were identified. 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 P05896 and P05897 were both conducted in accordance with Good Clinical Practice standards.

I requested that the Office of Scientific Investigations (OSI) conduct an inspection of site 135 in trial P05896 as part of the review of this supplement. This site was inspected on January 20-23, 2015, and a Clinical Inspection Summary was completed on February 9, 2015, by Dr. Jenn Sellers of OSI. There were no deviations from regulations and the data from this site were felt to be acceptable. The preliminary classification was NAI.

3.3 Financial Disclosures

Clinical Investigator Financial Disclosure
Review Template

Application Number: 22-117 S-018

Submission Date(s): September 12, 2014

Applicant: Forest Laboratories

Product: Saphris

Reviewer: Greg Dubitsky, M.D.

Date of Review: February 19, 2015

Covered Clinical Study (Name and/or Number): P05896

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 81		
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 P05896 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.

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5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Studies conducted 4 studies (b) (4) These investigations are listed in the table below.

Table 1: Table of Studies in Pediatric Schizophrenia	
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	
P05896	8-week, randomized, double-blind, placebo-controlled safety and efficacy trial in 306 patients (ages 12-17) with acute schizophrenia using fixed doses of 2.5mg BID, 5mg BID, or placebo.
P05897	26-week, open-label extension safety study for completers of trial P05896 using flexible dosing with 2.5mg BID or 5mg BID.

Hereafter in this review, the 2.5mg BID treatment group will be referred to as "2.5mg" and the 5mg BID treatment group will be referred to as "5mg."

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 23, 2015	0198	Requested information regarding the sponsor's literature search and cumulative exposure.

5.2 Review Strategy

(b) (4) review of this supplement is based solely on the results of trial P05896.

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 and 2) an evaluation of supportive safety findings from analyses of data primarily from trial P05896, to include an assessment of common adverse events, laboratory tests, vital signs, and ECGs.

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7 Review of Safety

Safety Summary

Safety data in pediatric schizophrenia was derived primarily from two Phase 3 trials: an 8-week placebo-controlled trial (P05896) and a 26-week open-label trial (P05897).

There was one death secondary to injuries after a fall from a sixth floor window. The fall apparently was accidental in nature.

Non-fatal serious adverse events were mostly related to exacerbation of the underlying illness or other psychiatric symptoms. Other serious adverse events were pneumonia and typhoid fever, both of which are felt to be unlikely drug-related.

The most common reason for dropout was exacerbation of schizophrenia. Other notable events that led to dropout were ALT elevation and a hypersensitivity reaction

(rash, fever, and increased CK), both of which are considered possibly related to asenapine treatment.

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, Parkinsonism, and dystonia).
- oral hypoesthesia.

The most common adverse events felt to be probably drug-related were somnolence, akathisia, dizziness, and oral hypoesthesia. Only somnolence and akathisia are considered possibly dose-related.

Remarkable laboratory test abnormalities with asenapine treatment were an increased mean change in platelet count in the asenapine 5mg dose group and increased creatine kinase. The clinical significance of these findings is uncertain.

Vital sign changes associated with asenapine treatment were increased blood pressure (1-3 mmHg in the 5mg dose group compared to placebo) and increased pulse (1-3 bpm in the 2.5mg group and 4-6 bpm in the 5mg group, adjusted for the placebo change).

Most of these safety findings are already known to be associated with asenapine treatment and are labeled. (b) (4)

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data were derived primarily from studies P05896 and P05897.

7.1.2 Categorization of Adverse Events

Adverse event verbatim terms were coded to preferred terms using MedDRA version 15.1 (trial P05896) and version 16.0 (trial P05897). Although an audit of the coding process revealed no major errors, the granularity of MedDRA does permit splitting of some adverse events to an extent that may not be clinically useful. Therefore, for

purposes of this review, the following related adverse event preferred terms were combined into a common term for calculation of reporting rates in the sections below.

Common Term	Subsumed Preferred Terms
Somnolence	Somnolence, sedation, hypersomnia.
Asthenia	Asthenia, fatigue, sluggishness.

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 prolongation of inpatient hospitalization.
- results in persistent or significant disability or incapacity.
- congenital abnormality or birth defect.
- an important medical event, that is, an event 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 outcomes listed above.

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 schizophrenia program, studies were not pooled.

For analyses of numeric data from the 26-week, open-label study P05897, baseline was defined by the sponsor as the last value in the short-term trial (P05896) just prior to extension study treatment, unless otherwise noted. Therefore, this review will focus on those analyses based on patients who received placebo in trial P05896 then asenapine in study P05897, designated as “placebo/asenapine” patients.

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.

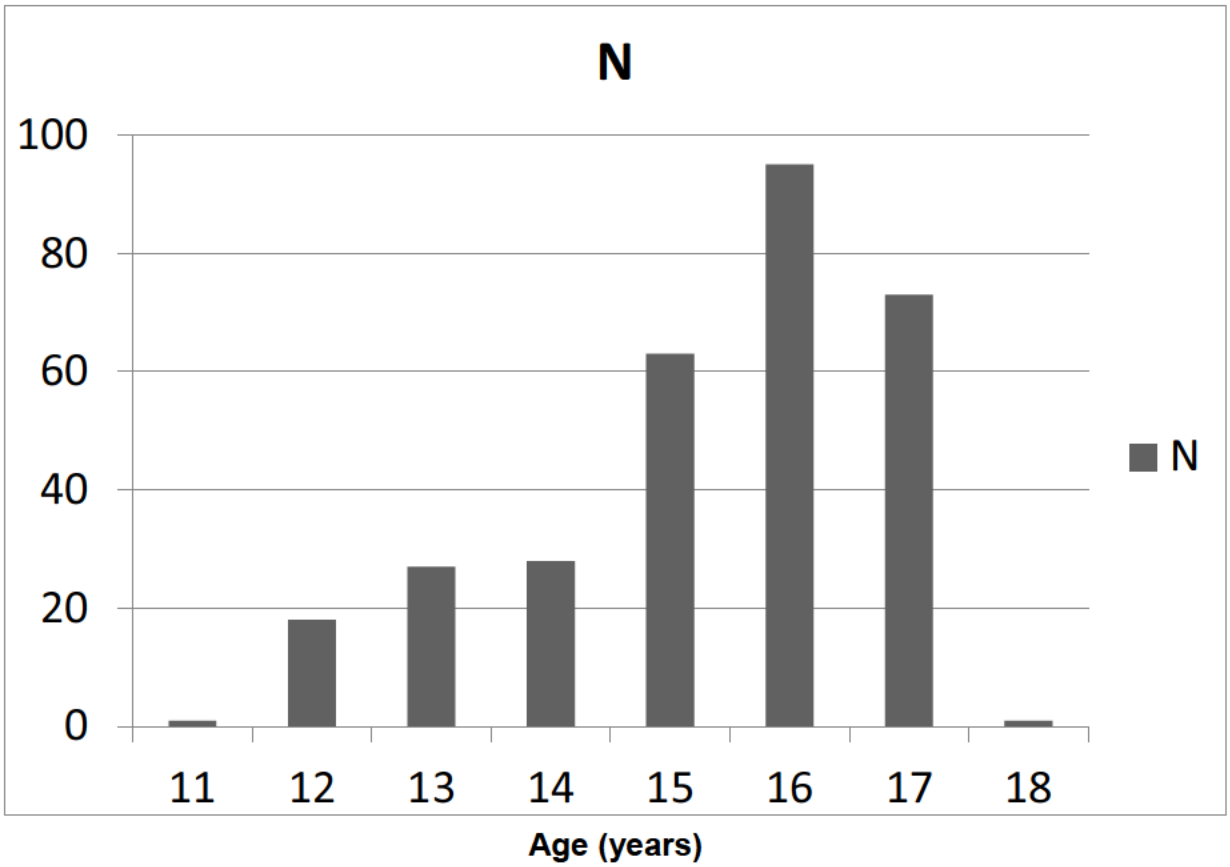
Across these 4 trials, patients were treated with sublingual asenapine in the dose range of 2.5mg BID to 10mg BID. As of October 31, 2014 (the cutoff date for the Four-Month Safety Update Report), a total of 651 patients received asenapine treatment for any duration, 352 received asenapine for 180 days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

Demographic characteristics of patients in trial P05896 were generally consistent across the three treatment groups. Overall, most patients were male (62%), the median age was 16.0 years, and the most common racial groups were white (54%), Asian (34%), and Black or African American (8%). Ethnically, most patients (93%) were classified as not Hispanic or Latino. The bulk of the patients were from outside the U.S. (84%). The mean weight and BMI percentiles adjusted for age and sex were 52% and 55%, respectively. In terms of height, the mean percentile adjusted for age and sex was 42%.

The distribution of patients by age in trial P05896 is shown in the figure below. The age distribution was skewed toward patients at the older end of the age range, with about 75% of the patients in the age range 15-17 years. This distribution is consistent with the fact that the onset of schizophrenia is typically between the late teenage years and mid-30's.[1]

[1] American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association, 2013.

Figure 2: Number of Patients By Age (Trial P05896)



7.2.2 Explorations for Dose Response

The fixed dose design of trial P05896 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 P05896 include the following:

• laboratory testing at screening and baseline and on days 14, 28, and 56. 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, 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, 21, 28, 42, and 56.
• 12-lead ECGs were done at screening and on days 28 and 56.
• Columbia-Suicide Severity Rating Scale (C-SSRS) was assessed at screening and baseline and on days 1, 4, 7, 14, 21, 28, 42, and 56.
• Extrapyramidal Symptom Rating Scale (ESRS) was conducted at baseline and on days 7, 28, and 56. 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 14, 28, 42, and 56.
• Tanner staging was assessed at screening and on day 56.
• Menstrual cycles were assessed in females at baseline and on days 28 and 56.
• Children's Depression Rating Scale-Revised (CDRS-R) was assessed at baseline and on days 28 and 56 to detect emergence of depression.
• a cognitive battery was administered prior to randomized treatment and on day 56. 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 in section 7.3.5.

These assessments were also performed during the open-label extension study P05897.

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 trial P05896 or in the Phase 1 studies A7501022 and P06522. There was one death in trial P05897: Subject #100187 was a 15 year old male who fell from a sixth floor window and sustained multiple bone fractures, internal organ failure, and a fatal outcome. There was no history of suicidal ideation, suicide attempt, or deliberate self-harm before or during the trial. Thus, the event was considered accidental by the investigator.

7.3.2 Nonfatal Serious Adverse Events

There were no non-fatal SAEs in the Phase 1 studies A7501022 and P06522. In trial P05896, there were 9 non-fatal SAEs, 3 cases in each treatment group. Seven of the 9

cases were hospitalizations for psychotic symptoms, likely representing an exacerbation of the underlying illness: 3 of these occurred in the placebo group, 2 in the 2.5mg group, and 2 in the 5mg group. The remaining 2 cases were pneumonia (in the 2.5mg group) and typhoid fever (in the 5mg group). I reviewed the narrative summaries for these 2 cases and concluded that neither are likely to be causally related to asenapine treatment.

There were 7 non-fatal SAEs during the open-label extension trial P05897. All 7 cases were psychiatric adverse events: exacerbation of schizophrenia (3 patients), aggression and anxiety (1 patient), aggression (1 patient), agitation (1 patient), and anxiety (1 patient).

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 P05896 because of adverse events are displayed in the following table. As noted above, I combined adverse event terms related to somnolence (i.e., somnolence, sedation, and hypersomnia) into the common term "somnolence" for purposes of computing reporting rates. Thus, for the common term, the proportions of patients who dropped out of trial P05896 because of somnolence were:

Placebo	0%	(0/102)
Asenapine 2.5mg	1%	(1/98)
Asenapine 5mg	1%	(1/106)

Except for schizophrenia, dropout rates secondary to adverse events were very low. The dropouts for polycythemia and ALT elevation are discussed below.

Subject #100478 was a 17 year old Asian male who had hematocrit and hemoglobin values of 56.6% and 17.6 g/dl, respectively, at screening and 60.0% and 18.1 g/dl at baseline. (Normal ranges were 31-41% and 11-14 g/dl, respectively.) Moderate polycythemia was diagnosed and the subject was discontinued after 9 days of asenapine treatment at a dose of 5mg BID based on these lab results. Given the abnormally high values prior to asenapine exposure, it seems that asenapine had no causal role in these findings.

Subject #100185 was a 17 year old Asian female who started asenapine treatment on July 12, 2012. On that date, she had a elevation in ALT (82 U/L, ULN =20 U/L). On July 16, the ALT rose to 163 U/L and medication was stopped on July 18. Subsequent ALT values declined: 137 U/L (July 19), 55 U/L (July 25), and 20 U/L (August 1). Total

bilirubin values remained within normal range throughout. The ALT elevation is considered to be possibly related to asenapine treatment.

Table 7: Adverse Events Leading to Dropout (Trial P05896)

System Organ Class (SOC)/ Preferred Term	Placebo N=102 n (%)	2.5 mg N=98 n (%)	5.0 mg N=106 n (%)
Subjects reporting any adverse event	3 (2.9)	6 (6.1)	8 (7.5)
Psychiatric disorders	2 (2.0)	4 (4.1)	4 (3.8)
Schizophrenia	2 (2.0)	1 (1.0)	3 (2.8)
Agitation	0 (0.0)	1 (1.0)	0 (0.0)
Depression	0 (0.0)	1 (1.0)	0 (0.0)
Hallucination, auditory	0 (0.0)	1 (1.0)	0 (0.0)
Insomnia	0 (0.0)	0 (0.0)	1 (0.9)
Nervous system disorders	0 (0.0)	1 (1.0)	3 (2.8)
Akathisia	0 (0.0)	0 (0.0)	1 (0.9)
Dysgeusia	0 (0.0)	0 (0.0)	1 (0.9)
Sedation	0 (0.0)	0 (0.0)	1 (0.9)
Somnolence	0 (0.0)	1 (1.0)	0 (0.0)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	1 (0.9)
Polycythaemia	0 (0.0)	0 (0.0)	1 (0.9)
Gastrointestinal disorders	1 (1.0)	0 (0.0)	0 (0.0)
Nausea	1 (1.0)	0 (0.0)	0 (0.0)
Infections and infestations	0 (0.0)	1 (1.0)	0 (0.0)
Pneumonia	0 (0.0)	1 (1.0)	0 (0.0)
Investigations	0 (0.0)	0 (0.0)	1 (0.9)
Alanine aminotransferase abnormal	0 (0.0)	0 (0.0)	1 (0.9)

Every subject is counted a single time for each applicable row and column.
MedDRA coding version 15.1.
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].

Adverse events that led to dropout in the 26-week open-label trial P05897 (total N=196) were mostly psychiatric in nature: schizophrenia (4 patients), aggression (2 patients), and agitation (1 patient). Other events were multi-organ failure, hypersensitivity, and somnolence, each of which led to dropout in one patient. The case of multi-organ failure (Subject #100187) was discussed above as a death. The case of somnolence (Subject #100089) involved moderate drowsiness on both doses of asenapine which was not considered serious but which led to discontinuation from the study. The case of hypersensitivity is described below.

Subject 100356 was a 16 year old Asian male who was treated with asenapine in study P05896 and experienced a hypersensitivity reaction characterized by an upper arm rash on study day 22 of study P05897. He subsequently had a fever lasting one day and was found to have elevated CPK value (4,115 U/L). It was felt that clinical evidence did not substantiate a diagnosis of neuroleptic malignant syndrome. The asenapine dose was initially reduced from 5mg BID to 2.5mg BID on study day 28 but was stopped altogether on day 32. He was closely followed for the next 2 months, over which time

his CPK values returned to normal range and the rash disappeared. This event was considered to be probably related to asenapine treatment. Hypersensitivity reactions associated with asenapine have been reported and this adverse event is prominently described under Warnings and Precautions in Saphris labeling.

7.3.4 Significant Adverse Events

There are a number of significant adverse effects of asenapine and other atypical antipsychotics. Data regarding these effects from the pediatric schizophrenia trials are discussed below.

Metabolic Changes

Hyperglycemia and Diabetes Mellitus

Mean changes from baseline to endpoint in glucose levels among fasted patients in trial P05896 were:

Placebo	-2.5 mg/dl (N=84)
Asenapine 2.5mg	-0.2 mg/dl (N=82)
Asenapine 5mg	+2.2 mg/dl (N=90)

The proportions of patients who had a fasting glucose level ≥126 mg/dl at any point during trial P05896 were about the same across treatment groups:

Placebo	2.4% (2/85)
Asenapine 2.5mg	2.4% (2/85)
Asenapine 5mg	2.2% (2/92)

The fraction of patients with significant shifts from baseline in fasting glucose at any time during treatment are displayed in the following table.

Table 8: Proportion of Patients with Shifts in Fasting Glucose Levels (Trial P05896)

Shift	Placebo	Asenapine 2.5mg	Asenapine 5mg
Normal to Low (>45 & <100) to <45 mg/dl	1% (1/84)	1% (1/82)	0% (0/90)
Normal to Borderline High (>45 & <100) to (≥100 & <126 mg/dl)	18% (15/84)	18% (15/82)	27% (24/90)
Normal to High (>45 & <100) to >126 mg/dl	0% (0/84)	1% (1/82)	1% (1/90)

No patients in any treatment group had a shift in HbA1c from <7.0% to ≥7.0%.

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	3.9% (4/102)
Asenapine 2.5mg	7.1% (7/98)
Asenapine 5mg	6.6% (7/106)

New onset metabolic syndrome (MBS) criteria were met by 0% (0/102) of placebo patients and 1% (1/98) and 2% (2/106) subjects in the asenapine 2.5mg and 5mg groups, respectively. Criteria were defined by the International Diabetes Federation and required obesity (waist circumference ≥90th percentile for children <16 years old), ≥2 specific lab abnormalities, and/or abnormal blood pressure measurements at the same visit.

A total of seven patients in the 26-week open-label study (P05897) met new-onset MBS criteria post-baseline during the study; 5 of the 7 had been treated with asenapine in the short-term trial. There were no cases of new-onset diabetes mellitus reported in this study.

Patients with uncontrolled or unstable diabetes or a clinically significant abnormal blood glucose level at screening and baseline were excluded from these studies.

Dyslipidemia
Mean changes from baseline to endpoint in lipid parameters in trial P05896 are displayed in the table below.

Table 9: Mean Change from Baseline to Endpoint in Lipid Measures (mg/dl) (Trial P05896)

	Placebo		Asenapine 2.5mg		Asenapine 5mg	
	N	**Mean Change**	**N**	**Mean Change**	**N**	**Mean Change**
Cholesterol	95	-12.3	94	-2.7	98	-4.4
HDL	90	-1.2	91	-0.6	93	-0.7
LDL	90	-8.1	91	-2.9	93	-3.8
Fasting Triglycerides	84	-9.4	82	-1.0	90	-1.8

The fraction of patients with significant shifts from baseline in lipid measurements during treatment are displayed in the following table.

Table 10: Proportion of Patients with Shifts in Lipid Parameters (Trial P05896)			
Shift	**Placebo**	**Asenapine 2.5mg**	**Asenapine 5mg**
Tot. Cholesterol Normal to High (<170 to ≥200 mg/dl)	2% (2/95)	5% (5/94)	3% (3/98)
HDL Normal to Low (>40 to <40 mg/dl)	17% (15/90)	15% (14/91)	22% (20/93)
LDL Normal to High (<130 to ≥130 mg/dl)	1% (1/90)	3% (3/91)	3% (3/93)
Fasting TGs Normal to High (<150 to >200 mg/dl)	5% (4/84)	5% (4/82)	11% (10/90)

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.

Table 11: Proportion of Patients with Outlying Cholesterol or Triglyceride Levels (Trial P05896)			
	Placebo	**Asenapine**	
		2.5mg	**5mg**
Total Cholesterol (≥200 mg/dl)	12% (11/95)	17% (16/94)	14% (14/98)
Fasted Triglycerides (≥200 mg/dl)	13% (11/85)	8% (7/85)	19% (17/92)

The mean changes from baseline to endpoint in total cholesterol and fasting triglycerides in the 26-week open-label study (P05897) for placebo/asenapine patients were +4.2 mg/dl (N=62) and +4.8 mg/dl (N=60), respectively.

Weight Gain
Mean changes from baseline to endpoint in body weight in trial P05896 were:

Placebo	+0.11 kg	(N=98)
Asenapine 2.5mg	+1.30 kg	(N=95)
Asenapine 5mg	+1.35 kg	(N=99)

The percentages of subjects in this trial who experienced a 7% or greater increase in body weight from baseline to endpoint were:

Placebo	3%	(3/98)
Asenapine 2.5mg	10%	(9/95)
Asenapine 5mg	10%	(10/99)

In study P05897, approximately 79% (155/196) of patients completed the 26-week treatment period. The mean change from baseline to endpoint in weight for placebo/asenapine patients was +1.63 kg (N=62). The weight percentile ranking change from baseline to endpoint for placebo/asenapine patients was +0.57% (N=62). The weight z-score change from baseline to endpoint (after adjustment for age and gender) was +0.01 SD (N=62). (Z-score changes less than 0.5 standard deviations are not considered clinically significant.)

Hypersensitivity Reactions

In trial P05896, pruritus occurred in 2 placebo-treated patients, rash in one patient in the 2.5mg group, and sneezing and facial flushing in another patient in the 2.5mg group. None were rated as severe or serious and none led to dropout.

In study P05897, one patient experienced a rash and elevated CPK that led to discontinuation; this patient (#100356) is discussed above under dropouts and/or discontinuations. Another patient in this study experienced a hypersensitivity reaction to codeine which was taken for an infected tooth. That reaction resolved the same day.

Hyperprolactinemia

Mean changes from baseline to endpoint in serum prolactin levels from trial P05896 reflected decreases and were not substantially different across treatment groups:

Placebo	-9.1 ng/ml (N=79)
Asenapine 2.5mg	-9.1 ng/ml (N=80)
Asenapine 5mg	-10.0 ng/ml (N=85)

The proportions of patients who had an elevated prolactin level (≥1.1 xULN) during treatment in trial P05896 were higher for asenapine than placebo:

Placebo	13% (10/79)
Asenapine 2.5mg	23% (18/80)
Asenapine 5mg	19% (16/85)

There was one patient (in the 2.5mg group of this trial) who had an adverse event potentially related to prolactin (severe dysmenorrhea). This event was not serious and did not lead to dropout.

In the 26-week open-label study, there were 2 adverse events potentially related to prolactin (moderate hyperprolactinemia and irregular menstruation).

I searched the ae.xpt files of both trials P05896 and P05897 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.

Only one patient was identified: Subject #100242 in study P05897 was a 16 year old female with the adverse event "breast engorgement."

Seizures

I searched the ae.xpt files of trials P05896 and P05897 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 into the common term "somnolence" 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	9%	(9/102)
Asenapine 2.5mg	24%	(24/98)
Asenapine 5mg	29%	(31/106)

Only 2 patients, one in each asenapine group, dropped out because of one of these events. Clearly, somnolence is related to asenapine treatment but infrequently led to dropout.

Extrapyramidal Symptoms (EPS)

The reporting rates for EPS-related adverse events (based on SMQ broad definitions) in trial P05896 are shown in the table below.

Rates of akathisia were substantially higher in both asenapine dose groups compared to placebo. Parkinsonism and dystonia were drug-related only at the higher dose.

There was no evidence of drug-related dyskinesia in this short-term trial. There was one case of dyskinesia (preferred terms "dyskinesia") in the 26-week open-label trial (P05897).

Changes from baseline to endpoint in the Extrapyramidal Symptom Rating Scale (ESRS) III (dystonia) and IV (dyskinesia) scores in trial P05896 were comparable across treatment groups.

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

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

	Placebo N=102 n (%)	2.5 mg N=98 n (%)	5.0 mg N=106 n (%)
SMQ EPS (broad)	7 (6.9)	7 (7.1)	19 (17.9)
SMQ Akathisia (broad)	2 (2.0)	6 (6.1)	9 (8.5)
Akathisia	1 (1.0)	4 (4.1)	7 (6.6)
Restlessness	1 (1.0)	1 (1.0)	2 (1.9)
Psychomotor hyperactivity	0 (0.0)	1 (1.0)	1 (0.9)
SMQ Parkinson-Like Events (broad)	4 (3.9)	1 (1.0)	10 (9.4)
Tremor	3 (2.9)	0 (0.0)	5 (4.7)
Parkinsonism	0 (0.0)	1 (1.0)	4 (3.8)
Muscle rigidity	2 (2.0)	0 (0.0)	0 (0.0)
Musculoskeletal stiffness	0 (0.0)	0 (0.0)	1 (0.9)
SMQ Dystonia (broad)	2 (2.0)	1 (1.0)	5 (4.7)
Dystonia	0 (0.0)	1 (1.0)	3 (2.8)
Muscle spasms	1 (1.0)	0 (0.0)	1 (0.9)
Musculoskeletal stiffness	0 (0.0)	0 (0.0)	1 (0.9)
Oculogyric crisis	1 (1.0)	0 (0.0)	0 (0.0)
SMQ Dyskinesia (broad)	2 (2.0)	0 (0.0)	0 (0.0)
Dyskinesia	1 (1.0)	0 (0.0)	0 (0.0)
Oculogyric crisis	1 (1.0)	0 (0.0)	0 (0.0)

Every subject is counted a single time for each applicable row and column.
MedDRA coding version 15.1.
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 assessments.
All-Patients-as-Treated = All randomized subjects who received at least one dose of trial medication.
Data Source: [16.4]

Suicidal Ideation and Behavior

Suicidal ideation and behavior was assessed during trial P05896 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. Combining the 2 asenapine dose groups, the rate of suicidal ideation for placebo was 2.0% (2/102) and for asenapine 3.9% (8/204). This difference was not statistically significant (p=0.50, 2-tailed Fishers exact test).

Table 13: Percentage of Patients with Positive Responses on the C-SSRS (Trial P05896)			
	Placebo (N=102)	Asenapine	
		2.5mg (N=98)	5mg (N=106)
Suicidal Ideation	2 (2%)	5 (5%)	3 (3%)
Passive	1 (1%)	5 (5%)	3 (3%)
Active - No method, intent, or plan	2 (2%)	2 (2%)	1 (1%)
Active - Method, no intent or plan	0%	1 (1%)	0%
Active - intent, no plan	0%	1 (1%)	0%
Active - method, intent, and plan	0%	1 (1%)	0%
Suicidal Behavior	0%	0%	0%
Self-Injurious behavior, no suicide intent	1 (1%)	2 (2%)	1 (1%)

There were no completed suicides or suicide attempts in this trial.

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 the trials.

Depression

Treatment-emergent depression was monitored in trial P05896 using the CDRS-R. CDRS-R total scores were roughly comparable across treatment groups at baseline (range of 34.4 to 35.3). Mean changes from baseline to endpoint reflected greater improvement for the two asenapine groups compared to placebo:

Placebo	-3.4	(N=91)
Asenapine 2.5mg	-4.9	(N=86)
Asenapine 5mg	-5.6	(N=90)

Similarly, 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	22%	(20/90)
Asenapine 2.5mg	29%	(25/86)
Asenapine 5mg	37%	(33/90)

These data suggest that the use of asenapine in treating pediatric patients with schizophrenia is not associated with an increase in depression.

Oral Hypoesthesia

Oral hypoesthesia (or mouth numbness) is an adverse event unique to asenapine attributable to its anesthetic properties when taken sublingually. In trial P05896, oral hypoesthesia was reported much more frequently in the asenapine treatment arms compared to placebo:

Placebo	1%	(1/102)
Asenapine 2.5mg	5%	(5/98)
Asenapine 5mg	5%	(5/106)

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

A related event, oral paraesthesia (e.g., tingling sensation in the mouth), was reported by a smaller number of patients. The proportions of patients who reported oral hypoesthesia or paraesthesia followed a similar pattern:

Placebo	1%	(1/102)
Asenapine 2.5mg	8%	(8/98)
Asenapine 5mg	6%	(6/106)

Dysphagia

There was one report of dysphagia in trial P05896 that occurred in the asenapine 5mg group (0.9% or 1/106). An additional case was reported in the 26-week open-label study (P05897). The adverse event datasets (ae.xpt) for both trials were surveyed 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

To assess the potential effects of asenapine treatment on learning and memory in pediatric patients, cognitive testing in trial P05896 consisted of the following:

• 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).

The sample size for cognitive data is considerably smaller than the total number of patients randomized in trial P05896. Prior to a protocol amendment, this testing was to be performed once at some point up to week 3 (preferably before randomization) and again at day 56. After the amendment, cognitive testing was to be done prior to randomization and at day 56. In the testing results, baseline was defined as the last non-missing value before first drug intake and only those patients with a baseline value are presented.

Results on the key metrics for each of these tests are summarized in the following table. The magnitudes of the mean changes relative to baseline scores were generally small across the treatment groups.

Table 14: Summary of Results of Cognitive Testing (Trial P05896)
Mean Change from Baseline to Endpoint in Key Metrics

Test/Units	Placebo		Asenapine 2.5mg		Asenapine 5mg	
	N	Mean Δ	N	Mean Δ	N	Mean Δ
CWIT (msec)	18	59.3	15	79.8	21	45.7
LFT (# correct)	32	-1.7	35	0.9	33	1.1
SFT (# correct)	34	0.5	37	1.9	34	-0.4
ANS (# correct)	25	1.2	30	0.8	26	0.6
STDT (total correct)	32	-4.7	26	1.7	30	0.5

Among patients in the long-term trial P05897 who had been treated with only asenapine during both the short-term and extension studies, the mean changes from the acute trial baseline to the extension study endpoint were as follows:

CWIT (msec)	+40.7 (N=46)
LFT (number correct)	+2.6 (N=76)
SFT (number correct)	+0.2 (N=78)
ANS (number correct)	+1.0 (N=61)
STDT (total correct)	+2.5 (N=64)

On average, patients improved performance during long-term asenapine on all cognitive scales except for the CWIT (baseline mean = -8.9msec (N=46)). This may reflect prolongation of response latency secondary to asenapine but cannot be definitively interpreted without a concurrent control arm.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The incidence of treatment-emergent adverse events that were reported in at least 2% of patients in at least one of the two asenapine arms and at a rate in at least one of the asenapine arms that was higher than the placebo rate in trial P05896 are displayed in the table below.

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: somnolence, akathisia, dizziness, and oral hypoesthesia/paresthesia.

Table 15: Reporting Rates (%) of Adverse Reactions (Trial P05896)

System Organ Class/ AE Preferred Term	Placebo N=102	Asenapine 2.5mg N=98	Asenapine 5mg N=106
Nervous System			
Somnolence*	9%	24%	29%
Headache	6%	7%	8%
Akathisia	1%	4%	7%
Dizziness	1%	7%	2%
Tremor	3%	0%	5%
Dysgeusia	2%	1%	3%
Parkinsonism	0%	1%	4%
Dystonia	0%	1%	3%
Psychiatric			
Insomnia	6%	5%	9%
Anxiety	3%	2%	4%
Sleep Disorder	0%	3%	1%
Suicidal Ideation	0%	2%	2%

Table 15: Reporting Rates (%) of Adverse Reactions (Trial P05896)			
System Organ Class/ AE Preferred Term	**Placebo N=102**	**Asenapine 2.5mg N=98**	**Asenapine 5mg N=106**
Gastrointestinal			
Oral Hypoesthesia/Paresthesia	1%	8%	6%
Oral Paresthesia	0%	3%	3%
Upper abdominal pain	2%	0%	3%
Constipation	0%	2%	2%
Infections			
Nasopharyngitis	2%	4%	3%
Influenza	0%	0%	3%
General Disorders			
Pyrexia	2%	3%	2%
Asthenia**	2%	4%	1%
Fatigue	1%	2%	0%
Metabolism and Nutrition			
Increased appetite	2%	3%	4%
Investigations			
Weight increased	1%	4%	3%
Respiratory			
Epistaxis	0%	2%	0%
Skin			
Acne	0%	2%	0%

* The term “somnolence” in this table includes the preferred terms somnolence, sedation, and hypersomnia.
** The term “asthenia” in this table includes the preferred terms asthenia, fatigue, and sluggishness.

7.4.2 Laboratory Findings

Hematology
In trial P05896, mean changes from baseline to endpoint in hematology parameters were similar across treatment groups except for platelet counts:

Placebo	-1.5 x10^9/L (N=92)
Asenapine 2.5mg	-2.6 x10^9/L (N=92)
Asenapine 5mg	+15.6 x10^9/L (N=97)

There was a large increase in platelet count in the 5mg group compared to small decreases in placebo and the 2.5mg group. The median increase in the 5mg group was also large (+16.0 x10^9/L).

The proportions of patients who met Predefined Limits of Change (PDLC) for hematology measures in trial P05896 are presented in the table below. The proportion of asenapine PLDC outliers was notably higher for asenapine than placebo for a number of variables:

- low hemoglobin (2.5 and 5mg).
- high RBC count (5mg).
- increased eosinophils (2.5 and 5mg).
- increased basophils (5mg).

One asenapine 5mg patient had a PDLC high platelet count (≥600,000/μL).

The adverse event dataset for this trial (ae.xpt) was searched for the preferred terms leukopenia, neutropenia, or "white blood cell count decreased." One patient in each treatment group, including placebo, experienced one of these events:

Placebo	1%	(1/102)
Asenapine 2.5mg	1%	(1/98)
Asenapine 5mg	1%	(1/106)

No patient dropped out because of any of these three events.

I searched the lab results dataset (labrslt.xpt) for the two Phase 3 pediatric schizophrenia trials for 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 26-week, open label schizophrenia study P05897, one patient (#100097) met the PDLC criterion for severe neutropenia during treatment (<500/μL), which resolved while remaining on asenapine treatment:

Baseline	4,410/μL
Day 71	90/μL
Day 127	6,020/μL
Day 186	4,760/μL

No adverse events were reported in association with this finding and study medication was not interrupted. This patient had no history of cyclical neutropenia and took no concomitant medication that might have reduced his neutrophil count.

There was one dropout secondary to polycythemia at baseline (#100478). This patient is discussed in section 7.3.3 of this review.

Table 16: Percentage of Patients With Hematology Values That Met PDLC During Treatment (Trial P05896)

Parameter	PDLC	Placebo N=102		2.5 mg N=98		5.0 mg N=106	
		n	%	n	%	n	%
Hemoglobin (g/L)	Number of subjects	95		94		97	
	<= 0.9 LLN	1	(1.1)	5	(5.3)	6	(6.2)
	>= 1.1 ULN	11	(11.6)	9	(9.6)	13	(13.4)
Hematocrit (V/V)	Number of subjects	95		94		97	
	<= 0.9 LLN	0		0		1	(1.0)
	>= 1.1 ULN	65	(68.4)	51	(54.3)	68	(70.1)
Erythrocyte count (10^{12}/L)	Number of subjects	95		94		97	
	<= 0.8 LLN	0		0		0	
	>= 1.2 ULN	3	(3.2)	3	(3.2)	6	(6.2)
Leukocyte count (10^{9}/L)	Number of subjects	95		94		97	
	<= 0.8 LLN	13	(13.7)	17	(18.1)	15	(15.5)
	>= 1.2 ULN	9	(9.5)	5	(5.3)	7	(7.2)
Platelet count (10^{9}/L)	Number of subjects	92		93		97	
	<= 100	0		2	(2.2)	0	
	>= 600	0		0		1	(1.0)
Neutrophils (10^{9}/L)	Number of subjects	95		94		97	
	<= 1.5 (Mild)	4	(4.2)	6	(6.4)	5	(5.2)
	<= 1.0 (Moderate)	2	(2.1)	2	(2.1)	1	(1.0)
	<= 0.5 (Severe)	1	(1.1)	0		0	
	>= 10.0	3	(3.2)	0		2	(2.1)
Lymphocytes (10^{9}/L)	Number of subjects	95		94		97	
	<= 0.8 LLN	2	(2.1)	1	(1.1)	3	(3.1)
	>= 1.2 ULN	33	(34.7)	31	(33.0)	26	(26.8)
Monocytes (10^{9}/L)	Number of subjects	95		94		97	
	>= 1.2 ULN	3	(3.2)	0		4	(4.1)
Eosinophils (10^{9}/L)	Number of subjects	95		94		97	
	>= 1.0	1	(1.1)	4	(4.3)	3	(3.1)
Basophils (10^{9}/L)	Number of subjects	95		94		97	
	>= 1.2 ULN	0		0		2	(2.1)

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]

Chemistry

Mean changes from baseline to endpoint in chemistry variables were comparable to placebo with the exception of creatine kinase, for which there were increases in both asenapine groups versus a decrease in placebo patients:

Placebo	-7.5 U/L (N=95)
Asenapine 2.5mg	+11.0 U/L (N=94)
Asenapine 5mg	+3.0 U/L (N=98)

The proportions of patients who met Predefined Limits of Change (PDLC) for chemistry measures in trial P05896 are presented in the table below. There were appreciable differences between asenapine and placebo for the following variables:

- BUN increased (2.5mg).
- phosphorus decreased (5mg) and increased (2.5mg).
- magnesium increased (5mg).
- ALT elevated (2.5 and 5mg).
- CK increased (2.5mg).

The clinical relevance of the findings with respect to BUN, phosphorus, magnesium, and CK is not clear.

To further evaluate the finding regarding increased ALT concentrations, I searched the laboratory results datasets (labrslt.xpt) to identify patients in trials P05896 or P05897 who met Hy's Law criteria (ALT or AST ≥3 xULN, total bilirubin ≥2 xULN, and alkaline phosphatase <2 xULN). I found none.

There was one dropout because of an ALT elevation (#100185). This patient is discussed in section 7.3.3 above.

Metabolic changes and hyperprolactinemia are discussed under section 7.3.4 of this review.

Table 17: Percentage of Patients With Chemistry Values That Met PDLC During Treatment (Trial P05896)

Treatment Phase (All Patients as Treated)

Parameter	PDLC	Placebo N=102		2.5 mg N=98		5.0 mg N=106	
		n	%	n	%	n	%
Sodium (mmol/L)	Number of subjects	95		94		98	
	<= 0.8 LLN	0		0		0	
	>= 1.2 ULN	0		0		0	
Potassium (mmol/L)	Number of subjects	95		94		98	
	<= 0.9 LLN	0		1	(1.1)	0	
	>= 1.1 ULN	1	(1.1)	0		0	
Chloride (mmol/L)	Number of subjects	95		94		98	
	<= 0.8 LLN	0		0		0	
	>= 1.2 ULN	0		0		0	
Bicarbonate (mmol/L)	Number of subjects	95		94		98	
	<= 0.8 LLN	3	(3.2)	1	(1.1)	2	(2.0)
	>= 1.5 ULN	0		0		0	
Blood urea nitrogen (mmol/L)	Number of subjects	95		94		98	
	>= 1.1 ULN	2	(2.1)	4	(4.3)	2	(2.0)
Creatinine (umol/L)	Number of subjects	95		94		98	
	>= 1.1 ULN	0		0		0	
Calcium (mmol/L)	Number of subjects	95		94		98	
	<= 0.9 LLN	0		0		0	
	>= 1.1 ULN	0		0		0	
Phosphorus (mmol/L)	Number of subjects	95		94		98	
	<= 0.9 LLN	0		0		2	(2.0)
	>= 1.1 ULN	5	(5.3)	8	(8.5)	3	(3.1)
Magnesium (mmol/L)	Number of subjects	95		94		98	
	<= 0.9 LLN	0		0		0	
	>= 1.1 ULN	2	(2.1)	0		4	(4.1)
Aspartate aminotransferase(AST) (U/L)	Number of subjects	95		94		98	
	>= 3 ULN	0		1	(1.1)	1	(1.0)
Alanine aminotransferase(ALT) (U/L)	Number of subjects	95		94		98	
	>= 3 ULN	1	(1.1)	2	(2.1)	6	(6.1)
Alkaline phosphatase (U/L)	Number of subjects	95		94		98	
	>= 3 ULN	0		0		0	

Table 17: Percentage of Patients With Chemistry Values That Met PDLC During Treatment (continued)

Treatment Phase (All Patients as Treated)

Parameter	PDLC	Placebo N=102		2.5 mg N=98		5.0 mg N=106	
		n	%	n	%	n	%
Total bilirubin (umol/L)	Number of subjects	95		94		98	
	>= 1.5 ULN	3	(3.2)	2	(2.1)	2	(2.0)
Protein, total (g/L)	Number of subjects	95		94		98	
	<= 0.8 LLN	0		0		0	
	>= 1.2 ULN	0		0		0	
Albumin (g/L)	Number of subjects	95		94		98	
	<= 0.8 LLN	0		0		0	
	>= 1.2 ULN	7	(7.4)	4	(4.3)	5	(5.1)
Gamma glutamyl transferase (U/L)	Number of subjects	95		94		98	
	>= 3 ULN	0		0		0	
Lactate dehydrogenase (U/L)	Number of subjects	95		94		98	
	>= 3 ULN	0		0		0	
Creatine kinase (U/L)	Number of subjects	95		94		98	
	>= 3 ULN	6	(6.3)	8	(8.5)	5	(5.1)

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 P05896.

The proportion of asenapine patients meeting PDLC criteria for any urinalysis parameter was substantially higher than that in the placebo group for only proteinuria (criterion = a non-negative result):

Placebo	13%	(12/95)
Asenapine 2.5mg	14%	(13/93)
Asenapine 5mg	18%	(17/96)

The difference between placebo and the 5mg group was not statistically significant (p =0.42, 2-tailed Fishers exact test).

7.4.3 Vital Signs

Mean changes from baseline to endpoint in supine and standing systolic and diastolic blood pressure and pulse in trial P05896 are shown in the table below.

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

- increased supine SBP (5mg).
- increased supine DBP (5mg).
- increased standing DBP (5mg).
- increased supine pulse (2.5 and 5mg).
- increased standing pulse (2.5 and 5mg).

The mean increase in supine pulse relative to placebo was especially noticeable at the 5mg dose (+4.5 bpm in supine pulse at endpoint).

Table 18: Mean Changes From Baseline To Endpoint in Blood Pressure and Pulse (Trial P05896)

		Placebo N=102			2.5 mg N=98			5.0 mg N=106		
Parameter		n	Mean (SD)	Median	n	Mean (SD)	Median	n	Mean (SD)	Median
Supine SBP (mmHg)	Baseline	101	114.2 (10.6)	112.0	97	113.9 (7.7)	114.0	106	113.0 (9.2)	112.0
	Endpoint	101	114.5 (10.5)	115.0	97	113.9 (9.7)	114.0	106	114.9 (9.8)	115.0
	Change	101	0.3 (8.3)	0.0	97	0.0 (7.7)	0.0	106	1.9 (9.4)	0.0
Standing SBP (mmHg)	Baseline	100	114.5 (9.5)	115.0	97	113.2 (7.7)	113.0	104	114.8 (8.2)	115.0
	Endpoint	100	115.3 (9.8)	116.0	97	114.7 (9.8)	115.0	104	115.6 (9.0)	116.0
	Change	100	0.9 (7.8)	0.0	97	1.5 (9.0)	0.0	104	0.8 (9.0)	0.0
Supine DBP (mmHg)	Baseline	101	72.9 (8.5)	72.0	97	72.1 (7.5)	72.0	106	70.9 (8.5)	70.0
	Endpoint	101	72.1 (8.2)	72.0	97	71.6 (8.3)	72.0	106	72.0 (8.9)	71.0
	Change	101	-0.8 (7.9)	0.0	97	-0.5 (7.5)	0.0	106	1.1 (7.8)	0.0
Standing DBP (mmHg)	Baseline	100	74.4 (7.0)	75.0	97	74.3 (6.9)	74.0	104	74.1 (7.4)	74.0
	Endpoint	100	74.2 (7.7)	75.0	97	74.3 (6.7)	74.0	104	75.4 (7.2)	75.0
	Change	100	-0.2 (7.0)	0.0	97	0.1 (7.8)	0.0	104	1.3 (6.3)	0.0
Supine pulse (bpm)	Baseline	101	78.8 (11.8)	76.0	97	77.1 (10.5)	76.0	104	76.1 (10.2)	76.0
	Endpoint	101	76.5 (10.7)	76.0	97	76.7 (9.6)	76.0	104	78.3 (11.3)	78.0
	Change	101	-2.3 (10.7)	-2.0	97	-0.4 (9.6)	-1.0	104	2.2 (10.2)	0.5
Standing pulse (bpm)	Baseline	100	84.7 (11.6)	83.0	97	81.7 (9.4)	80.0	103	82.2 (11.7)	80.0
	Endpoint	100	82.3 (12.1)	80.0	97	82.4 (11.2)	81.0	103	83.2 (11.0)	82.0
	Change	100	-2.4 (11.4)	-2.0	97	0.7 (10.5)	0.0	103	1.0 (11.0)	0.0

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]

Examination of the mean changes in supine pulse relative to placebo by visit revealed that, in both dose groups, the increases relative to placebo began during the first week and persisted over time; increases were greater in the 5mg dose group:

Table 19: Placebo-Adjusted Changes From Baseline in Supine Pulse (bpm) By Visit (Trial P05896)

Visit	2.5mg	5mg
Day 7	+1.8	+6.4
Day 14	+2.7	+5.5
Day 21	+3.2	+4.9
Day 28	+1.2	+4.0
Day 42	+2.3	+4.6
Day 56	+1.7	+4.3

Mean changes in supine systolic and diastolic blood pressure over time, adjusted for placebo, were generally small and variable in the 2.5mg dose group, with larger increases consistently observed in the 5mg group, as shown in the following table.

Table 20: Placebo-Adjusted Changes From Baseline in Supine Blood Pressure By Visit (Trial P05896)

Visit	Systolic BP Δ (mmHg)		Diastolic BP Δ (mmHg)	
	2.5mg	5mg	2.5mg	5mg
Day 7	-0.9	+2.0	+0.6	+2.4
Day 14	+0.4	+2.3	+1.2	+3.0
Day 21	-0.4	+2.0	-0.3	+1.5
Day 28	-0.4	+1.9	+0.9	+1.4
Day 42	-2.3	+2.2	-1.1	+0.7
Day 56	-0.5	+1.5	-0.4	+1.3

In sum, vital sign changes associated with asenapine treatment were increased pulse (1-3 bpm in the 2.5mg group and 4-6 bpm in the 5mg group after adjustment for the placebo change) and increases in blood pressure of 1-3 mmHg in the 5mg dose group compared to placebo.

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

Table 21: 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 trail P05896 are presented in the following table.

Table 22: Percentage of Patients With Vital Sign Measurements That Met PDLC During Treatment (Trial P05896)

Parameter	PDLC	Placebo N=102 n (%)	2.5 mg N=98 n (%)	5.0 mg N=106 n (%)
Supine SBP (mmHg)	Number of Subjects	101	97	106
	Upper limit	1 (1.0)	1 (1.0)	5 (4.7)
	Lower limit	3 (3.0)	2 (2.1)	1 (0.9)
Standing SBP (mmHg)	Number of Subjects	100	97	104
	Upper limit	1 (1.0)	1 (1.0)	4 (3.8)
	Lower limit	2 (2.0)	0 (0.0)	5 (4.8)
Supine DBP (mmHg)	Number of Subjects	101	97	106
	Upper limit	10 (9.9)	9 (9.3)	13 (12.3)
	Lower limit	5 (5.0)	5 (5.2)	4 (3.8)
Standing DBP (mmHg)	Number of Subjects	100	97	104
	Upper limit	7 (7.0)	9 (9.3)	16 (15.4)
	Lower limit	2 (2.0)	2 (2.1)	2 (1.9)
Supine pulse (bpm)	Number of Subjects	101	97	104
	Upper limit	0 (0.0)	0 (0.0)	2 (1.9)
	Lower limit	1 (1.0)	0 (0.0)	0 (0.0)
Standing pulse (bpm)	Number of Subjects	100	97	103
	Upper limit	2 (2.0)	2 (2.1)	5 (4.9)
	Lower limit	0 (0.0)	0 (0.0)	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:

- high supine and standing SBP (at 5mg).
- low standing SBP (5mg).
- high supine and standing DBP (5mg).
- high supine and standing pulse (5mg).

These data further indicate the tendency for asenapine at the 5mg BID dose level to increase blood pressure and pulse.

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 P05896 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) and reveal no increased risk for asenapine versus placebo:

Placebo	8.6% (6/70)
Asenapine 2.5mg	4.3% (3/69)
Asenapine 5mg	8.2% (6/73)

There were no cases of syncope in trial P05896.

There were no dropouts in either trial P05896 or P05897 because of a vital sign abnormality.

7.4.4 Electrocardiograms (ECGs)

Mean changes from baseline to endpoint in ECG measures for patients in trial P05896 are displayed in the table that follows. The only remarkable difference was an increase in heart rate relative to placebo of +3.9 bpm in the asenapine 5mg group, consistent with the vital sign data presented above.

Table 23: Changes From Baseline To Endpoint in ECG Parameters (Trial P05896)

		Placebo N=102			2.5 mg N=98			5.0 mg N=106		
Parameter		n	Mean (SD)	Median	n	Mean (SD)	Median	n	Mean (SD)	Median
Heart rate (bpm)	Baseline	90	79.0 (14.1)	78.0	92	78.7 (13.7)	78.5	94	79.4 (15.7)	77.0
	Endpoint	90	75.3 (14.0)	75.0	92	76.0 (12.7)	76.0	94	79.6 (13.9)	78.0
	Change	90	-3.7 (15.5)	-4.0	92	-2.7 (14.0)	-5.0	94	0.2 (15.1)	0.5
RR interval (msec)	Baseline	90	785.7 (153.8)	770.5	92	785.3 (135.3)	764.0	94	784.5 (150.0)	779.0
	Endpoint	90	823.4 (148.1)	804.5	92	811.2 (135.5)	789.0	94	777.0 (136.1)	765.5
	Change	90	37.7 (154.5)	39.5	92	25.9 (143.4)	56.5	94	-7.6 (138.8)	-2.5
PR interval (msec)	Baseline	90	137.0 (19.0)	137.5	92	138.8 (18.7)	138.0	94	141.3 (19.0)	139.5
	Endpoint	90	136.4 (17.9)	137.0	92	139.4 (17.7)	138.0	94	143.1 (18.3)	142.0
	Change	90	-0.6 (13.5)	0.0	92	0.6 (10.5)	1.0	94	1.7 (11.7)	1.5
QRS complex (msec)	Baseline	90	90.0 (9.0)	89.0	92	90.3 (8.2)	90.0	94	90.4 (9.8)	90.5
	Endpoint	90	91.3 (9.5)	90.0	92	91.2 (8.6)	90.0	94	90.2 (10.3)	90.0
	Change	90	1.2 (5.1)	1.0	92	0.9 (6.7)	1.0	94	-0.2 (5.9)	0.0
QT interval (msec)	Baseline	90	366.1 (30.6)	364.5	92	368.3 (25.5)	367.0	94	364.8 (31.3)	368.5
	Endpoint	90	375.2 (29.6)	377.5	92	372.3 (25.2)	372.0	94	364.1 (27.2)	363.0
	Change	90	9.0 (30.0)	13.0	92	4.0 (23.9)	3.0	94	-0.7 (25.2)	0.5
QTc Bazett (msec)	Baseline	90	415.8 (20.9)	417.5	92	418.2 (23.1)	416.0	94	414.6 (21.9)	415.5
	Endpoint	90	416.2 (22.9)	413.5	92	415.9 (23.5)	419.5	94	415.6 (21.7)	416.0
	Change	90	0.4 (21.1)	-1.5	92	-2.3 (19.8)	-5.0	94	0.9 (20.1)	2.0
QTc Fridericia (msec)	Baseline	90	398.1 (18.1)	398.0	92	400.6 (18.0)	398.5	94	397.0 (19.2)	398.0
	Endpoint	90	401.7 (19.3)	401.0	92	400.5 (18.5)	399.5	94	397.4 (17.8)	397.0
	Change	90	3.5 (17.0)	2.0	92	-0.1 (13.3)	-1.5	94	0.4 (14.5)	0.5

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 are provided in the table below.

Table 24: 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***
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

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

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

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

[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 P05896 are shown in the following table. There were no remarkable differences between the asenapine treatment arms and placebo for any parameter.

Table 25: Proportion of Patients With PDLC Changes in ECG Parameters

Parameter	PDLC	Placebo N=102 n (%)	2.5 mg N=98 n (%)	5.0 mg N=106 n (%)
Heart rate (bpm)	Number of Subjects	90	92	94
	Upper limit	1 (1.1)	0 (0.0)	0 (0.0)
	Lower limit	0 (0.0)	0 (0.0)	0 (0.0)
RR interval (msec)	Number of Subjects	90	92	94
	Upper limit	0 (0.0)	0 (0.0)	0 (0.0)
	Lower limit	0 (0.0)	0 (0.0)	0 (0.0)
RR interval (msec)	Number of Subjects	91	92	94
	Value <500 msec	1 (1.1)	0 (0.0)	0 (0.0)
	Value >1200 msec	1 (1.1)	0 (0.0)	1 (1.1)
PR interval (msec)	Number of Subjects	90	92	94
	Upper limit	0 (0.0)	0 (0.0)	0 (0.0)
QRS complex (msec)	Number of Subjects	90	92	94
	Upper limit	0 (0.0)	0 (0.0)	0 (0.0)
QTc Bazett (msec)	Number of Subjects	91	92	94
	Value >=450 msec	8 (8.8)	5 (5.4)	8 (8.5)
	Value >=480 msec	0 (0.0)	1 (1.1)	0 (0.0)
	Value >=500 msec	0 (0.0)	1 (1.1)	0 (0.0)
QTc Bazett (msec)	Number of Subjects	90	92	94
	Increase >=30 msec	10 (11.1)	6 (6.5)	10 (10.6)
	Increase >=60 msec	2 (2.2)	0 (0.0)	0 (0.0)
QTc Fridericia (msec)	Number of Subjects	91	92	94
	Value >=450 msec	0 (0.0)	2 (2.2)	0 (0.0)
	Value >=480 msec	0 (0.0)	1 (1.1)	0 (0.0)
	Value >=500 msec	0 (0.0)	0 (0.0)	0 (0.0)
QTc Fridericia (msec)	Number of Subjects	90	92	94
	Increase >=30 msec	5 (5.6)	2 (2.2)	2 (2.1)
	Increase >=60 msec	0 (0.0)	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]

One subject (#100535) in the 2.5mg group had a QTcB ≥500 msec (505 msec) (QT=421 and QTcF=476 msec on that date). On the same day as the high QTcB reading, this patient reported somnolence, vomiting, and dizziness. A relationship between these adverse events and the prolonged QTcB is considered speculative. No subsequent ECG readings were available for this patient.

There were no dropouts in either trial P05896 or P05897 because of an ECG abnormality.

There were no reports of events within the torsades de pointe/QT prolongation broad SMQ in this trial.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Among the common and probably drug-related adverse reactions (somnolence, akathisia, dizziness, and oral hypoesthesia), only somnolence and akathisia showed some evidence of being dose-related:

	Placebo	2.5mg	5mg
Somnolence	9%	25%	30%
Akathisia	1%	4%	7%

7.5.3 Drug-Demographic Interactions

The sponsor conducted analyses of the effect of gender and race for treatment-emergent adverse events in trial P05896 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 revealed no significant differences at a nominal alpha level of 0.10.

7.6 Additional Safety Evaluations

7.6.2 Human Reproduction and Pregnancy Data

No pregnancies were reported in either trial P05896 or P05897.

7.6.3 Pediatrics and Assessment of Effects on Growth

Age- and sex-adjusted growth percentile rankings were determined for patients in trial P05896. At baseline, mean percentiles indicated that the patient sample was shorter than average (percentiles about 40-42%). There was a greater decrease from baseline to endpoint in height percentile ranking among asenapine-treated patients than among placebo patients, although all were well under 1%:

Placebo	-0.06% (N=98)
Asenapine 2.5mg	-0.54% (N=95)
Asenapine 5mg	-0.38% (N=99)

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

Placebo	-0.01 SD (N=98)
Asenapine 2.5mg	-0.02 SD (N=95)
Asenapine 5mg	-0.01 SD (N=99)

The changes in percentile rankings and z-scores for height from the 26-week open-label study P05897 (based on all placebo/asenapine patients) were +0.22% (N=62) and 0.00 SD (N=62).

To evaluate the potential effects of asenapine on sexual maturation, Tanner staging in patients of both sexes and assessment of menstrual cycles in females was performed.

Tanner staging consisted of breast staging for females, genital growth staging for males, and pubic hair staging for females and males. Over 90% of patients in all treatment groups in trial P05896 had no shift in either Tanner stage parameter except for breast staging in the placebo group (85% had no shift, 9% had a increase of 1 stage).

Among placebo/asenapine patients in the long-term study P05897, shifts in Tanner stage from baseline to endpoint are displayed in the following table.

Table 26: Enumeration of Patients (N(%)) with Tanner Stage Shifts Study P05897 (Placebo/Asenapine-Treated Patients)

Sex	Stage Shift	Genital Growth/Breast	Pubic Hair
Males (N=36)	0	32 (89%)	32 (89%)
	+1	4 (11%)	4 (11%)
Females (N=24)	0	21 (88%)	22 (92%)
	+1	3 (12%)	2 (8%)

Most females in all treatment groups of trial P05896 reported the onset of menses at baseline (85%-92%). Among these, the proportions of patients who did not report any menses during treatment were comparable across treatment groups:

Placebo	21% (7/34)
Asenapine 2.5mg	19% (6/32)
Asenapine 5mg	22% (8/36)

Among females with no menses reported at baseline, those reporting onset during treatment were:

Placebo	83% (5/6)
Asenapine 2.5mg	25% (1/4)
Asenapine 5mg	100% (3/3)

Among placebo/asenapine female patients in the 26-week open-label study P05897, most (96% or 24/25) reported the onset at menses at baseline; 2 of these 24 did not report menses during extension study treatment. For the one female who did not report the onset of menstrual cycles at baseline, onset of menses was not reported during treatment. In view of the small numbers of patients and lack of a concurrent control group in this study, there is no clear signal of an adverse effect of asenapine on sexual maturation.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Five patients had accidental overdoses of asenapine in the schizophrenia trials (one in P05896 and four in P05897). Some involved ingestion of a single extra dose and others involved multiple extra doses detected over periods of several days. None were classified as serious or resulted in dropout.

There were no intentional overdoses in these studies.

There were no studies to assess drug abuse potential, withdrawal, or rebound in pediatric patients with schizophrenia.

Patients with a history of substance abuse or dependence (except nicotine) within the previous 6 months were excluded from the schizophrenia 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) (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

Safety information from the pediatric schizophrenia trials must be summarized in section 8.4 (Pediatric Use) of Saphris labeling.

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
02/19/2015

JING ZHANG
02/20/2015

Study P05896 is adequately design and conducted. [redacted] (b) (4) The safety data from this study can be included in the product labeling. No additional PMR or PMC are required. We consider Study P05896 fulfilled PMR and WR. [redacted] (b) (4).