FDA Psychopharmacologic Drugs Advisory Committee Meeting

SAPHRIS® (asenapine) Sublingual Tablets (NDA 22-117)

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Briefing Document (Background Package)

ADVISORY COMMITTEE BRIEFING MATERIALS:

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Schering-Plough Research Institute,

A Division of Schering Corporation

Kenilworth, New Jersey

USA

SCHERING-PLOUGH RESEARCH INSTITUTE

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List of Abbreviations

Abbreviation	Term
5-HT2A	5-Hydroxytryptamine receptor subtype 2A
AC	Active controlled
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT/ALAT (SGPT)	Alanine aminotransferase (serum glutamic-pyruvic transaminase)
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST/ASAT (SGOT)	Aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)
AUC	Area under the curve
BARS	Barnes Akathisia Rating Scale
BID	Twice daily (bis in die)
BL	Baseline
BMI	Body mass index
CGI-BP	Clinical Global Impressions Scale for Use in Bipolar Disorder
CGI-I	Clinical Global Impressions of Improvement
CGI-S	Clinical Global Impressions of Severity of Illness
CI	Confidence interval
C_{max}	Maximum concentration
CNS	Central nervous system
CRF	Case report form
CYP	Cytochrome P450
D_2	Dopamine receptor subtype 2
DB	Double blind
DF	Dose finding
dQTcF	change in QTcF
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders (version IV, text version)
ECG	Electrocardiogram
EP	Endpoint
EPS	Extrapyramidal symptom(s)
FD	Fixed dose
FDA	Food and Drug Administration
GGT	gamma-glutamyl transferase
HbA1c	glycated hemoglobin
HDL	High density lipoprotein
HLGT	High level group term
ISST	InterSePT Scale for Suicidal Thinking
ITT	Intent-to-treat
IU	International unit

Abbreviation	Term
LDL	Low density lipoprotein
LOCF	Last observation carried forward
LSMEANs	Least Square Means
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed model for repeated measures
NDA	New Drug Application
NMS	Neuroleptic malignant syndrome
OC	Observed case
OL	Open label
PANSS	Positive and Negative Syndrome Scale
PC	Placebo controlled
PD	Pharmacodynamic
PET	Positron emission topography
PK	Pharmacokinetic
PO	per os (orally)
QD	Once daily dosing
QT	Time from the beginning of the QRS complex to the end of the T wave; represents both ventricular depolarization and repolarization
QTc	QT interval corrected for heart rate
QTcF	Fridericia-corrected QTc interval: $QTcF=QT*(HR/60)^{1/3}$ (where HR=heart rate in beats per minute)
SAE	Serious adverse event
SARS	Simpson-Angus Rating Scale
SE	Standard error
SL	Sublingual
SOC	System organ class
t_{max}	Time of maximal concentration
UGT	UDP-glucuronosyltransferase
ULN	Upper limit of normal
US, USA	United States of America
YMRS	Young Mania Rating Scale

1. EXECUTIVE SUMMARY

Organon USA Inc., now a part of Schering-Plough Corporation, has submitted a New Drug Application (NDA 22-117) for SAPHRIS® (asenapine) Sublingual Tablets for the following indications:

- treatment of acute schizophrenia in adults, and
- acute treatment of manic or mixed episodes associated with bipolar I disorder in adults.

The question before this Advisory Committee is whether asenapine has been shown to be safe and effective for these indications.

This briefing document outlines the benefit-risk profile of asenapine in these indications. The document is based on the extensive clinical development program for asenapine in schizophrenia and bipolar I disorder, which included 2251 subjects who were exposed to asenapine in phase 2/3 studies that were completed at the time of the NDA submission. Of these subjects, 252 were exposed for at least 26 weeks, and 225 for at least 52 weeks.

Schizophrenia is a severe and disabling disorder, affecting approximately 1% of the adult population, with approximately two million people affected in the United States.

Bipolar I disorder is a chronic, severe, and recurrent psychiatric disorder with a lifetime prevalence of up to 1-2%. The annual costs exceed those of diabetes or unipolar depression.

For both disorders, currently available treatment options have clinically important limitations. They appear effective only in a subset of patients and individual treatment response can not be reliably predicted prior to the initiation of drug therapy. In addition, many of the available treatments are associated with safety and tolerability issues (such as extrapyramidal symptoms [EPS], prolactin increases, metabolic changes, and weight gain). In clinical practice, as a result of limited efficacy and/or tolerability, the frequency at which patients with schizophrenia or bipolar disorder are switched from an initial treatment to a second or third treatment option is extremely high. Thus, additional treatment options which combine clinical efficacy with a favorable safety and tolerability profile are needed for the treatment of acute schizophrenia and manic or mixed episodes associated with bipolar 1 disorder.

Schering-Plough concludes that:

- ***Asenapine offers a new treatment option in the atypical antipsychotic armamentarium***

Asenapine, which is formulated as a fast dissolving tablet for sublingual administration, is a novel psychopharmacologic agent with demonstrated efficacy and a safety profile that has been well characterized from an extensive clinical development program. The receptor binding profile of asenapine demonstrates the highest affinity for blocking serotonin receptors, followed by dopamine, alpha-adrenergic, and histamine receptors, with minimal affinity for muscarinic receptors. The exact mechanism of action of asenapine, as with other drugs having efficacy in schizophrenia and bipolar disorder, is unknown. The efficacy of asenapine is hypothesized to be mediated in part through a combination of antagonist activity at dopamine subtype 2 (D_2) and 5-hydroxytryptamine subtype 2A (5-HT_{2A}) receptors.

- ***Asenapine is an efficacious treatment for acute schizophrenia.***

Evidence of efficacy in schizophrenia comes from two well controlled double-blind trials in which asenapine, at a dose of 5 mg twice daily, was demonstrated to be significantly superior to placebo on the primary efficacy endpoint (change in Positive and Negative Syndrome Scale [PANSS] total score from baseline to endpoint) according to the primary analysis (analysis of variance/analysis of covariance [ANOVA/ANCOVA] with last observation carried forward [LOCF]) with supportive evidence from various secondary endpoints and analyses. The 10 mg twice daily dose was statistically significantly superior to placebo in one of two trials based on a mixed model for repeated measures (MMRM), a prespecified secondary statistical analysis.

- ***Asenapine is an efficacious treatment for acute manic or mixed episodes associated with bipolar I disorder.***

Evidence of efficacy in bipolar I disorder comes from two well controlled double-blind studies in which asenapine, at flexible doses of 10 mg twice daily with the option to down titrate to 5 mg twice daily, was significantly superior to placebo on the primary efficacy endpoint (change in Young Mania Rating Scale [YMRS] total score from baseline to endpoint) according to the primary analysis (ANCOVA with LOCF) with supportive evidence from various secondary endpoints and analyses.

- ***Asenapine is well tolerated and has a favorable safety profile.***

Commonly observed adverse reactions (related adverse events as judged by the investigator) with an incidence ≥5% and at least twice that for placebo for subjects with schizophrenia were akathisia (6%) and oral hypoesthesia (5%).

Commonly observed adverse reactions with an incidence ≥5% and at least twice that for placebo for subjects with bipolar disorder were somnolence/sedation/hypersomnia (23%), dizziness (10%), extrapyramidal symptoms other than akathisia (7%), oral hypoesthesia (5%) and weight increased (5%).

With respect to safety topics of interest, asenapine showed limited effects on body weight, metabolic laboratory parameters, orthostasis, and prolactin levels. Additionally, asenapine has a low propensity to induce EPS, has no increased risk of suicidality, and has no clinically relevant effects on the QT interval or liver parameters. As such, asenapine is a promising alternative to existing approved therapies.

In terms of overall benefit and risk profile, Schering-Plough concludes that:

- ***Asenapine has a positive benefit-risk profile in both schizophrenia and bipolar I disorder.***

Asenapine balances demonstrated efficacy with limited impact on weight gain, lipids and prolactin. Therefore, asenapine is an important treatment option for patients with schizophrenia and bipolar I disorder.

2. INTRODUCTION

The New Drug Application (NDA) for asenapine Sublingual Tablets, which was submitted in August 2007, presents the results of trials conducted to assess the efficacy, safety, and tolerability of asenapine for the following indications (1) acute treatment of schizophrenia in adults and (2) acute treatment of manic or mixed episodes associated with bipolar I disorder in adults. The Food and Drug Administration (FDA) issued a complete response letter in January 2009 which included proposed labeling for both indications and a request for supplemental data from the existing asenapine database. No additional clinical trials were requested. A complete response was submitted in February 2009.

This briefing document includes data from the pending NDA and has been specifically prepared for the FDA Psychopharmacologic Drugs Advisory Committee. Information regarding the pharmacology, biopharmaceutics, clinical pharmacokinetics, and data on the efficacy and safety of asenapine in the treatment of schizophrenia and acute manic or mixed episodes associated with bipolar I disorder are provided. This document concludes with an assessment of the benefits and risks of asenapine and shows that asenapine is a safe and effective treatment for schizophrenia and for acute manic or mixed episodes associated with bipolar I disorder.

2.1. Review of Disease States

2.1.1. Schizophrenia

Schizophrenia is a severe, disabling disorder that affects about 1% of the world's population (Diagnostic and Statistical Manual of Mental Disorders [version IV, text version, DSM-IV-TR). The DSM-IV-TR]) diagnosis of schizophrenia requires the presence of at least two of the following symptoms over a period of at least one month: delusion, hallucinations, disorganized speech, catatonic or grossly disorganized behavior, negative symptoms. Additional unspecific symptoms (often termed prodromal or residual symptoms) are required to be present for at least 6 months. In addition, the clinical symptoms are required to be associated with a significant social/occupational dysfunction, often in the sense of a decline in performance. It is necessary to exclude that the psychopathological symptoms are better accounted for by a medical condition, substance abuse, a pervasive developmental disorder or a schizoaffective or a mood disorder.

From the set of diagnostic criteria it is evident that schizophrenia is not a homogeneous disorder, but is disease that can present in a variety of clinical syndromes which, moreover, can fluctuate and change over time. In a majority of individuals, schizophrenia is a chronic disorder in the sense that, after initial onset, which typically occurs in early adulthood, individuals experience disabling symptoms over long periods of time. There is substantial inter-individual variability in the time course of the disorder, with some individuals experiencing more episodically exacerbating symptoms followed by intervals with a low degree of interepisode residual symptoms, while others display more chronic or continuous

symptoms without partial or full resolution of the symptoms. Complete remission is uncommon in this disorder.

In addition to the positive symptoms (such as delusions and hallucinations) and negative symptoms (such as alogia, affective flattening, and avolition) that are listed as diagnostic criteria in DSM-IV-TR, many patients also experience various cognitive deficits as well as symptoms of depression and anxiety. Moreover, schizophrenia is a disorder associated with a high risk of suicide, with a frequently reported modal rate of suicide being approximately 10% (Siris, 2001).

2.1.2. Bipolar I disorder

Bipolar disorder is a chronic, typically cyclic mood disorder with a lifetime prevalence of approximately 0.8% to 1.6% (DSM-IV-TR). The disorder is characterized by the occurrence of episodes of significantly altered mood, which may be manic, depressive (meeting criteria for major depressive episode), or mixed. Bipolar I disorder is characterized by the occurrence of at least one manic or mixed episode according to the criteria of DSM-IV-TR.

Typical symptoms of a manic episode include abnormally and persistently elevated or irritable mood accompanied by inflated self-esteem, ideas of grandiosity, decreased need for sleep, increased drive, logorrhoea, or flight of ideas. Manic patients are at increased risk to engage in behaviors such as unrestrained buying sprees, sexual indiscretions, foolish business investments, etc. The duration of a manic episode can extend from days to months. Patients with mixed episodes experience rapidly alternating moods meeting the criteria for both a manic and major depressive episode over a prolonged period of time of at least one week.

Similar to schizophrenia, individuals with bipolar I disorder have a substantially elevated risk of suicide, with 10-15% of affected individuals eventually committing suicide (DSM-IV-TR). Treatment of bipolar I disorders comprises an effective treatment of manic or mixed symptoms as well as treatment of bipolar depression, which differs substantially from the treatment of unipolar depression due to the increased risk of a switch into mania. An important long term goal is mood stabilization, ideally in the state of euthymia.

2.2. Continuing Medical Need

Considerable continuing medical need in both schizophrenia and bipolar I disorder remains.

2.2.1. Schizophrenia

Although many antipsychotics are available in the United States (US) today, no single medication is effective for all patients with schizophrenia. The severity of this mental illness is such that a broad range of treatment modalities is needed and is especially important because between 20% and 45%, of patients fail to show a satisfactory response to antipsychotic medications (Lambert 2006; Conley and Kelly 2001; Kane 2006). Treatment of

chronic illnesses like schizophrenia requires new therapies to increase the proportion of patients who achieve sustained improvements in function.

With the discovery of antipsychotic drugs like chlorpromazine and haloperidol, some of the core symptoms of schizophrenia became treatable. First generation (typical) antipsychotic drugs characteristically show efficacy in the treatment of positive symptoms. However, due to their pharmacological profile, many first generation antipsychotics were associated with the troubling and frequent occurrence of extrapyramidal motor symptoms, which often strongly limit their acceptance among patients. With the development of second generation (atypical) antipsychotics, the frequency of this important side effect could be reduced, although different adverse experiences occur. However, there are still substantial unmet needs in the treatment of schizophrenia. Even today, it is still not possible to predict in clinical practice whether a particular patient will respond to any chosen antipsychotic drug. It holds true for all available antipsychotics that, while a significant number of patients will experience clinically relevant benefits, a substantial number of patients will not profit sufficiently. On average, this results in a limited treatment effect compared with placebo in the acute treatment of schizophrenia (Khan et al., 2001). Moreover, available treatment options are effective mainly in treating positive and general psychopathology symptoms, while their potential in the treatment of negative symptoms, cognitive deficits, and affective symptoms is largely unexplored or the compounds have not been found to be effective. Finally, available second generation (atypical) antipsychotics are also associated with adverse effects such as elevated prolactin levels, agranulocytosis, cardiac side effects or excessive weight gain, which limit their use in some patient populations.

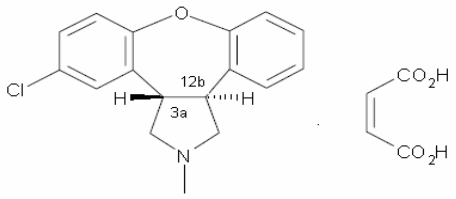
2.2.2. Bipolar I disorder

For the treatment of manic symptoms, a variety of drug treatment options have been used in the past decades. Lithium and antiepileptic drugs such as valproate or carbamazepine have demonstrated antimanic effects. First generation (typical) antipsychotics have frequently been used to control manic symptoms; their use however, was often limited by the occurrence of EPS. More recently, second generation (atypical) antipsychotics have increasingly been used successfully and approved to treat manic or mixed episodes associated with bipolar I disorder. As stated above, second generation (atypical) antipsychotics are also associated with adverse effects that limit their use.

2.3. Clinical Pharmacology

Asenapine (Figure 1) is a psychopharmacologic agent with a human receptor binding profile predictive of efficacy in the treatment of schizophrenia or mania associated with bipolar disorder. The clinical pharmacology package for asenapine consists of 18 studies with human biomaterials as well as 37 completed clinical trials, in which one of the objectives was to evaluate the pharmacokinetics and/or the pharmacodynamics of asenapine in humans, including drug-drug interactions and the pharmacokinetics in special populations.

Figure 1 Asenapine maleate



2.3.1. Formulation

Asenapine was initially developed as an oral formulation but, due to low bioavailablity (<2%), development of this formulation was discontinued in favor of a fast dissolving tablet for sublingual administration. The low bioavailability of oral asenapine is caused by extensive first-pass metabolism in the liver and probably the gut. The sublingual formulation was developed to circumvent the hepato-gastro-intestinal first-pass metabolism. The absolute bioavailability after sublingual dosing is much higher (~ 35%) than after oral dosing. Approval is being sought for the sublingual formulation.

A fast dissolving tablet for sublingual administration was developed using proprietary freeze-drying technology. The asenapine tablet formulation contains asenapine maleate, mannitol, and gelatin. The tablet begins disintegrating in saliva within seconds. The rapid dissolution is due to the highly porous tablet structure and the high aqueous solubility of the active substance.

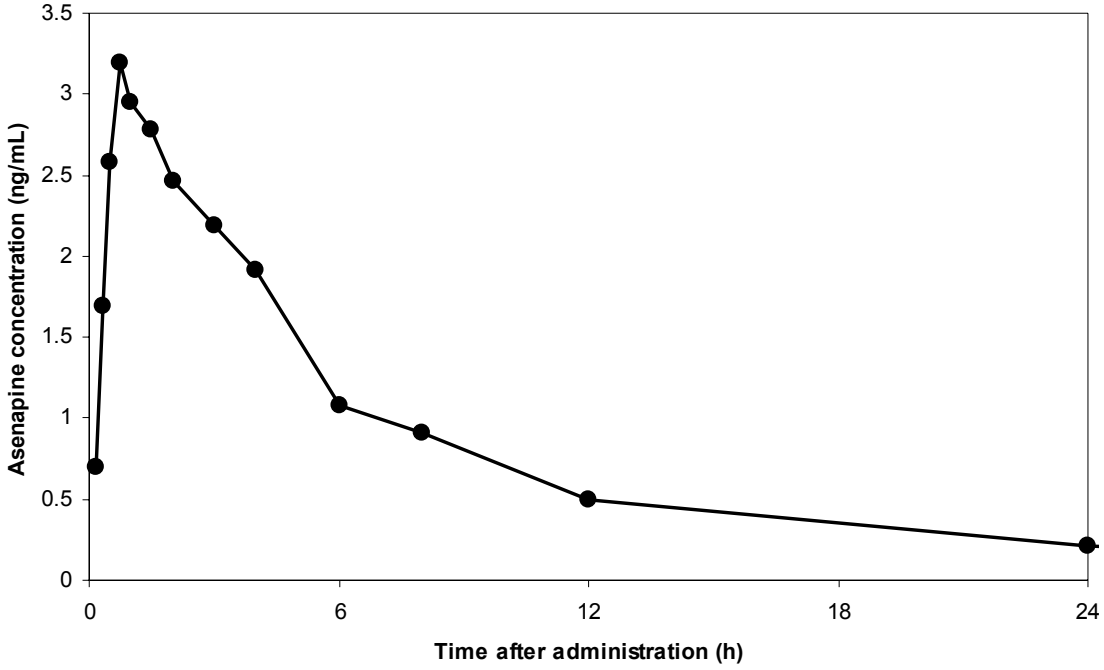
2.3.2. Pharmacokinetics

2.3.2.1. Absorption, Metabolism, Distribution, and Elimination

Following sublingual administration, asenapine is rapidly absorbed, with peak plasma concentrations occurring within 0.5 to 1.5 hours (Figure 2). The absolute bioavailability of a single 5 mg sublingual dose of asenapine is 35 %. Increasing the dose from 5 to 10 mg twice daily (a two-fold increase) results in a less than linear (1.7 times) increase in both the extent of exposure and maximum concentration. At supratherapeutic doses (> 10 mg twice daily), this deviation from dose-proportionality is more pronounced. Small differences exist in asenapine pharmacokinetics following administration of the tablet at different sites of the

oral cavity (sublingual, buccal, supralingual). Sublingual administration is the indicated route and was used in the phase 3 efficacy and safety trials.

Figure 2 Mean asenapine plasma concentrations vs time after a single sublingual dose of 5 mg in the intended commercial formulation (N=33)



Asenapine has a large distribution volume (~1700 L), indicating extensive extravascular distribution. At therapeutic and supratherapeutic concentrations, asenapine is highly bound (95% to 97%) to plasma proteins, including albumin and α1-acid glycoprotein. Asenapine does not appear to be a substrate for P-glycoprotein. While an efflux polarity for asenapine was observed in Caco-2 cells, data from a cell line specifically expressing human P-glycoprotein showed that asenapine does not undergo transport by this protein.

Asenapine is a high clearance drug with a clearance after intravenous administration of 52 L/h. In this circumstance, hepatic clearance is influenced primarily by changes in liver blood flow rather than by changes in the intrinsic clearance, i.e. the metabolizing enzymatic activity. Following an initial more rapid distribution phase, the terminal half life of asenapine is approximately 24 hours. Steady-state concentrations of asenapine are reached within 3 days of twice daily dosing. Overall, steady state asenapine pharmacokinetics are similar to single-dose pharmacokinetics.

After administration of a single dose of [^{14}C]-labeled asenapine, about 90% of the dose was recovered; approximately 50% was recovered in urine, and 40% recovered in feces. About 50% of the circulating species in plasma have been identified. The predominant species was

asenapine N^+-glucuronide; others included N-desmethylasenapine, N-desmethylasenapine N-carbamoyl glucuronide, and unchanged asenapine in smaller amounts. As these metabolites have a greatly reduced receptor affinity and/or do not penetrate into the brain, the activity of asenapine is considered to be primarily due to the parent drug.

Direct glucuronidation by glucuronidyl transferases and oxidative metabolism by cytochrome P450 isoenzymes are the primary metabolic pathways for asenapine. *In vitro* studies indicate that asenapine is a substrate for UGT1A4, CYP1A2 and to a lesser extent CYP3A4 and CYP2D6. Asenapine is a weak inhibitor of CYP2D6. Asenapine does not cause induction of CYP1A2 or CYP3A4 activities in cultured human hepatocytes. Coadministration of asenapine with known inhibitors, inducers or substrates of these metabolic pathways has been studied in a number of drug-drug interaction studies (see Section 2.3.2.3, Extrinsic factors and Interactions).

2.3.2.2. Intrinsic Factors and Special Populations

A population pharmacokinetic analysis including asenapine concentration data from 1137 subjects with schizophrenia or bipolar mania indicated that asenapine pharmacokinetics are similar in men and women, schizophrenia and bipolar patients, across races and body weight ranges, and between smokers and non-smokers. Age was found to be a significant covariate for asenapine clearance. In elderly subjects with psychotic symptoms, probably due to decreased liver blood flow, asenapine concentrations were found to be approximately 30% higher than in younger adult subjects with schizophrenia.

Hepatic

In a dedicated study, the pharmacokinetics of asenapine following a single dose of 5 mg asenapine were unaltered in subjects with mild or moderate hepatic impairment (Child-Pugh Class A and B), indicating that dosage adjustment is not required for these subjects. In subjects with severe hepatic impairment (Child-Pugh Class C), a 7-fold increase in asenapine exposure was observed. Therefore, asenapine is not recommended in patients with severe hepatic impairment (Child-Pugh C).

Renal

In a separate study, the pharmacokinetics of asenapine following a single dose of 5 mg asenapine were similar among subjects with varying degrees of renal impairment and subjects with normal renal function, indicating that dosage adjustment based upon the degree of renal impairment is not required.

2.3.2.3. Extrinsic Factors and Interactions

The oral cavity is the major site of absorption of sublingually administered asenapine. Accordingly, clinical trials have been conducted to examine the effect of drinking and concomitant smoking on absorption of sublingual asenapine. However, because it is also expected that the unabsorbed amount of the dose can be swallowed and thus reach the

stomach and intestinal tract, the effect of food on the pharmacokinetics of asenapine was also examined.

Concomitant smoking during administration has no effect on the pharmacokinetics of sublingual asenapine. Drinking water 10 minutes or more after asenapine did not affect bioavailability. In contrast, drinking water sooner than 10 minutes after sublingual asenapine reduces bioavailability to some extent. The mean asenapine exposure for subjects given water at 2 min was ~20% lower and at 5 min was ~10% lower. Therefore, drinking as well as eating should be avoided for 10 minutes after administration. This restriction was applied in the clinical trials establishing the efficacy and safety of asenapine.

A high fat meal immediately before asenapine administration reduced exposure by about 20%, and AUC was reduced by 13% when food was given 4 hours after asenapine. Both observations are likely due to increased clearance of asenapine related to higher hepatic blood flow following food intake. Other than the 10 minute wait after asenapine administration, no restrictions with regard to food intake were applied in the clinical trials establishing the efficacy and safety of asenapine.

In the drug interaction trials, asenapine pharmacokinetics were not altered in a clinically meaningful way by co-administration with most CYP450 inhibitors or inducers or with glucuronyltransferase inhibitors. Only co-administration with fluvoxamine, a strong CYP1A2 inhibitor, can be expected to result in relevant increases in asenapine plasma concentrations. Therefore, co-administration of asenapine with fluvoxamine should be done cautiously. In vivo, asenapine appears to be at most a weak inhibitor of CYP2D6. However, when asenapine (5 mg twice daily) was coadministered with a single 20 mg dose of paroxetine (a CYP2D6 substrate and inhibitor), an almost two-fold increase in paroxetine concentrations was observed. It appears that asenapine can enhance the inhibitory effects of paroxetine on its own metabolism. Asenapine should be coadministered cautiously with drugs that are both substrates and inhibitors for CYP2D6.

In addition, given the primary central nervous system (CNS) effects of asenapine, caution should be used when it is taken in combination with other centrally acting drugs. Patients should be advised to avoid alcohol while taking asenapine. Because of its potential for inducing hypotension, asenapine may enhance the effects of certain antihypertensive agents.

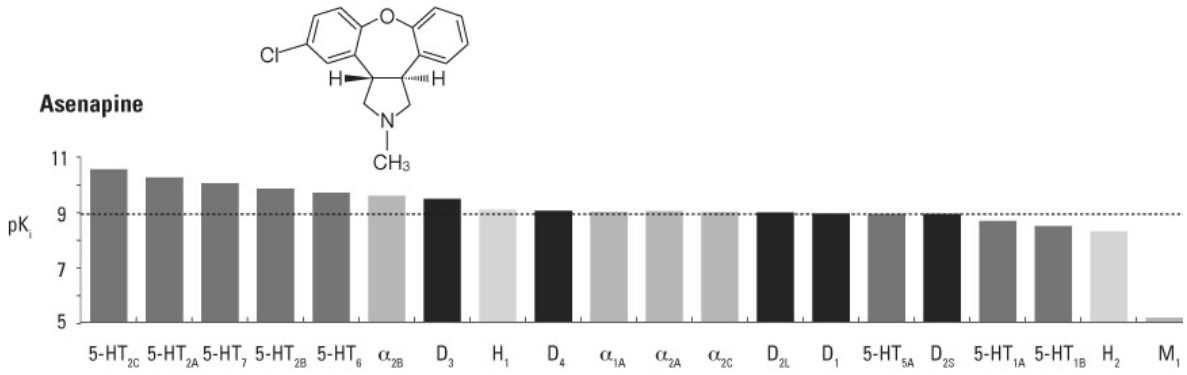
2.3.3. Pharmacodynamics

2.3.3.1. Mechanism of action

The pharmacological profile of asenapine displays potent multi-receptor antagonism for a combination of serotonin, dopamine, noradrenaline, and histamine receptors (Figure 3). Asenapine demonstrates higher absolute affinity for a subset of serotonergic (5-HT_{2A}/5-HT_{2B}/5-HT_{2C}/5-HT_6/5-HT_7), noradrenergic (α_1/α_2), and dopaminergic (D_3/D_4) receptors than

currently available antipsychotics, and no appreciable activity at muscarinic cholinergic receptors.

Figure 3 Pharmacological profile of asenapine relative to its D_2 affinity



------ = D2 receptor affinity

The efficacy of asenapine is hypothesized to be mediated through a combination of potent antagonist activity at D_2 and 5-HT_{2A} receptors. Based on preclinical research, actions at other receptors (e.g., 5-HT_{2C}, 5-HT_6, 5-HT_7, 5-HT_{1A}, 5-HT_{1B}, D_3, and α_2-adrenergic receptors) raise the potential for additional therapeutic benefits (e.g. improvements in negative and affective symptoms). In common with second generation (atypical) antipsychotics,, asenapine shows a higher binding affinity for the 5-HT_{2A} receptor than the D_2 receptor, which indicates a lower risk for extrapyramidal symptoms when compared with first generation (typical) antipsychotic drugs. Antagonism of histamine H_1 receptors may be associated with somnolence in clinical practice. In general, however, the exact mechanism of action of asenapine, as with other drugs having efficacy in schizophrenia and bipolar disorder, is unknown.

2.3.3.2. Pharmacodynamic effects in humans

As antagonism at the dopamine D_2 receptor is believed to be a major driver for the antipsychotic activity of asenapine, in vivo occupancy of this receptor in the striatal regions of the brain was an important pharmacodynamic marker in the clinical program of asenapine. Pharmacokinetic-pharmacodynamic (PK-PD) modeling has been applied to characterize the relationship between asenapine plasma concentrations and D_2 occupancy. These data are described in more detail in section 3.1.2, D_2 receptor occupancy.

Additionally, the clinical pharmacodynamics of asenapine have been characterized by PK-PD modeling of the effects on primary efficacy parameters in both schizophrenia and bipolar mania indications. Moreover, PK-PD relationships for QTc prolongation have been investigated. The results of these analyses are described in the respective sections for each of these parameters.

3. SUMMARY OF EFFICACY

The asenapine clinical development program was designed to investigate efficacy in two different indications in parallel:

1. acute treatment of schizophrenia

2. acute treatment of manic or mixed episodes associated with bipolar I disorder

Efficacy of asenapine in both indications was demonstrated in two adequate and well controlled trials. The efficacy results for the relevant asenapine trials in each indication are presented below. Analyses using the primary analysis are presented; results of prespecified secondary analyses are included as supportive information.

The prespecified primary efficacy analysis for the schizophrenia and bipolar mania trials was either an analysis of variance (ANOVA) model with pooled site and treatment as factors (phase 2) or an analysis of covariance (ANCOVA) model with fixed effects for treatment and investigative site (or pooled site), and baseline value as a covariate included in the model (phase 3). Missing values were imputed using the last observation carried forward (LOCF) method.

Prespecified secondary analyses included the primary analysis with observed cases (OC) and MMRM analysis. The MMRM model includes treatment group, site (or pooled site), visit, and treatment by visit interaction as factors and baseline score as a covariate, with covariance structure specified as unstructured. The robustness of the efficacy results is indicated by the agreement between the multiple analyses.

3.1. Schizophrenia

3.1.1. General information and background

The asenapine schizophrenia clinical development program comprises a total of 20 trials, of which 11 were completed (Table 1) and 9 were ongoing as of the NDA data cutoff date of 15 January 2007 (Table 2). The phase 2 trial 041004 and the phase 3 trial 041023 are considered to provide the primary data in support of the efficacy of asenapine in the acute treatment of schizophrenia.

The data presented in the NDA support the following conclusion:

- Asenapine twice daily was efficacious in the acute treatment of adults with schizophrenia in two adequate and well-controlled 6-week trials.

Table 1 Overview of completed trials in the asenapine schizophrenia clinical development program (Intent-to-Treat)

Trial / design	Trial Dates	Number of subjects evaluable for efficacy												
		Asenapine								Olanzapine		Risp 3 mg BID	Halo 4 mg BID	Placebo
		200 μg BID	400 μg BID	800 μg BID	1600 μg BID	2400 μg BID	5 mg BID	10 mg BID	5/10 mg BID	15 mg QD	10-20 mg QD			
Phase 2														
041002 / DB, PC, AC, FD DF, 42-d	May 1998-May 2000	58	55	59										
041013 / DB, PC, FD, DF, 42-d	Feb 2000 - Jun 2001				54	54								62
041004 / DB, PC, DF, AC, FD, 42-d	Aug 2001-May 2002						58				57		54	
041500: extension to 041002 / DB, PC, AC, FD, DF, 1-yr[a]	June 1998-Nov 2000	(8)	(6)	(14)							56	(13)	60	(8)
041502: extension to 041004 / DB, PC, AC, FD, 1-yr[a]	Oct 2001-May 2003						(15)					(17)		(7)
041505: extension to 041013 / DB, PC, FD, DF, 1-yr[a]	June 2000-Jan 2002				(10)	(10)								(8)
041590: humanitarian extension to 041500 and 041505 / OL FD[a]	Nov 2000-Mar 2003			[1]	[3]	[1]								
Phase 3														
041022 / DB, PC AC, Flex D, 42-d	Feb 2005–Feb 2006								85		85			
041021 / DB, PC, AC, FD, 42-d	May 2005-May 2006						102	96						93
041023 / DB, FD, PC, AC, 42-d	Jun 2005-Sep 2006						109	105					89 112	122
25517 / DB, AC, FlexD / 52-wk	Sep 2003-Feb 2006								95 869		297			
Total number of evaluable subjects in feeder (extension) trials by dose group[a]		**58 (8)**	**55 (6)**	**59 (14)**	**54 (10)**	**54 (10)**	**269 (15)**	**201**	**954**	**95**	**382**	**113 (30)**	**112**	**480 (23)**

a Numbers and totals (in parentheses) include subjects who completed a short-term trial and were enrolled and treated in an extension trial. Numbers in square brackets include subjects who completed treatment in both a short term trial and an extension trial and who were assessed by the investigator as potentially benefiting from continued therapy at the same dosage

AC= active control; BID = twice daily; DB = double blind; DF = dose-finding; FD = fixed dose; Flex D = flexible dose; PC = placebo control; PO = per os (orally); QD = once daily; OL = open label; SL = sublingual

Table 2 Overview of trials in the schizophrenia clinical development program that were ongoing as of the NDA data cutoff date: 15 January 2007

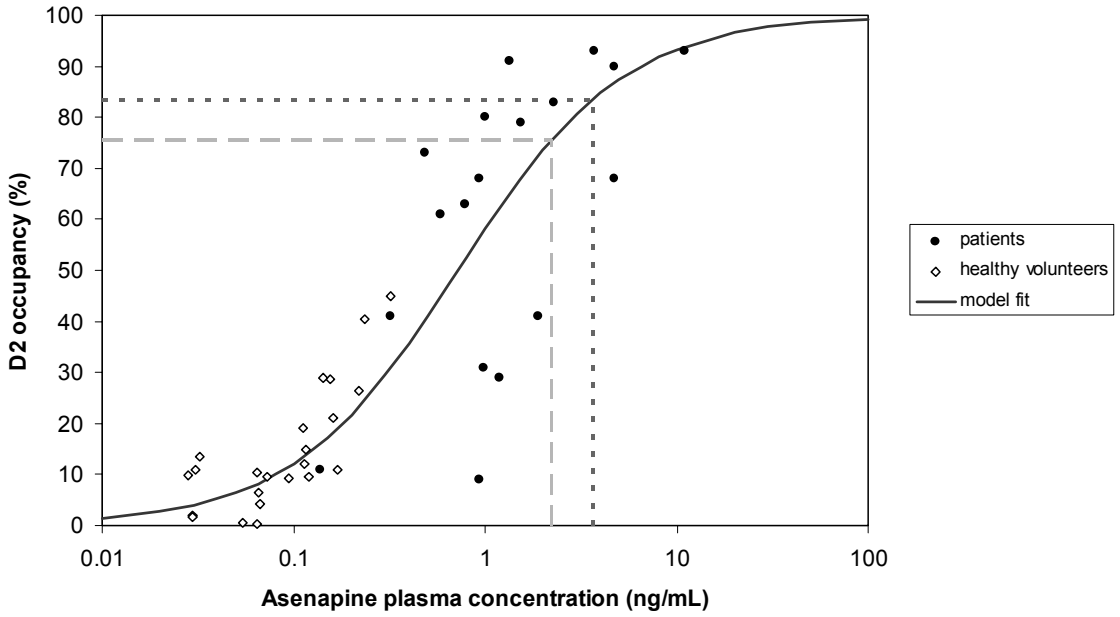
Trial	Description
041512 (extension to Trials 041021/022)	52-week double-blind extension trial (after treatment of acute exacerbation of schizophrenia) asenapine 5-10 mg BID, olanzapine 5-20mg QD, placebo→asenapine. Current status: Complete
25520 (extension to Trial 25517)	long-term double-blind extension in subjects with schizophrenia or schizoaffective disorder; was to continue until trial was stopped for administrative, safety, or other reasons; asenapine 5-10 mg BID, olanzapine 10-20mg QD (randomized 3:1 in trial 25517). Current status: Complete
041513 (extension to Trial 041023)	12-month double-blind extension asenapine 5-10 mg BID, haloperidol 2-8 mg BID, placebo→asenapine Current status: Complete
25543	6-month double-blind trial in the treatment of schizophrenia subjects with predominant and persistent negative symptoms asenapine 5-10 mg BID, olanzapine 5-20 mg QD. Current status: Complete
25544 (extension to Trial 25543)	6-month double-blind extension. Current status: Complete
A7501013	6-month double-blind trial in the treatment of schizophrenia subjects with predominant and persistent negative symptoms asenapine 5-10 mg BID, olanzapine 5-20 mg QD. Current status: Complete
A7501014	6-month double-blind extension. Current status: Complete
A7501012	prevention of relapse after long-term treatment of schizophrenia asenapine 5-10 mg BID, placebo; Current status: Complete
A7501021	6-week open-label safety in elderly subjects with psychosis (≥65 yrs); blinded to dose. Current status: Complete

BID = twice daily; NDA = New Drug Application; QD = once per day

3.1.2. D_2 receptor occupancy

In human positron emission topography (PET) studies, the occupancy of asenapine at the dopamine D_2 receptor in the striatum was assessed as a biomarker for the clinical effects. In clinical PET studies asenapine showed dose-dependent dopamine D_2 receptor occupancy (dose range 0.1 to 4.8 mg). A good correlation between D_2 occupancy and plasma concentration was observed (Figure 4). The analysis indicated no time delay between asenapine plasma concentrations and receptor occupancy. This direct relationship, in combination with the rapid initial decrease in asenapine plasma concentrations following the time of maximal concentration (t_{max}), indicates that a twice daily dosing regimen is required to maintain sufficient D_2 occupancy over time.

Figure 4 D_2 occupancy (%) versus asenapine plasma concentrations across healthy volunteers and schizophrenia patients



Dashed line: average concentration and associated occupancy at 5 mg BID.

Dotted line: average concentration and associated occupancy at 10 mg BID.

Solid line: fit of E_{max} model to patient data.

BID = twice daily; D2 = dopamine receptor subtype 2; PET = positron emission topography

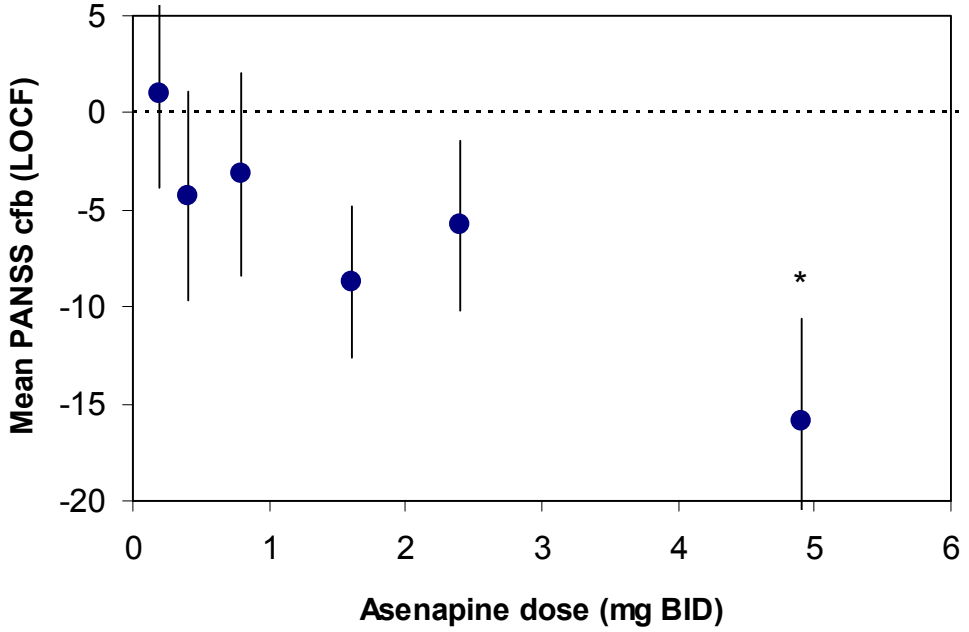
A modeling analysis based on public domain pharmacokinetic, D_2 occupancy, and short-term phase 2 clinical efficacy data in the treatment of schizophrenia of several antipsychotics established a quantitative relationship between D_2 occupancy and effects on total Positive and Negative Syndrome Scale (PANSS). In combination with the available PET data for asenapine, the results from this analysis indicated that relevant clinical efficacy of asenapine is expected at doses of 5 mg twice daily and higher.

3.1.3. Dose finding in schizophrenia

The early phase 2 trials 041002 and 041013 explored the efficacy of asenapine doses ranging from 200 μg to 2400 μg twice daily (BID). None of the asenapine groups in these two trials showed statistical differences from placebo on the primary endpoint analysis. The asenapine 200, 400 and 800 μg BID groups showed numerically similar or less change in the primary endpoint than placebo; the asenapine 1600 μg and 2400 μg BID groups were numerically better than placebo. Figure 5 illustrates the comparative efficacy of these dose groups compared with the asenapine 5 mg BID dose group in Trial 041004. Over the range of doses studied in these sufficiently powered trials, the mean change at the primary endpoint was statistically significantly different from placebo only for the asenapine 5 mg twice daily dose. These results, in combination with the data from the above-mentioned PET trials (Section 3.1.2, D_2 receptor occupancy), were

helpful in determining 5 mg twice daily as the minimal effective dose in the treatment of schizophrenia, as demonstrated in Trial 041004.

Figure 5 Dose response for asenapine on Total PANSS score, phase 2 placebo-controlled short-term fixed dose efficacy trials



Markers represent mean Total PANSS change from baseline at endpoint (LOCF) – bars represent 95% confidence interval of the mean

* = statistically significantly different from placebo

BID = twice daily; cfb = change from baseline; ITT = intent to treat; LOCF = last observation carried forward; PANSS = Positive and Negative Syndrome Scale

3.1.4. Efficacy assessments

The primary efficacy endpoint was defined as the change in the total score of the PANSS from baseline to the end of treatment, a well established outcome parameter for trials in schizophrenia. Rater-administered efficacy scales, such as the PANSS, were administered at each site by a trained rater.

Table 3 lists the primary and select secondary efficacy measures used in the phase 2 and phase 3 trials and provides a brief description of each.

Table 3 Select efficacy measures in phase 2/3 schizophrenia trials

Parameter	Measure
Primary efficacy measure	
Schizophrenia symptoms	Positive and Negative Syndrome Scale (PANSS): a 30-item clinician-rated instrument for assessing the symptoms of schizophrenia. Minimum and maximum scores: 30-210.
Select secondary efficacy measures	
Schizophrenia symptoms	The PANSS includes 3 subscales: PANSS positive, negative, and general psychopathology. Minimum and maximum scores: 7-49, 7-49, and 16-112, respectively.
Schizophrenia symptoms	Marder et al (1997) identified the following PANSS factors: PANSS positive, negative, hostility/excitement, anxiety/depression, and disorganized thoughts. Minimum and maximum scores: 8-56, 7-49, 4-28, 4-28, and 7-49, respectively.
PANSS responders	Subjects with ≥30% decrease in PANSS total score
Clinical Global Impression of Improvement	CGI-I: measures the impression of the investigator or trained rater about the overall clinical state of the patient. Minimum and maximum scores: 1-7.
Clinical Global Impression of Severity of Illness	CGI-S: measures the impression of the investigator or trained rater about the global severity of the subject's illness. Minimum and maximum scores: 1-7.

CGI-I = Clinical Global Impression of Improvement; CGI-S = Clinical Global Impression of Severity; PANSS = Positive and Negative Syndrome Scale

3.1.5. Short-term trials in schizophrenia

Four short-term (6-week) placebo- and active-controlled phase 2/3 trials explored the safety and efficacy of asenapine at doses greater than or equal to 5 mg twice daily in the acute treatment of schizophrenia. Subjects were eligible if they were men or women from 18 to 65 (phase 2) or ≥18 (phase 3) years of age. Female subjects were to be non-lactating and non-pregnant. Subjects were eligible if they had a DSM-IV (phase 2) or DSM-IV-TR (phase 3) diagnosis of schizophrenia of paranoid, disorganized, catatonic, or undifferentiated subtypes. Subjects were not eligible for participation if they had schizophrenia of residual subtype or schizoaffective disorder. In all trials, subjects were ineligible if they had a primary diagnosis other than schizophrenia. Subjects were eligible to enter the trial if they were experiencing an acute exacerbation of their disease, as evidenced by a minimum PANSS score of 60 at both screening and baseline, a minimum Clinical Global Impression of Severity (CGI-S) score of 4 (moderately ill) at baseline, and a PANSS score of at least 4 on two of the five core positive symptoms items (delusions, conceptual disorganization, hallucinatory behaviour, grandiosity, and suspiciousness/persecution) at screening and baseline. Eligibility criteria pertaining to the prior use of clozapine was slightly different between the phase 2 and phase 3 short-term trials: in phase 3 trials, subjects must have responded previously to an antipsychotic agent other than clozapine, while in phase 2 trials, subjects must have responded to an antipsychotic agent other than clozapine if they had previously been treated. In the phase 3 trials, subjects were ineligible if they had used clozapine for the treatment of schizophrenia within the previous 12 weeks or had another Axis I diagnosis.

The primary endpoint in all four trials was a comparison between each asenapine dose group and placebo of the mean change from baseline in PANSS total score. All four trials were adequately powered to demonstrate significant differences versus placebo in the primary efficacy variable. All four trials included an active control group (Trial 041004 = risperidone, Trial 041021, Trial 041022 = olanzapine, and Trial 041023 = haloperidol) but were not powered to allow for a comparison of asenapine and the active comparator. Study medication was provided using a double-dummy design.

Three of the short-term placebo/active controlled trials were fixed-dose trials: a phase 2 trial with asenapine 5 mg twice daily (Trial 041041) and two phase 3 trials with asenapine 5 mg twice daily and 10 mg twice daily (Trials 041021 and 041023). In these three trials, 269 subjects received asenapine at a fixed dose of 5 mg twice daily and 201 subjects received asenapine at a fixed dose of 10 mg twice daily. Asenapine distinguished from placebo on the primary efficacy endpoint in two of the fixed-dose trials, Trials 041004 and 041023, which are considered pivotal, and not in the third trial, Trial 041021, which is considered supportive.

The fourth short-term trial (Trial 041022) was similar to Trials 041021 and 041023 but with a flexible dose design (asenapine 5-10 mg twice daily). Trial 041022, in which both asenapine and the active comparator (olanzapine) failed to separate from placebo on any efficacy measure, will not be discussed further. Safety data from Trial 041022 were included in the NDA safety database.

3.1.5.1. Trial 041004 results (pivotal trial)

This phase 2 trial was conducted at 21 sites in the US. Subjects were randomly assigned to receive placebo, asenapine 5 mg twice daily, or risperidone 3 mg twice daily. Subjects who received asenapine 5 mg twice daily were titrated up to their final dose over a 5-day period. Subjects who received risperidone were titrated up to their final dose over a 3-day period. Of 182 subjects randomly assigned to treatment, 180 subjects received at least 1 dose of trial medication: placebo, 62 subjects; asenapine 5 mg BID, 59 subjects; and risperidone 3 mg BID, 59 subjects. The Intent to Treat (ITT) group included 174 subjects: placebo, 60 subjects; asenapine 5 mg BID, 58 subjects; and risperidone 3 mg BID, 56 subjects. Subject characteristics and disposition are tabulated below (Table 4, Table 5).

Table 4 Summary of subject characteristics, Trial 041004

	Placebo N = 62	Asenapine 5 mg BID N = 59	Risperidone 3 mg BID N = 59
Male gender, %	79	78	61
Race, %			
Caucasian	32	42	32
Black	52	44	52
Asian	0	3	0
Other	16	10	16
Mean (range) age (years)	42 (22 – 68)	39 (21 – 70)	43 (22 – 61)
Mean (range) weight (kg)	90 (55 – 150)	89 (59 – 155)	85 (57 – 162)
Schizophrenia diagnosis, %			
Paranoid	98	86	86
Disorganized	0	2	5
Undifferentiated	2	12	7

BID = twice daily

Table 5 Summary of subject disposition, Trial 041004

	Placebo	Asenapine 5 mg BID	Risperidone 3 mg BID	Total
All-Subjects-Randomized	62	60	60	182
All-Subjects-Treated	62	59	59	180
Intent-to-Treat	60	58	56	174
Completed	21 (33.9)	27 (45.8)	25 (42.4)	73 (40.6)
Discontinued	41 (66.1)	32 (54.2)	34 (57.6)	107 (59.4)
AE/SAE	7 (11.3)	7 (11.9)	4 (6.8)	18 (10.0)
Lack of Efficacy	18 (29.0)	9 (15.3)	16 (27.1)	43 (23.9)
Other	16 (25.8)	16 (27.1)	14 (23.7)	46 (25.6)

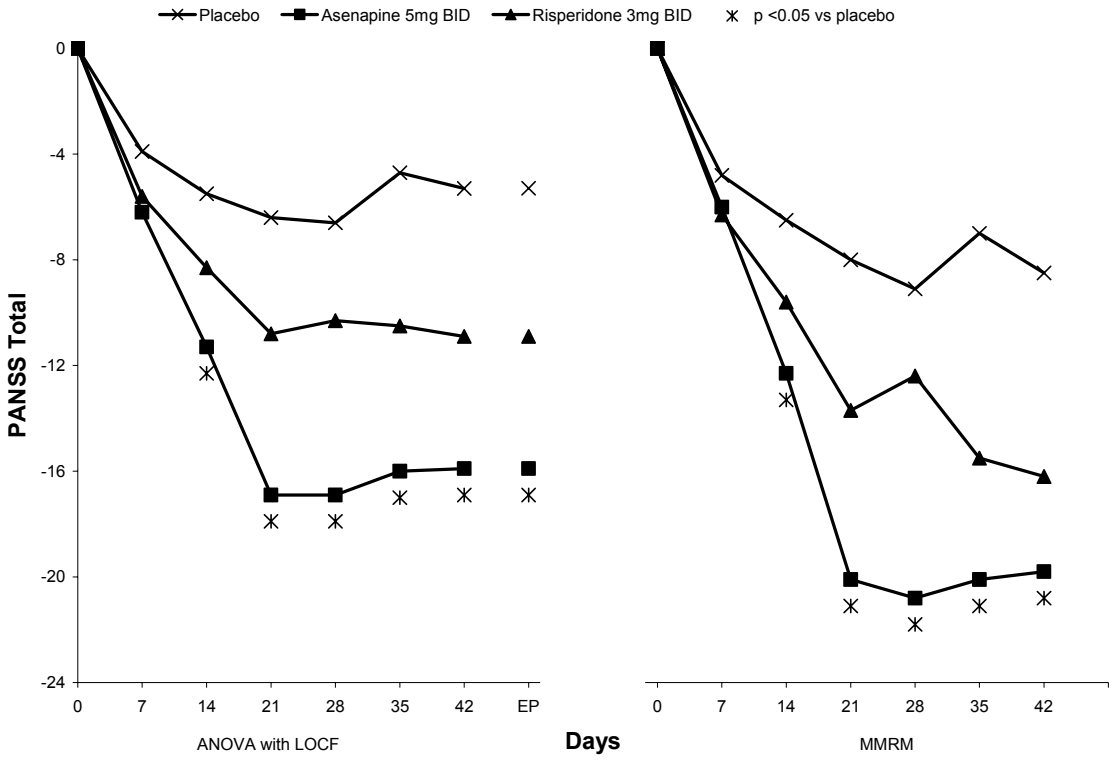
AE = adverse event; BID = twice daily; SAE = serious adverse event

Subject demographics, history of schizophrenic illness, and extent of disease at trial entry appeared to be similar across treatment groups.

Primary efficacy analysis

The primary efficacy analysis demonstrated that asenapine 5 mg twice daily was statistically significantly ($p < 0.05$) more effective than placebo in reducing the symptoms of schizophrenia, as measured by change from baseline to Day 42/endpoint in the PANSS total score. Sustained, statistically significant ($p < 0.05$) improvement in the PANSS total score compared with placebo was observed for asenapine 5 mg twice daily starting at Day 14 (Figure 6).

Figure 6 Trial 041004 primary efficacy parameter: Change from baseline in total PANSS score



Baseline mean: Placebo: 92.4, Asenapine 5 mg BID: 96.5Risperidone 3 mg BID: 92.2

ANOVA = analysis of variance; BID = twice daily; EP = endpoint; LOCF = last observation carried forward; MMRM = mixed model for repeated measures; PANSS = Positive and Negative Syndrome Scale

Analyses of the primary efficacy endpoint, Trial 041004

Using an MMRM analysis, asenapine 5 mg twice daily was statistically significantly ($p < 0.05$) more effective than placebo in reducing the symptoms of schizophrenia, as measured by change from baseline to Day 42 in the PANSS total score (ITT). Sustained, statistically significant ($p < 0.05$) improvement in the PANSS total score compared with placebo was observed for asenapine 5 mg twice daily starting at Day 14 (Table 6).

Risperidone 3 mg twice daily was not shown to be statistically different from placebo on the primary endpoint. Consistent with the LOCF analysis, risperidone 3 mg twice daily was not shown to be statistically superior to placebo at Day 42 using an MMRM analysis (Table 6).

Table 6 Analyses of the primary efficacy endpoint, Trial 041004

	Inferential analysis of change from baseline in PANSS total score (ANOVA with LOCF, ITT group)			**Inferential analysis of change from baseline in PANSS total score (ANOVA with OC, ITT group)**			**MMRM analysis of change from baseline in PANSS total score (ITT Group)**		
	Placebo N = 60	Asenapine 5 mg BID N = 58	Risperidone 3 mg BID N = 56	Placebo ***N***	Asenapine 5 mg BID ***N***	Risperidone 3 mg BID ***N***	Placebo N = 60	Asenapine 5 mg BID N = 58	Risperidone 3 mg BID N = 56
BL mean (SE)	92.4 (1.9)	96.5 (2.2)	92.2 (2.1)	***60*** 92.4 (1.9)	***58*** 96.5 (2.2)	***56*** 92.2 (2.1)	92.4 (1.9)	96.5 (2.2)	92.2 (2.1)
Mean (SE) Δ to:									
Day 7	-3.9 (1.5)	-6.2 (1.7)	-5.6 (1.8)	***57*** -4.09 (1.52)	***56*** -6.45 (1.72)	***56*** -5.61 (1.81)	-4.8 (1.5)	-6.0 (1.6)	-6.3 (1.6)
Day 14	-5.5 (1.6)	-11.3 (2.0)*	-8.3 (2.4)	***48*** -6.56 (1.83)	***47*** -14.11 (2.21)	***50*** -10.28 (2.29)	-6.5 (2.0)	-12.3 (2.0)*	-9.6 (2.0)
Day 21	-6.4 (2.1)	-16.9 (2.4)*	-10.8 (2.8)	***43*** -8.35 (2.61)	***42*** -23.60 (2.45)	***44*** -14.32 (2.82)	-8.0 (2.4)	-20.1 (2.4)*	-13.7 (2.4)
Day 28	-6.6 (2.3)	-16.9 (2.5)*	-10.3 (2.7)	***27*** -15.67 (3.04)	***32*** -25.38 (3.11)	***30*** -18.47 (3.30)	-9.1 (2.9)	-20.8 (2.9)*	-12.4 (2.8)
Day 35	-4.7 (2.2)	-16.0 (2.6)*	-10.5 (2.7)	***25*** -14.40 (3.15)	***29*** -24.38 (3.69)	***28*** -19.14 (3.37)	-7.0 (3.3)	-20.1 (3.2)	-15.5 (3.2)
Day 42	-5.3 (2.3)	-15.9 (2.6)*	-10.9 (2.7)	***22*** -14.36 (3.55)	***27*** -25.22 (4.00)	***25*** -22.60 (3.08)	-8.5 (3.4)	-19.8 (3.3)*	-16.2 (3.3)
EP	-5.3 (2.3)	-15.9 (2.6)*	10.9 (2.7)						

* indicates p<0.05. P-values were based on a two-sided t-test comparing each active treatment group with the placebo group; an ANOVA model with fixed effects for treatment and pooled investigative site was used.

An ANOVA model with fixed effects for treatment and pooled investigative site was used

A mixed model with fixed effects for treatment, pooled investigator site, visit, treatment by visit interaction, and a covariate for baseline value was used. Covariance structure: UN (Unstructured)

ANOVA = analysis of variance; BL = baseline; EP = endpoint; ITT = intent to treat; LOCF = last observation carried forward; MMRM = mixed model for repeated measures; N = total number of subjects in the ITT group; OC = observed cases; PANSS = Positive and Negative Syndrome Scale; SE = standard error

Secondary efficacy analyses

- Treatment with asenapine 5 mg twice daily also resulted in statistically significantly ($p < 0.05$) greater improvement from baseline to Days 21, 28, 35, and 42/endpoint in the PANSS positive and negative subscale scores, and from baseline to Days 14, 21, 28, 35, and 42/endpoint in the general psychopathology subscale score. There were no statistically significant differences between risperidone and placebo at any timepoint on the PANSS negative and general psychopathology subscale scores. Additionally, a statistically significant treatment effect was apparent at endpoint for asenapine for the PANSS Marder positive, negative, and disorganized thoughts factors. CGI-S and CGI-I results were consistent with the primary efficacy results and results of secondary PANSS analyses.

- Risperidone 3 mg twice daily was statistically significantly more effective than placebo in treating positive symptoms of schizophrenia, as measured by changes from baseline to Days 7, 21, 35, and 42/endpoint in the PANSS positive subscale score. Risperidone 3 mg twice daily was also significantly more effective than placebo on the CGI-S at Days 7, 28, 35, and 42/endpoint and on the CGI-I at Days 21, 35, 42/endpoint.

- According to MMRM analysis, treatment with asenapine 5 mg twice daily also resulted in statistically significantly ($p < 0.05$) greater improvement from baseline to Days 21, 28 and 35 in the PANSS positive subscale and on Days 21 and 28 in the PANSS negative subscale scores, and from baseline to Days 14, 21, 28, 35, and 42 in the general PANSS psychopathology subscale score. Additionally, a statistically significant treatment effect was apparent for asenapine 5 mg twice daily at Day 42 for the PANSS positive, negative, and disorganized Marder factors as well as other time points. CGI-S results with MMRM analysis were consistent with the primary efficacy results.

- According to MMRM analysis, risperidone 3 mg twice daily was statistically significantly more effective than placebo at various time points in PANSS subscales and Marder factors. Risperidone 3 mg twice daily was also significantly more effective than placebo on the CGI-S at Day 42 as well as earlier time points.

- The proportion of subjects who achieved a 30% or greater reduction from baseline to day 42/endpoint in the PANSS total score was 25% in the placebo treatment group, 38% in the asenapine 5 mg BID treatment group, and 39% in the risperidone 3 mg BID treatment group. These data were not analyzed inferentially.

Conclusion

Short-term treatment with asenapine 5 mg twice daily was effective in the treatment of subjects with schizophrenia in Trial 041004.

3.1.5.2. Trial 041023 results (pivotal trial)

This phase 3 trial was conducted at 43 sites that randomly assigned subjects to treatment, including 17 in the United States, 11 in Russia, 7 in India, 7 in Romania, and 1 in Canada. Subjects were randomly assigned to receive placebo, 5 mg asenapine twice daily, 10 mg asenapine twice daily, or haloperidol 4 mg twice daily. Of 458 subjects randomly assigned to treatment, 455 subjects received at least 1 dose of trial medication: placebo, 123 subjects; asenapine 5 mg BID, 111 subjects; asenapine 10 mg BID, 106 subjects; and haloperidol, 115 subjects. The ITT group included 448 subjects: placebo, 122 subjects; asenapine 5 mg BID, 109 subjects; asenapine 10 mg BID, 105 subjects; and haloperidol, 112 subjects. Subject characteristics and disposition are tabulated below (Table 7, Table 8).

Table 7 Summary of subject characteristics, Trial 041023

	Placebo	Asenapine BID		Haloperidol 4 mg BID
		5 mg	10 mg	
	N = 123	N = 111	N = 106	N = 115
Male gender, %	52.0	67.6	63.2	54.8
Race, %				
Caucasian	61.8	64.0	63.2	59.1
Black	25.2	19.8	27.4	30.4
Asian	8.9	9.9	9.4	10.4
Other	4.1	6.3	0.0	0.0
Mean (range) age (years)	40.1 (18, 70)	38.0 (18, 69)	37.1 (19, 68)	39.0 (18, 67)
Mean (range) weight (kg)	74.5 (45, 120)	77.6 (48, 135)	77.8 (39, 154)	76.5 (42, 128)
Schizophrenia diagnosis, %				
Paranoid	91.9	91.0	89.6	89.6
Disorganized	0.8	1.8	2.8	1.7
Catatonic	0.0	0.0	0.0	0.9
Undifferentiated	7.3	7.2	7.5	7.8

BID = twice daily

Table 8 Summary of subject disposition, Trial 041023

	Placebo	Asenapine BID		Haloperidol 4 mg BID	Total
		5 mg	10 mg		
All-Subjects-Randomized	123	114	106	115	458
All-Subjects-Treated	123	111	106	115	455
Intent-to-Treat	122	109	105	112	448
Completed	70 (56.9)	70 (63.1)	71 (67.0)	68 (59.1)	279 (61.3)
Discontinued	53 (43.1)	41 (36.9)	35 (33.0)	47 (40.9)	176 (38.7)
AE/SAE	13 (10.6)	5 (4.5)	10 (9.4)	12 (10.4)	40 (8.8)
Disease under study	9 (7.3)	2 (1.8)	9 (8.5)	6 (5.2)	26 (5.7)
Lack of efficacy	22 (17.9)	12 (10.8)	8 (7.5)	4 (3.5)	46 (10.1)
Withdrew consent	13 (10.6)	21 (18.9)	11 (10.4)	26 (22.6)	71 (15.6)
Lost to follow-up	2 (1.6)	3 (2.7)	2 (1.9)	4 (3.5)	11 (2.4)
Other	3 (2.4)	0 (0.0)	4 (3.8)	1 (0.9)	8 (1.8)

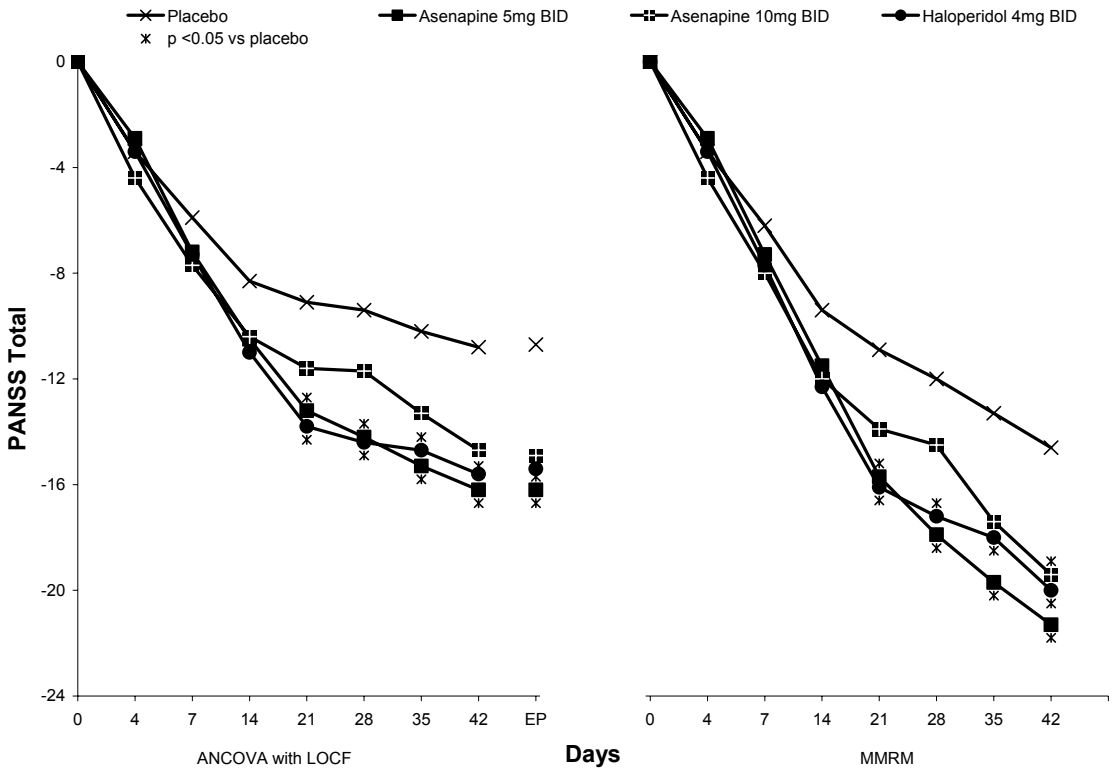
AE = adverse event; BID = twice daily; SAE = serious adverse event

Subject demographics, history of schizophrenic illness, and extent of disease at trial entry appeared to be similar across treatment groups with the following exceptions: (1) The proportion of men was lower in the placebo (52.0%) and haloperidol (54.8%) treatment groups than in the asenapine 5 mg BID (67.6%) or 10 mg BID (63.2%) treatment groups, and (2) The duration of the current episode of schizophrenia was greater than 1 year in 15.7% of subjects treated with haloperidol versus 7.5 to 9.9% of subjects in the other treatment groups. Mean scores at baseline on all efficacy parameters were similar across treatment groups.

Primary efficacy analysis

The primary efficacy analysis demonstrated that treatment with asenapine 5 mg twice daily was statistically significantly ($p < 0.05$) more effective than placebo in reducing the symptoms of schizophrenia, as measured by change from baseline to Day 42/endpoint in PANSS total score. Statistically significant differences in favor of asenapine 5 mg twice daily relative to placebo were consistently apparent starting on Day 21 (Figure 7).

Figure 7 Trial 041023 primary efficacy parameter: Change from baseline in total PANSS score



Baseline mean: Placebo: 89.0; Asenapine 5 mg BID: 88.9; Asenapine 10 mg BID: 89.4; Haloperidol 4 mg BID: 88.5

ANOVA = analysis of variance; BID = twice daily; EP = endpoint; LOCF = last observation carried forward; MMRM = mixed model for repeated measures; PANSS = Positive and Negative Syndrome Scale

Analyses of the primary efficacy endpoint, Trial 041023

According to the primary analysis (ANCOVA with LOCF), no statistically significant difference between asenapine 10 mg twice daily and placebo was observed in change from baseline to Day 42/endpoint endpoint in the PANSS total score. Change from baseline to Day 42/endpoint in the PANSS total score was statistically significantly greater in the haloperidol treatment group compared with the placebo treatment group ($p < 0.05$).

Statistical analysis of the change from baseline in PANSS total scores using MMRM analysis confirmed the primary findings of the LOCF analysis for asenapine 5 mg twice daily. Treatment with asenapine 5 mg twice daily and asenapine 10 mg twice daily resulted in a statistically significantly greater change from baseline to Day 42 in the PANSS total score compared with that in the placebo treatment group by MMRM analysis ($p < 0.05$). Statistically significant differences in favor of asenapine 5 mg twice daily relative to placebo were consistently apparent starting on Day 21. Using an MMRM analysis, Day 42 change from baseline in PANSS total score was statistically significantly greater in the haloperidol treatment group compared with the placebo treatment group ($p < 0.05$), starting at Day 21.

Statistical analysis of the change from baseline in the PANSS total scores using the OC method confirmed the primary findings of the LOCF analysis for asenapine 5 mg twice daily. In the OC analysis of the primary endpoint, a statistically significant difference in favor of asenapine 10 mg twice daily compared with placebo was observed (Table 9).

Table 9 Analyses of the primary efficacy endpoint, Trial 041023

	Inferential analysis of change from baseline in PANSS total score (ANCOVA with LOCF, ITT group)				**Inferential analysis of change from baseline in PANSS total score (ANCOVA with OC, ITT group)**				**MMRM analysis of change from baseline in PANSS total score (ITT Group)**			
	Placebo	Asenapine BID		Haloperidol	Placebo	Asenapine BID		Haloperidol	Placebo	Asenapine BID		Haloperidol
	N = 122	5 mg N = 109	10 mg N = 105	4 mg BID N = 112	***N***	5 mg ***N***	10 mg ***N***	4 mg BID ***N***	N = 122	5 mg N = 109	10 mg N = 105	4 mg BID N = 112
BL LS mean (SE)	89.0(0.9)	88.9 (1.0)	89.4 (1.0)	88.5 (1.0)	***122*** 89.0 (0.92)	***109*** 88.9 (0.97)	***105*** 89.4 (0.99)	***112*** 88.5 (0.96)	89.0 (0.9)	88.9 (1.0)	89.4 (1.0)	88.5 (1.0)
95% CI	87.2, 90.8	87.0, 90.8	87.4, 91.3	86.7,90.4	87.2, 90.8	87.0, 90.8	87.4, 91.3	86.7, 90.4	87.2, 90.8	87.0, 90.8	87.4, 91.3	86.7, 90.4
LS Mean (SE) Δ to:												
Day 4	-3.4 (0.7)	-2.9 (0.8)	-4.4 (0.8)	-3.4 (0.8)	***122*** -3.4 (0.7)	***109*** -2.9 (0.8)	***105*** -4.4 (0.8)	***111*** -3.4 (0.8)	-3.4 (0.7)	-2.9 (0.8)	-4.4 (0.8)	-3.4 (0.8)
Day 7	-5.9 (0.9)	-7.2 (1.0)	-7.7 (1.0)	-7.3 (1.0)	***114*** -6.8 (0.9)	***105*** -7.6 (1.0)	***99*** -8.6 (1.00)	***104*** -8.1 (1.0)	-6.2 (0.9)	-7.3 (1.0)	-8.0 (1.0)	-7.7 (1.0)
Day 14	-8.3 (1.1)	-10.5 (1.2)	-10.4 (1.2)	-11.0 (1.2)	***105*** -10.0 (1.2)	***92*** -11.9 (1.2)	***93*** -13.0 (1.2)	***94*** -13.0 (1.2)	-9.4 (1.2)	-11.5 (1.3)	-12.0 (1.3)	-12.3 (1.2)
Day 21	-9.1 (1.3)	-13.2 (1.4)*	-11.6 (1.4)	-13.8 (1.4)*	***96*** -13.1 (1.2)	***80*** -17.1 (1.4)*	***87*** -15.8 (1.3)	***83*** -17.2 (1.3)*	-10.9 (1.3)	-15.7 (1.4)*	-13.9 (1.4)	-16.1 (1.4)*
Day 28	-9.4 (1.4)	-14.2 (1.5)*	-11.7 (1.5)	-14.4 (1.5)*	***85*** -15.1 (1.4)	***74*** -20.1 (1.5)*	***77*** -17.9 (1.4)	***73*** -17.8 (1.5)	-12.0 (1.4)	-17.9 (1.5)*	-14.5 (1.5)	-17.2 (1.5)*
Day 35	-10.2 (1.5)	-15.3 (1.6)*	-13.3 (1.6)	-14.7 (1.5)*	***75*** -16.7 (1.4)	***71*** -22.0 (1.5)*	***71*** -21.2 (1.4)*	***70*** -19.3 (1.4)	-13.3 (1.5)	-19.7 (1.6)*	-17.4 (1.6)	-18.0 (1.6)*
Day 42	-10.8 (1.6)	-16.2 (1.7)*	-14.7 (1.7)	-15.6 (1.6)*	***68*** -19.1 (1.5)	***70*** -23.9 (1.5)*	***67*** -23.2 (1.5)*	***64*** -21.9 (1.5)	-14.6 (1.6)	-21.3 (1.7)*	-19.4 (1.7)*	-20.0 (1.7)*
Endpoint	-10.7 (1.6)	-16.2 (1.7)*†	-14.9 (1.7)	-15.4 (1.6)*								

* indicates p≤0.05, p-values are based on the difference in the LS means for active treatment versus placebo

† indicates adjusted p≤0.05. Adjusted p-values were determined using Hochberg method for testing 2 asenapine groups versus the placebo group.

An ANCOVA model with treatment and pooled investigative site as fixed effects and baseline as a covariate was used.

A mixed model with fixed effects for treatment, pooled investigator site, visit, treatment by visit interaction, and a covariate for baseline value was used. Covariance structure: UN (Unstructured)

ANCOVA = analysis of covariance; BL = baseline; CI = confidence interval; LOCF = last observation carried forward; MMRM = mixed model for repeated measures; N = total number of subjects in the ITT group; PANSS = Positive and Negative Syndrome Scale; SE = standard error

Secondary efficacy analyses

- A statistically significant treatment effect was apparent for asenapine 5 mg twice daily at Day 42/endpoint on the PANSS positive and general psychopathology subscale scores, the PANSS Marder positive symptoms and disorganized thoughts factor scores, the PANSS (30%) and CGI-I responder rates, and the CGI-S score.

- Asenapine 10 mg twice daily was superior (statistically significant) to placebo in reducing the positive symptoms of schizophrenia, as measured by changes from baseline to Day 42/endpoint on both the PANSS positive subscale and Marder positive symptoms factor. The higher dose also resulted in a statistically significantly greater proportion of PANSS (30%) responders at endpoint compared with placebo.

- According to MMRM analysis, a statistically significant treatment effect was seen for asenapine 5 mg twice daily and 10 mg twice daily on select secondary efficacy measures at Day 42. For the asenapine 5 mg BID group, these included the PANSS positive, negative, and general psychopathology subscale scores, the PANSS Marder positive symptoms, anxiety/depression, disorganized thoughts factor scores, and the CGI-S score at Day 42 as well as at various earlier time points. For the asenapine 10 mg BID group, these included the PANSS positive subscale score and the PANSS Marder positive factor at Day 42 and the CGI-S at Day 42 as well as various earlier time points.

- Using an MMRM analysis, change from baseline in PANSS total score was statistically significantly greater in the haloperidol treatment group compared with the placebo treatment group ($p < 0.05$) starting at Day 21, as well as at various time points on other select secondary parameters.

Conclusion

Short-term treatment with asenapine at the 5 mg twice daily dose level was effective in the treatment of subjects with schizophrenia in Trial 041023. The 10 mg twice daily dose level was significantly superior to placebo on the primary endpoint according to MMRM analysis and ANCOVA analysis using the OC method.

3.1.5.3. Trial 041021 results (supportive trial)

This phase 3 trial was conducted at 45 sites that enrolled subjects, including 31 in the United States, 5 in Russia, and 9 in Ukraine. Subjects were randomly assigned to receive placebo, 5 mg asenapine twice daily, 10 mg asenapine twice daily, or olanzapine 15 mg once daily. Of 417 subjects randomly assigned to treatment, 408 subjects received double-blind trial medication: placebo, 100 subjects; asenapine 5 mg BID, 104 subjects; asenapine 10 mg BID, 102 subjects; and olanzapine 15 mg QD, 102 subjects. A total of 386 subjects were included in the ITT group: placebo, 93 subjects; asenapine

5 mg BID, 102 subjects; asenapine 10 mg BID, 96 subjects; olanzapine 15 QD, 95 subjects. Subject characteristics and disposition are tabulated below (Table 10, Table 11).

Table 10 Summary of subject characteristics, Trial 041021

	Placebo	Asenapine BID		Olanzapine 15 mg QD
	N = 100	5 mg N = 104	10 mg N = 102	N = 102
Male gender, %	58.0	74.0	70.6	78.4
Race, %				
Caucasian	46.0	48.1	48.0	43.1
Black	45.0	45.2	43.1	46.1
Asian	0.0	2.9	2.0	2.0
Other	9.0	3.8	6.9	8.8
Mean (range) age (years)	39.5 (18, 62)	40.4 (18, 70)	41.2 (18, 60)	39.7 (19, 61)
Mean (range) weight (kg)	83.0 (47, 133)	81.9 (48, 132)	83.9 (55, 179)	85.9 (53, 159)
Schizophrenia diagnosis, %				
Paranoid	87.0	89.4	90.2	87.3
Disorganized	1.0	1.0	2.0	2.0
Undifferentiated	12.0	9.6	7.8	10.8

BID = twice daily; QD = once daily

Table 11 Summary of subject disposition, Trial 041021

	Placebo	Asenapine BID		Olanzapine 15 mg QD	Total
		5 mg	10 mg		
All-Subjects-Randomized	106	106	102	103	417
All-Subjects-Treated	100	104	102	102	408
Intent-to-Treat	93	102	96	95	386
Completed	50 (50.0)	60 (57.7)	51 (50.0)	58 (56.9)	219 (53.7)
Discontinued					
AE/SAE	11 (11.0)	8 (7.7)	10 (9.8)	10 (9.8)	39 (9.6)
Disease under study	10 (10.0)	6 (5.8)	3 (2.9)	4 (3.9)	23 (5.6)
Lack of efficacy	16 (16.0)	9 (8.7)	12 (11.8)	8 (7.8)	45 (11.0)
Withdrew consent	15 (15.0)	13 (12.5)	17 (16.7)	11 (10.8)	56 (13.7)
Lost to follow-up	3 (3.0)	7 (6.7)	3 (2.9)	7 (6.9)	20 (4.9)
Other	5 (5.0)	7 (6.7)	9 (8.8)	8 (7.8)	29 (7.1)

AE = adverse event; BID = twice daily; QD = once daily; SAE = serious adverse event

Subject demographics, history of schizophrenic illness, and extent of disease at trial entry appeared to be similar across treatment groups with the following exceptions: (1) The proportion of men was lower in the placebo treatment group (58.0%) than the other groups (70.6-78.4%); (2) The duration of the current episode of schizophrenia was less than 1 month in 60.8% of olanzapine-treated subjects versus 50.0-52.9% in the other treatment groups, and greater than 1 year in 16.7% of subjects treated with asenapine 10 mg twice daily versus 6.9-12.0% of subjects in the other treatment groups; and (3) The time since onset of schizophrenia was 20 or more years prior to the start of the trial in greater than 40% of subjects treated with asenapine 10 mg twice daily or olanzapine versus 28.0% of subjects treated with placebo. Mean scores at baseline on all efficacy parameters were similar across treatment groups.

Analyses of the primary efficacy endpoint, Trial 041021

No statistically significant difference in change from baseline to Day 42/endpoint in the PANSS total score was observed between placebo and asenapine 5 mg twice daily or between placebo and asenapine 10 mg twice daily according to the primary analysis. Compared with placebo, olanzapine treatment resulted in a statistically significantly greater change from baseline to Day 42/endpoint in the PANSS total score.

Statistical analysis of the change from baseline in PANSS total score using MMRM analysis was consistent with the findings of the primary analysis. Using an MMRM analysis, no statistically significant difference in the change from baseline to endpoint in the PANSS total score was observed between placebo and asenapine 5 mg twice daily or between placebo and asenapine 10 mg twice daily. Using MMRM analysis, a statistically significant difference in the mean change from baseline to endpoint in the PANSS total score was observed between placebo and olanzapine at Day 42 as well as at earlier time points (Table 12).

Table 12 Analyses of the primary efficacy endpoint, Trial 041021

	Inferential analysis of change from baseline in PANSS total score (ANCOVA with LOCF, ITT group)				Inferential analysis of change from baseline in PANSS total score (ANCOVA with OC, ITT group)				MMRM analysis of change from baseline in PANSS total score (ITT Group)			
	Placebo	Asenapine BID		Olanzapine	Placebo	Asenapine BID		Olanzapine	Placebo	Asenapine BID		Olanzapine
		5 mg	10 mg	15 mg QD		5 mg	10 mg	15 mg QD		5 mg	10 mg	15 mg QD
	N=93	N=102	N=96	N=95	***N***	***N***	***N***	***N***	N=93	N=109	N=105	N=95
LS mean					***93***	***102***	***96***	***95***				
(SE) at BL	93.7 (1.1)	90.8 (1.0)	93.2 (1.1)	92.6 (1.1)	93.7 (1.1)	90.8 (1.0)	93.2 (1.1)	92.6 (1.1)	93.7 (1.1)	90.8 (1.0)	93.2 (1.1)	92.6 (1.1)
95% CI	91.7 , 95.8	88.8, 92.8	91.1, 95.3	90.5, 94.7	91.7 , 95.8	88.8, 92.8	91.1, 95.3	90.5, 94.7	91.7 , 95.8	88.8, 92.8	91.1, 95.3	90.5, 94.7
LS Mean (SE) Δ to:												
					92	***102***	***93***	***93***				
Day 4	-3.9 (.8)	-4.0 (0.8)	-5.5 (0.8)	-3.3 (0.8)	-3.9 (0.79)	-4.0 (0.76)	-5.5 (0.80)	-3.3 (0.80)	-3.9 (0.8)	-4.0 (0.8)	-5.5 (0.8)	-3.3 (0.8)
					90	***97***	***91***	***92***				
Day 7	-6.5 (1.0)	-7.8 (1.0)	-8.8 (1.0)	-7.1 (1.0)	-6.6 (1.04)	-7.7 (1.03)	-9.2 (1.06)	-7.4 (1.05)	-6.4 (1.0)	-7.6 (1.0)	-8.9 (1.0)	-7.2 (1.0)
					82	***93***	***86***	***85***				
Day 14	-9.8 (1.3)	-13.1 (1.3)	-11.5 (1.3)	-11.6 (1.3)	-11.6 (1.21)	-14.4 (1.15)	-14.0 (1.19)	-13.2 (1.21)	-10.0 (1.4)	-13.1 (1.3)	-11.9 (1.4)	-11.8 (1.4)
					69	***80***	***69***	***69***				
Day 21	-10.5 (1.4)	-12.9 (1.4)	-11.9 (1.4)	-12.8 (1.4)	-13.4 (1.44)	-14.7 (1.36)	-16.0 (1.45)	-15.9 (1.48)	-11.1 (1.6)	-13.3 (1.5)	-13.7 (1.6)	-14.0 (1.6)
					60	***69***	***61***	***64***				
Day 28	-10.7 (1.5)	-14.0 (1.5)	-12.0 (1.5)	-14.6 (1.5)	-15.6 (1.61)	-17.6 (1.55)	-16.8 (1.63)	-17.9 (1.62)	-11.4 (1.7)	-15.2 (1.6)	-14.2 (1.7)	-16.7 (1.7)*
					55	***62***	***56***	***62***				
Day 35	-10.2 (1.6)	-14.5 (1.5)*	-13.1 (1.6)	-15.8 (1.6) *	-16.4 (1.74)	-19.7 (1.68)	-19.1 (1.76)	-19.9 (1.69)	-11.6 (1.8)	-16.3 (1.7)	-16.3 (1.8)	-18.7 (1.8)*
					50	***58***	***52***	***57***				
Day 42	-11.1 (1.6)	-14.4 (1.6)	-13.5 (1.6)	-16.5 (1.6) *	-18.1 (1.90)	-19.7 (1.84)	-19.9 (1.93)	-20.7 (1.89)	-13.2 (2.0)	-16.4 (1.8)	-17.1 (1.9)	-19.9 (1.9)*
Endpoint	-11.1 (1.6)	-14.5 (1.6)	-13.4 (1.6)	-16.5 (1.6) *								

* indicates p≤0.05, p-values are based on the difference in the LS means for active treatment versus placebo

An ANCOVA model with treatment and pooled investigative site as fixed effects and baseline as a covariate was used.

A mixed model with fixed effects for treatment, pooled investigator site, visit, treatment by visit interaction, and a covariate for baseline value was used. Covariance structure: UN (Unstructured)

ANCOVA = analysis of covariance; BL = baseline; CI = confidence interval; LOCF = last observation carried forward; MMRM = mixed model for repeated measures; N = total number of subjects in the ITT group; PANSS = Positive and Negative Syndrome Scale; SE = standard error

Secondary efficacy analyses

- Asenapine 5 mg twice daily treatment resulted in statistically significantly greater decreases from baseline to Day 42/endpoint than placebo in the PANSS positive subscale score, Marder positive symptoms factor score, and the PANSS Marder hostility/excitement factor score. Asenapine 10 mg twice daily was not different from placebo on any of the PANSS subscale or Marder factor scores at Day 42/endpoint, but the earliest statistically significant response (Day 4) on the PANSS positive subscale and PANSS Marder positive symptom factor for any group was seen with this treatment.

- Using MMRM analysis, a statistically significant treatment effect was seen for asenapine 5 mg on the PANSS positive subscale and the Marder hostility/excitement factor at Day 42 as well as at various earlier time points in these and other secondary assessments. For the asenapine 10 mg BID group, statistically significant treatment effects were seen on various select secondary measures at earlier time points but not at Day 42.

- Using MMRM analysis, a statistically significant treatment effect was seen for olanzapine on the PANSS positive and general psychopathology scales; the PANSS Marder positive, disorganized thought, and hostility/excitement factors; and the CGI-S at Day 42 and earlier time points.

- Statistical analysis of the change from baseline in the PANSS total score using the observed-case method was consistent with the findings of the LOCF analysis.

- The proportion of PANSS (30%) responders at endpoint was significantly greater in the asenapine 5 mg BID treatment group than in the placebo treatment group.

Conclusion

Asenapine at the 5 mg twice daily and 10 mg twice daily dose levels did not achieve statistical significance on the primary endpoint, change from baseline to endpoint in the PANSS total score, in Trial 041021. Statistical significance was achieved at various time points on select secondary endpoints. Compared with placebo, olanzapine treatment resulted in a statistically significantly greater change from baseline to endpoint in the PANSS total score.

3.1.6. Summary of treatment effect observed in the short-term, fixed-dose schizophrenia trials

Statistically significant improvement compared with placebo was achieved for asenapine 5 mg twice daily in Trials 041004 and 041023 on the primary efficacy endpoint, change from PANSS baseline total score to endpoint. In both trials, the decreases from baseline to Day 42/endpoint in the PANSS total score were statistically significantly ($p < 0.05$)

greater with asenapine 5 mg twice daily treatment than with placebo treatment (Table 13). Sustained, statistically significant improvement was apparent for asenapine 5 mg twice daily starting on Day 14 in Trial 041004 (Table 6) and starting on Day 21 in Trial 04023 (Table 9).

A statistically significant difference from placebo on the primary endpoint was not achieved for asenapine 10 mg twice daily according to primary efficacy analysis in Trial 041023. Statistically significant improvement ($p < 0.05$) with asenapine 10 mg twice daily treatment compared with placebo was observed on the primary endpoint according to the supportive MMRM analysis (Table 13).

A significant treatment-by-center interaction ($p < 0.0210$), driven by one site was detected in Trial 041023. Dropping this site from the analysis did not affect the primary efficacy results. The treatment by center interaction was not observed in the supportive MMRM analysis.

The primary efficacy endpoint results were negative for the risperidone active comparator in Trial 041004 and positive for the haloperidol active comparator in Trial 041023 (Table 6).

In Trial 041021, no statistically significant differences between asenapine 5 mg twice daily and placebo or between asenapine 10 mg twice daily and placebo were observed in the change from baseline to endpoint in PANSS total score. Results of the MMRM analysis were consistent with the primary efficacy analysis (Table 13). Olanzapine was statistically superior to placebo in reducing PANSS total scores (Table 12).

Table 13 Treatment effect change from baseline to endpoint (ANCOVA with LOCF)/Day 42 (MMRM), 95% confidence intervals, and p-values for PANSS total scores (Intent-to-Treat): Trials 041004, 041023, and 041021

Asenapine Treatment	**Trial**		
Analysis	041004	041023	041021
5 mg BID			
ANCOVA[a] with LOCF			
Estimate	−9.72	−5.48	−3.38
CI (95%)	−16.70, −2.74	−9.86, −1.09	−7.73, 0.97
p-value (adjusted p-value[b])	0.007	0.014 (0.029)	0.128 (0.256)
MMRM[c]			
Estimate	−11.33	−6.77	−3.13
CI (95%)	−20.64, −2.02	−11.37, −2.18	−8.37, 2.12
p-value (adjusted p-value)	0.018	0.004 (0.008)	0.241 (0.241)
10 mg BID			
ANCOVA[a] with LOCF			
Estimate		−4.11	−2.30
CI (95%)		−8.53, 0.31	−6.70, 2.10
p-value (adjusted p-value[b])		0.068 (0.068)	0.305 (0.305)
MMRM[c]			
Estimate		−4.86	−3.88
CI (95%)		−9.43, −0.28	−9.26 1.51
p-value (adjusted p-value[b])		0.037 (0.037)	0.157 (0.241)

Estimates, 95% confidence intervals, and p−values based on differences of LS means between active treatment and placebo.

a Based on ANCOVA model with fixed effects for treatment, pooled investigator site, and a covariate for baseline value

b Adjusted p−values by Hochberg method for multiple comparisons

c Based on a mixed model with fixed effects for treatment, pooled investigator site, visit, treatment by visit interaction, and a covariate for baseline value. Covariance structure: UN (Unstructured)

ANCOVA = analysis of covariance; BID = twice daily; CI = confidence interval; LOCF = last observation carried forward; MMRM = mixed model for repeated measures; PANSS = Positive and Negative Syndrome Scale

3.1.7. PK-PD modeling

A pooled exposure-response analysis of PANSS total score has been performed across data from the 6 short-term placebo-controlled efficacy studies for the schizophrenia indication (dose range 0.2 – 10 mg twice daily). A population pharmacokinetic-pharmacodynamic model for the time course of PANSS total score was developed using area under the curve (AUC) as measure of asenapine exposure. The results from the analysis indicated that there is a significant exposure response for asenapine on the primary endpoint in the treatment of schizophrenia. Based on this exposure-response relationship, within the proposed therapeutic dose range, 10 mg is predicted to have an overall effect on the primary endpoint score across the population that is at least of similar magnitude as the effect of 5 mg twice daily.

3.1.8. Summary

- Asenapine 5 mg twice daily was efficacious in the acute treatment of schizophrenia in two adequate and well-controlled 6-week trials. The analysis of the primary endpoint was supported by secondary analyses and analysis of secondary endpoints.

- Asenapine 10 mg twice daily was significantly superior to placebo in the acute treatment of schizophrenia in one adequate and well-controlled 6-week trial according to MMRM analysis and analysis of secondary endpoints.

3.1.9. Dosing recommendation for schizophrenia

The recommended starting and target dose of asenapine is 5 mg given twice daily. In controlled trials, there was no suggestion of added benefit with the higher dose, but there was a clear increase in certain adverse reactions. The safety of doses above 10 mg twice daily has not been evaluated in clinical trials.

3.2. Bipolar disorder

3.2.1. General information and background

For the evaluation of the therapeutic effects of asenapine in subjects with acute manic or mixed episodes associated with bipolar I disorder, data from 3 dedicated trials (A7501004, A7501005, and A7501006) that were completed as of the NDA cutoff date of January 15, 2007 have been analyzed (Table 14). Trials A7501004 and A7501005 were identical 3-week, randomized, double-blind, placebo- and comparator- (olanzapine) controlled trials of asenapine in subjects who met DSM-IV-TR diagnostic criteria for acute manic or mixed episodes associated with bipolar I disorder and are considered to provide the primary data in support of the efficacy of asenapine in bipolar mania. Trial A7501006 was a 9-week extension trial that provided supportive data. Two trials in bipolar mania were ongoing as of the NDA cutoff (Table 15).

The data presented in the NDA support the following conclusion:

- Asenapine at flexible doses of 5 to 10 mg twice daily (with a 10 mg starting dose and the option to downtitrate to 5 mg) was efficacious in the acute treatment of manic or mixed episodes associated with bipolar I disorder in two adequate and well-controlled 3-week trials.

Table 14 Overview of completed trials in the asenapine bipolar mania clinical development program

Trial & Design	Dates	Treatments[a]	Dosing Regimen	Number of subjects evaluable for efficacy[b,c]		
				placebo	asenapine	olanzapine
A7501004 DB, PC, AC 21-day treatment	30 Nov 2004 – 29 April 2006 (last Day 30 follow up)	asenapine olanzapine placebo	10 mg SL BID on Day 1, then 5-10 mg SL BID Days 2-21 15 mg PO QD on Day 1, then 5-20 mg PO QD Days 2-21 SL BID, PO QD	94	183	203
A7501005 DB, PC, AC 21-day treatment	14 Dec 2004 – 28 April 2006 (last Day 30 follow up)	asenapine olanzapine placebo	10 mg SL BID on Day 1, then 5-10 mg SL BID Days 2-21 15 mg PO QD on Day 1, then 5-20 mg PO QD Days 2-21 SL BID, PO QD	103	189	188
A7501006 DB, AC 63-day treatment	07 Jan 2005 – 28 June 2006	asenapine[d] asenapine olanzapine	10 mg SL BID on Day 1, then 5-10 mg SL BID Days 2-63 5-10 mg SL BID 5-20 mg PO QD	--	173	221

a Asenapine administered as fast-dissolving tablets; olanzapine as film-coated tablets

b For protocols A7501004 and A7501005, represents the intent-to-treat group (ITT, full analysis set), defined as all randomized subjects who took at least one dose of double-blind study medication and had at least one post-baseline YMRS assessment.

c For protocol A7501006, the sample size represents the per-protocol population, defined as randomized subjects assigned to active treatment in A7501004/ A7501005 who had at least one YMRS assessment during the extension period and had no major protocol violations.

d Blinded transfer of 94 placebo subjects from A7501004/A7501005 into asenapine treatment group

AC = active controlled; BID = twice daily; DB = double-blind; NDA = New Drug Application; PC = placebo-controlled; PO = by mouth; QD = once daily; SL = sublingual

Table 15 Overview of trials in the bipolar mania clinical development program that were ongoing as of the NDA cut-off date of 15-January-2007

Trial	Description
A7501007 (extension to A7501006)	40 week extension trial (after treatment of acute manic episode) asenapine 5-10 mg BID, olanzapine 5-20 mg QD, placebo→ asenapine (during A7510006). Current Status: Complete
A7501008	12 weeks adjunctive treatment (lithium or VPA) of acute mania associated with bipolar I disorder asenapine 5-10 mg BID, placebo. Current Status: Complete
A7501009 (extension to A7501008)	40 week extension. Current Status: Complete

BID= twice daily, NDA = New Drug Application; PO= by mouth, QD= once daily, VPA= valproic acid or divalproex sodium or sodium valproate

3.2.2. Dose selection for the bipolar mania indication

The dose selection for asenapine sublingual tablets was based on the following:

Antipsychotic drugs, which effectively treat schizophrenia and bipolar mania, usually are effective in the same dose range for both indications.

In clinical practice the starting dose for acute manic patients is usually chosen at the higher end of the effective dose range for antipsychotic drugs, with the intention to quickly achieve effective control of manic symptoms.

Dose finding data from the schizophrenia trials indicated that the effective dose range was predicted to be between 5 and 10 mg twice daily, with lower doses displaying too low D_2 occupancy, and with higher doses anticipated to induce EPS at a higher and undesired frequency.

Therefore, the initial dose was chosen to be 10 mg twice daily, with the option to downtitrate to 5 mg twice daily in a flexible dose design according to tolerability and safety requirements.

3.2.3. Efficacy assessments

For the pivotal 3-week trials, Trials A7501004 and A7501005, the primary endpoint was defined as the change from baseline to the end of treatment on the Young Mania Rating Scale (YMRS), a validated, widely used and well-established instrument. The primary comparison was the change in total YMRS score from baseline to Week 3/end of treatment between asenapine and placebo. Rater-administered efficacy scales, such as the YMRS, were administered at each site by a trained rater.

The primary efficacy endpoint in the supportive extension trial, Trial A7501006, was the change from baseline (of the feeder trial) to end of treatment on the YMRS. The primary comparison was the change in total YMRS scores from baseline to Week 12/end of treatment between asenapine and olanzapine.

Table 16 lists the primary and select secondary efficacy measures used in the bipolar mania trials and provides a brief description of each.

Table 16 Select efficacy measures in bipolar mania trials

Parameter	Measure
Primary efficacy rating measure	
Mania symptoms	Young Mania Rating Scale (YMRS): an 11-item clinician-rated instrument for assessing the symptoms of mania. Minimum and maximum scores: 0 to 60.
Select secondary efficacy rating measures	
Global severity of illness	Clinical Global Impressions scale for use in Bipolar Disorder (CGI BP): a 7-point clinician-rated scale for assessing the severity and change from preceding phase of illness of manic, depressive, and overall symptoms of bipolar disorder during the treatment of an acute episode or in longer-term illness prophylaxis. Minimum and maximum scores: 0 to 7

3.2.4. Trials in bipolar mania

Men and women with bipolar I disorder who were at least 18 years old were eligible for Trials A7501004 and A7501005 if they had a primary diagnosis of bipolar I disorder, current episode manic (DSM-IV 296.4x) or mixed (DSM-IV 296.6x), were experiencing an acute phase of mania of less than 3 months duration, had a minimum YMRS score of 20, and had at least one prior moderate to severe mood (manic or mixed) episode.

Eligible subjects were randomly assigned to asenapine, olanzapine, or placebo treatment in a ratio of 2:2:1. The active treatment period was initiated on Day 1 with placebo, asenapine 10 mg twice daily, or olanzapine 15 mg once daily. From Day 2 onward, active treatment was continued with flexible dosing of asenapine (5-10 mg twice daily) and olanzapine (5-20 mg once daily), with the dose selection based on efficacy, safety, and tolerability. Subjects were confined to an inpatient research facility through at least Day 7, but were subsequently discharged if deemed clinically stable by the investigator.

Subjects who completed trial A7501004 or A7501005 without a major protocol violation were eligible for participation in the 9-week extension trial A7501006.

3.2.4.1. Trial A7501004 results (pivotal trial)

Trial A7501004 was conducted at 61 centers in 9 countries, including the US (32 sites), Bulgaria (2), India (6), Korea (2), Malaysia (3), Philippines (3), Romania (2), Russia (4), the Ukraine (7). Of 488 subjects randomly assigned to treatment, all (98 placebo, 185 asenapine, and 205 olanzapine) were assessed for safety and 480 (94 placebo, 183 asenapine, and 203 olanzapine) were assessed for efficacy. A total of 342 (57 placebo, 124 asenapine, 161 olanzapine) subjects completed the trial. The overall total mean daily dose of asenapine in this trial was 18.4 mg, and the overall extent of exposure to asenapine in this trial was 3090 subject-days.

Approximately 30% of the included subjects fulfilled the criteria for a current mixed episode (DSM-IV 296.6x) and approximately 70% fulfilled the criteria for manic episodes (DSM-IV 296.4x). The percentage of male subjects was 52.7% in A7501004. In accordance with the protocol, no subjects were less than 18 years of age. A small percentage of subjects was 65 years of age or older (2.0%). With respect to race, 55.1% of the subjects were Caucasian, 21.7% Asian, 19.5% Black, and 3.7% belonged to other racial groups. Subject disposition is tabulated below (Table 17).

Table 17 Summary of subject disposition, Trial A7501004

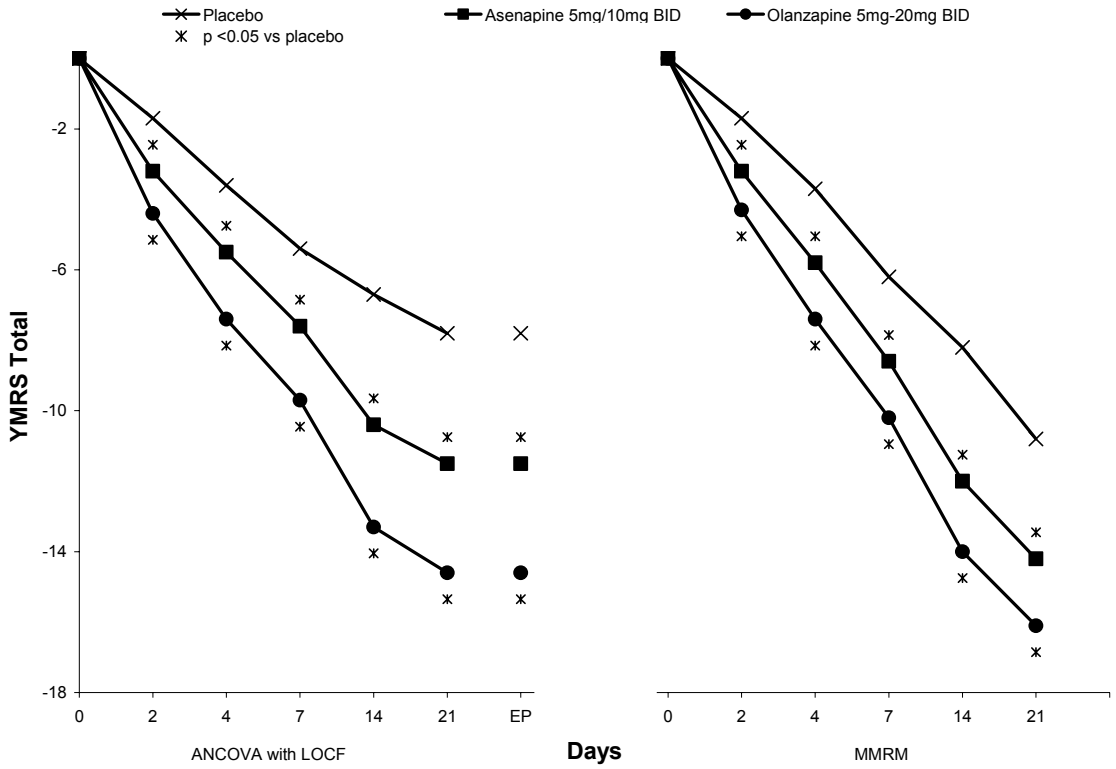
	Placebo	Asenapine 5-10 mg BID	Olanzapine 5-20 mg QD	Total
All-Subjects-Randomized	98	185	205	488
All-Subjects-Treated	98	185	205	488
Intent-to-Treat	94	183	203	480
Completed	57 (58.2)	124 (67.0)	161 (78.5)	342 (70.1)
Discontinued	41 (41.8)	61 (33.0)	44 (21.5)	146 (29.9)
AE/SAE	4 (4.1)	17 (9.2)	7 (3.4)	28 (5.7)
Disease under study	4 (4.1)	6 (3.2)	2 (1.0)	12 (2.5)
Lack of efficacy	14 (14.3)	14 (7.6)	13 (6.3)	41 (8.4)
Withdrew consent	13 (13.3)	25 (13.5)	15 (7.3)	53 (10.9)
Lost to follow-up	4 (4.1)	1 (0.5)	6 (2.9)	11 (2.3)
Other	6 (6.1)	4 (2.2)	3 (1.5)	13 (2.7)

AE = adverse event; BID = twice daily; QD = once daily; SAE = serious adverse event

Primary efficacy analysis

The primary efficacy analysis demonstrated that asenapine at flexible doses of 5 mg twice daily to 10 mg twice daily (with 10 mg as the starting dose and the option to downtitrate to 5 mg) was statistically significantly ($p < 0.05$) more effective than placebo in reducing the symptoms of mania, as measured by change from baseline to Day 21/endpoint in the YMRS total score. Sustained statistically significant ($p < 0.05$) improvement in the primary efficacy variable (YMRS) compared with placebo was noted for asenapine at Day 2 onwards (Figure 8). A treatment-by-center interaction was observed for the primary endpoint.

Figure 8 Trial A7501004 primary efficacy parameter: Change from baseline in YMRS total score



LOCF Baseline mean: Placebo: 28.1; Asenapine 5/10 mg BID: 29.3; Olanzapine 5-20 mg QD: 29.7

ANOVA = analysis of variance; BID = twice daily; EP = endpoint; LOCF = last observation carried forward; MMRM = mixed model for repeated measures; YMRS = Young Mania Rating Scale

Analyses of the primary efficacy endpoint, Trial A7501004

MMRM analysis confirmed the results of the primary efficacy analysis. A treatment by center interaction was not evident with the MMRM model.

Compared with placebo, olanzapine, the active control, was statistically significantly more effective in reducing the symptoms of mania on the primary endpoint, change from baseline to Day 21/endpoint in the YMRS total score.

Table 18 Analyses of the primary efficacy endpoint, Trial A7501004

	Inferential analysis of change from baseline in YMRS total score (ANCOVA with LOCF, ITT group)			Inferential analysis of change from baseline in YMRS total score (ANCOVA with OC, ITT group)			MMRM analysis of change from baseline in YMRS total score (ITT Group)		
	Placebo N=94	Asenapine 5-10 mg BID N=183	Olanzapine 5-20 mg QD N=203	Placebo N	Asenapine 5-10 mg BID N	Olanzapine 5-20 mg QD N	Placebo N=94	Asenapine 5-10 mg BID N=183	Olanzapine 5-20 mg QD N=203
Baseline LS mean (SE)	28.1 (0.59)	29.3 (0.42)	29.7 (0.40)	***94*** 28.1 (0.59)	***183*** 29.3 (0.42)	***203*** 29.7 (0.40)	28.1 (0.59)	29.3 (0.42)	29.7 (0.40)
95% CI*	26.9, 29.2	28.5, 30.2	28.9, 30.5	26.9, 29.2	28.5, 30.2	28.9, 30.5	26.9, 29.2	28.5, 30.2	28.9, 30.5
Mean (SE) Δ to:									
Day 2	-1.7 (0.54)	-3.2 (0.40) *	-4.4 (0.37) *	***93*** -1.7 (0.54)	***175*** -3.2 (0.40) *	***200*** -4.4 (0.37) *	-1.7 (0.55)	-3.2 (0.4) *	-4.3 (0.37) *
Day4	-3.6 (0.65)	-5.5 (0.46) *	7.4 (0.44) *	***85*** -4.1 (0.66)	***170*** -5.8 (0.47) *	***185*** -7.4 (0.45) *	-3.7 (0.66)	-5.8 (0.47) *	-7.4 (0.45) *
Day 7	-5.4 (0.80)	-7.6 (0.58) *	-9.7 (0.55) *	***66*** -7.0 (0.99)	***124*** -8.5 (0.75)	***156*** -10.2 (0.66) *	-6.2 (0.93)	-8.6 (0.68) *	-10.2 (0.62) *
Day 14	6.7 (1.02)	-10.4 (0.74) *	-13.3 (0.70) *	***71*** -9.6 (1.03)	***142*** -12.7 (0.73) *	***170*** -14.3 (0.67) *	-8.2 (1.06)	-12 (0.76) *	-14 (0.69) *
Day 21	-7.8 (1.11)	-11.5 (0.80) *	-14.6 (0.76) *	***55*** -13.6 (1.14)	***122*** -15.4 (0.77)	***155*** -16.9 (0.69) *	-10.8 (1.22)	-14.2 (0.85) *	-16.1 (0.77) *
EP	-7.9 (1.11)	-11.6 (0.80) *	-14.7 (0.76) *	***94*** -7.9 (1.11)	***183*** -11.6 (0.80) *	***203*** -14.7 (0.76) *			

* indicates p≤0.05, p-values are based on the difference in the LS means for active treatment versus placebo

An ANCOVA model with treatment and pooled investigative site as fixed effects and baseline as a covariate was used.

A mixed model with fixed effects for treatment, pooled investigator site, visit, treatment by visit interaction, and a covariate for baseline value was used. Covariance structure: UN (Unstructured)

ANCOVA = analysis of covariance; BL = baseline; CI = confidence interval; EP = endpoint; LOCF = last observation carried forward; MMRM = mixed model for repeated measures; N = total number of subjects in the ITT group; SE = standard error; YMRS = Young Mania Rating Scale

Secondary efficacy analyses

- The primary efficacy analysis result was supported by the results of the primary analysis of the CGI-BP, severity of mania and severity of overall bipolar illness, which also showed statistically significant improvements in the asenapine group compared with placebo at Day 21.

- The percentage of subjects who were Y-MRS responders (subjects with a 50% decrease from baseline in Y-MRS total score) and Y-MRS remitters (subjects with a Y-MRS total score of 12 or lower) was higher in asenapine-treated subjects compared with placebo-treated subjects. However, these treatment group differences were not statistically significant.

Conclusion

Short-term treatment with asenapine 5-10 mg twice daily in Trial A7501004 was effective in the treatment of subjects with a manic or mixed bipolar episode.

3.2.4.2. Trial A7501005 results (pivotal trial)

Trial A7501005 was conducted at 55 centers in 10 countries, including the US (29 sites), Bulgaria (2), India (6), Korea (3), Malaysia (1), Philippines (2), Romania (2), Russia (4), Turkey (2), and the Ukraine (4). Of 489 subjects randomly assigned to treatment, 488 (194 asenapine, 190 olanzapine, 104 placebo) were assessed for safety, 480 (189 asenapine, 188 olanzapine, 103 placebo) were assessed for efficacy, and 338 (122 asenapine, 152 olanzapine, 64 placebo) completed the trial. The overall total mean daily dose of asenapine in this trial was 18.2 mg. The overall extent of exposure to asenapine in this trial was 3201 subject-days.

Approximately 30% of the included subjects fulfilled the criteria for a current mixed episode (DSM-IV 296.6x) and approximately 70% fulfilled the criteria for manic episodes (DSM-IV 296.4x). The percentage of male subjects was 57.4%. In accordance with the protocol, no subjects were less than 18 years of age. A small percentage of subjects was 65 years of age or older (1.2%). With respect to race, 60.5% of the subjects were Caucasian, 18.0% Asian, 16.6% Black, and 4.9% belonged to other racial groups. Subject disposition is tabulated below (Table 19).

Table 19 Summary of subject disposition, Trial A7501005

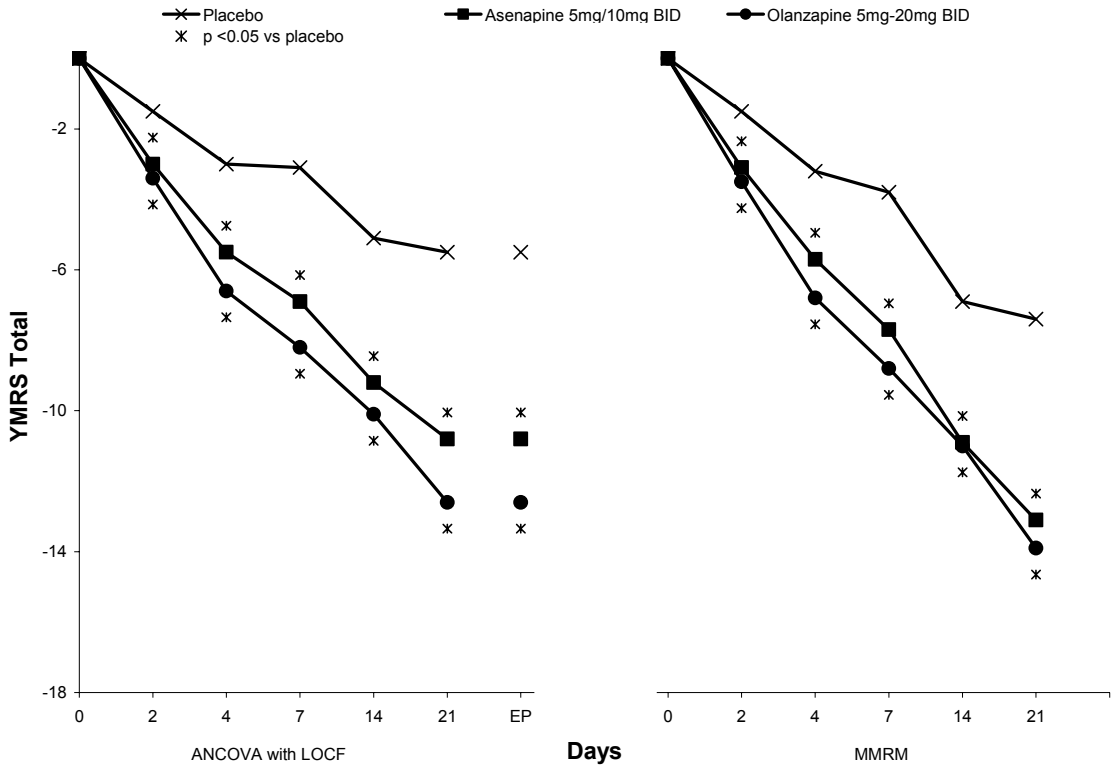
	Placebo	Asenapine 5-10 mg BID	Olanzapine 5-20 mg QD	Total
All-Subjects-Randomized	104	194	191	489
All-Subjects-Treated	104	194	190	488
Intent-to-Treat	103	189	188	480
Completed	64 (61.5)	122 (62.9)	152 (80.0)	338 (69.3)
Discontinued	40 (38.5)	72 (37.1)	38 (20.0)	150 (30.7)
AE/SAE	7 (6.7)	20 (10.3)	8 (4.2)	35 (7.2)
Disease under study	5 (4.8)	11 (5.7)	2 (1.1)	18 (3.7)
Lack of efficacy	17 (16.4)	16 (8.3)	11 (5.8)	44 (9.0)
Withdrew consent	13 (12.5)	28 (14.4)	16 (8.4)	57 (11.7)
Lost to follow-up	2 (1.9)	5 (2.6)	2 (1.1)	9 (1.8)
Other	1 (1.0)	3 (1.6)	1 (0.5)	5 (1.0)

AE = adverse event; BID = twice daily; QD = once daily; SAE = serious adverse event

Primary efficacy analysis

The primary efficacy analysis demonstrated that asenapine at flexible doses of 5 mg twice daily to 10 mg twice daily (with 10 mg as the starting dose and the option to downtitrate to 5 mg) was statistically significantly ($p < 0.01$) more effective than placebo in reducing the symptoms of mania, as measured by change from baseline to Day 21/endpoint in the YMRS total score. Sustained statistically significant ($p < 0.05$) improvement in the primary efficacy variable (YMRS) compared with placebo was noted for asenapine at Day 2 onwards (Figure 9).

Figure 9 Trial A7501005 primary efficacy parameter: Change from baseline in YMRS total score



LOCF Baseline mean: Placebo: 29.6; Asenapine 5/10 mg BID: 28.7; Olanzapine 5-20 mg QD: 29.1

ANOVA = analysis of variance; BID = twice daily; EP = endpoint; LOCF = last observation carried forward; MMRM = mixed model for repeated measures; YMRS = Young Mania Rating Scale

Analyses of the primary efficacy endpoint, Trial A7501005

Compared with placebo, the positive control olanzapine also demonstrated statistically significant improvement in symptoms of mania on the primary endpoint.

Table 20 Analyses of the primary efficacy endpoint, Trial A7501005

	Inferential analysis of change from baseline in YMRS total score (ANCOVA with LOCF, ITT group)			Inferential analysis of change from baseline in YMRS total score (ANCOVA with OC, ITT group)			MMRM analysis of change from baseline in YMRS total score (ITT Group)		
	Placebo N = 103	**Asenapine 5-10 mg BID N = 189**	**Olanzapine 5mg-20mg QD N = 188**	**Placebo *N***	**Asenapine 5-10 mg BID *N***	**Olanzapine 5mg-20mg QD *N***	**Placebo N = 103**	**Asenapine 5-10 mg BID N = 189**	**Olanzapine 5mg-20mgQD N = 188**
Baseline LS mean (SE)	29.6 (0.52)	28.7 (0.39)	29.1 (0.39)	***103*** 29.6 (0.52)	***189*** 28.7 (0.39)	***188*** 29.1 (0.39)	29.6 (0.52)	28.7 (0.39)	29.1 (0.39)
95% CI*	28.5, 30.6	27.9, 29.4	28.4, 29.9	28.5, 30.6	27.9, 29.4	28.4, 29.9	28.5, 30.6	27.9, 29.4	28.4, 29.9
Mean (SE) Δ to:									
				N=101	***N=183***	***N=182***			
Day 2	-1.5 (0.47)	-3.0 (0.35)*	-3.4 (0.35)*	-1.5 (0.47)	-3.0 (0.35)*	-3.4 (0.35)*	-1.5 (0.47)	-3.1 (0.35)*	-3.5 (0.35)*
				N=96	***N=178***	***N=174***			
Day4	-3.0 (0.56)	-5.5 (0.41)*	-6.6 (0.42)*	-3.4 (0.55)	-5.9 (0.40)*	-7.0 (0.41)*	-3.2 (0.56)	-5.7 (0.41)*	-6.8 (0.41)*
				N=67	***N=130***	***N=134***			
Day 7	-3.1 (0.72)	-6.9 (0.53)*	-8.2 (0.54)*	-3.7 (0.95)	-7.8 (0.69)*	-8.9 (0.69)*	-3.8 (0.84)	-7.7 (0.61)*	-8.8 (0.6)*
				N=77	***N=142***	***N=157***			
Day 14	-5.1 (0.92)	-9.2 (0.68)*	-10.1 (0.69)*	-8.6 (0.95)	-12.2 (0.70)*	-11.4 (0.66)*	-6.9 (0.97)	-10.9 (0.71)*	-11 (0.69)*
				N=59	***N=117***	***N=147***			
Day 21	-5.5 (1.01)	-10.8 (0.75)*	-12.6 (0.76)*	-10.0 (1.10)	-15.2 (0.78)*	-15.1 (0.70)*	-7.4 (1.14)	-13.1 (0.82)*	-13.9 (0.78)*
				N=103	***N=189***	***N=188***			
EP	-5.5 (1.01)	-10.8 (0.75)*	-12.7 (0.76)*	-5.5 (1.01)	-10.7 (0.75)*	-12.7 (0.76)*			

* indicates p≤0.05, p-values are based on the difference in the LS means for active treatment versus placebo

An ANCOVA model with treatment and pooled investigative site as fixed effects and baseline as a covariate was used.

A mixed model with fixed effects for treatment, pooled investigator site, visit, treatment by visit interaction, and a covariate for baseline value was used. Covariance structure: UN (Unstructured)

ANCOVA = analysis of covariance; BL = baseline; CI = confidence interval; EP = endpoint; LOCF = last observation carried forward; MMRM = mixed model for repeated measures; N = total number of subjects in the ITT group; SE = standard error; YMRS = Young Mania Rating Scale

Secondary efficacy analyses

- The primary efficacy endpoint analysis result was supported by the analysis of the CGI-BP, severity of mania and severity of overall bipolar illness, which also showed statistically significant improvements in the asenapine group over placebo at Day 21 with both LOCF and MMRM analyses, as well as the significantly higher rate of responders (Day 7, 14, and 21) and remitters (Day 14 and 21) in comparison to placebo.

Conclusion

Short-term treatment with asenapine 5-10 mg twice daily in Trial A7501005 was effective in the treatment of subjects with a manic or mixed bipolar episode.

3.2.4.3. Extension trial A7501006 results (supportive trial)

Trial A7501006 was conducted at 126 centers in 10 countries, including the US (68 centers), Bulgaria (4), India (12), Korea (5), Malaysia (4), Philippines (9), Romania (4), Russia (7), Turkey (2), and the Ukraine (11). The 504 subjects who received at least one dose of double-blind trial medication during this 9-week extension trial make up the all subjects-treated group (the safety analysis set). These subjects included 181 asenapine-treated and 229 olanzapine-treated subjects from the feeder trials A7501004 and A7501005, who continued on the same treatment in the extension. In addition, 94 subjects treated with placebo in the feeder trials were blindly allocated to receive asenapine (5 to 10 mg twice daily) in the extension trial.

The A7501006 ITT group (full analysis set) was comprised of 175 asenapine subjects and 222 olanzapine subjects who received at least one dose of double-blind medication and who had at least one YMRS assessment during the extension period. Subjects who received placebo in the feeder trials were not included in the ITT population. The per-protocol data set, which was used for the primary efficacy endpoint analysis, was comprised of the 394 subjects in the ITT group who did not have major protocol violations. Subject disposition is tabulated below (Table 21).

Table 21 Summary of subject disposition, Trial A7501006

	Placebo/Asenapine	Asenapine 5-10 mg BID	Olanzapine 5-20 mg QD	Total
All-Subjects-Randomized	94	181	229	504
All-Subjects-Treated	94	181	229	504
Intent-to-Treat	0	175	222	397
Per protocol	0	173	221	394
Completed	50 (53.2)	112 (61.9)	146 (63.8)	308 (61.1)
Discontinued	44 (46.8)	69 (38.1)	83 (36.2)	196 (38.9)
AE/SAE	18 (19.1)	24 (13.3)	22 (9.6)	64 (12.7)
Disease under study	9 (9.6)	16 (8.8)	11 (4.8)	36 (7.1)
Lack of efficacy	5 (5.3)	6 (3.3)	9 (3.9)	20 (4.0)
Withdrew consent	7 (7.4)	23 (12.7)	26 (11.4)	56 (11.1)
Lost to follow-up	12 (12.8)	12 (6.6)	18 (7.9)	42 (8.3)
Other	2 (2.1)	4 (2.2)	8 (3.5)	14 (2.8)

AE = adverse event; BID = twice daily; QD = once daily; SAE = serious adverse event

Primary efficacy analysis

The primary efficacy analysis demonstrated that asenapine treatment at flexible doses of 5 mg to 10 mg twice daily (with 10 mg as the starting dose and the option to downtitrate to 5 mg in the feeder trials A7501004 and A7501005), was statistically non-inferior to olanzapine in reducing the symptoms of mania, as measured by the change in YMRS total score from baseline to Day 84 (OC analysis). A significant treatment-by-center interaction was observed, due to the same trial sites as in Trial A7501004.

Secondary efficacy analyses

The primary efficacy result was supported by analysis of the CGI-BP, severity of mania and severity of overall bipolar illness and by the percentages of subjects who were YMRS responders and YMRS remitters. All were similar in the asenapine and olanzapine groups.

Conclusion

The efficacy of asenapine was not inferior to olanzapine in the treatment of subjects with a manic or mixed bipolar episode who had 3 weeks of previous exposure to study medication.

3.2.5. Summary of treatment effect observed in the pivotal mania trials

Both Trial A7501004 and A7501005 demonstrated that asenapine at flexible doses of 5 mg twice daily to 10 mg twice daily (with 10 mg as the starting dose and the option to downtitrate to 5 mg) was statistically significant more effective than placebo in reducing the symptoms of mania as measured by the YMRS total score at endpoint/Day 21. Table 22 summarizes the treatment effect change from baseline in YMRS total score for asenapine and olanzapine as estimated from the primary efficacy analysis (ANCOVA with LOCF) and from the supportive MMRM analysis in both trials.

The positive findings on primary efficacy analysis for olanzapine in both trials demonstrated that the design and conduct of the trials were adequate to assess the efficacy of asenapine in the treatment of mania.

Table 22 Treatment effect change from baseline to endpoint (ANCOVA with LOCF)/Day 21 (MMRM), 95% confidence intervals, and p-values for YMRS total scores (Intent-to-Treat): Trials A7501004 and A7501005

Treatment	Trial	
Analysis	A7501004	A7501005
Asenapine 5 mg – 10 mg BID (flexible)		
ANCOVA[a] with LOCF		
Estimate	-3.73	-5.20
CI (95%)	(−6.38, −1.09)	(−7.64, −2.77)
p-value	0.006	<.0001
MMRM[b]		
Estimate	−3.33	−5.70
CI (95%)	(−6.24, −0.41)	(−8.45, −2.94)
p-value (adjusted p-value)	0.025	<.0001
Olanzapine 5 mg – 20 mg QD (flexible)		
ANCOVA[a] with LOCF		
Estimate	-6.83	-7.12
CI (95%)	(−9.44, −4.23)	(−9.56, −4.68)
p-value	<.0001	<.0001
MMRM[b]		
Estimate	−5.25	−6.59
CI (95%)	(−8.08, −2.43)	(−9.29, −3.89)
p-value (adjusted p-value[b])	<.001	<.0001

a Based on ANCOVA model with fixed effects for treatment, pooled investigator site, and a covariate for baseline value

b Based on a mixed model with fixed effects for treatment, pooled investigator site, visit, treatment by visit interaction, and a covariate for baseline value. Covariance structure: UN (Unstructured)

P-values were not adjusted by any multiple comparison procedures.

ANCOVA = analysis of covariance; BID = twice daily; CI = confidence interval; LOCF = last observation carried forward; MMRM = mixed model for repeated measures; QD = once daily; YMRS = Young Mania Rating Scale

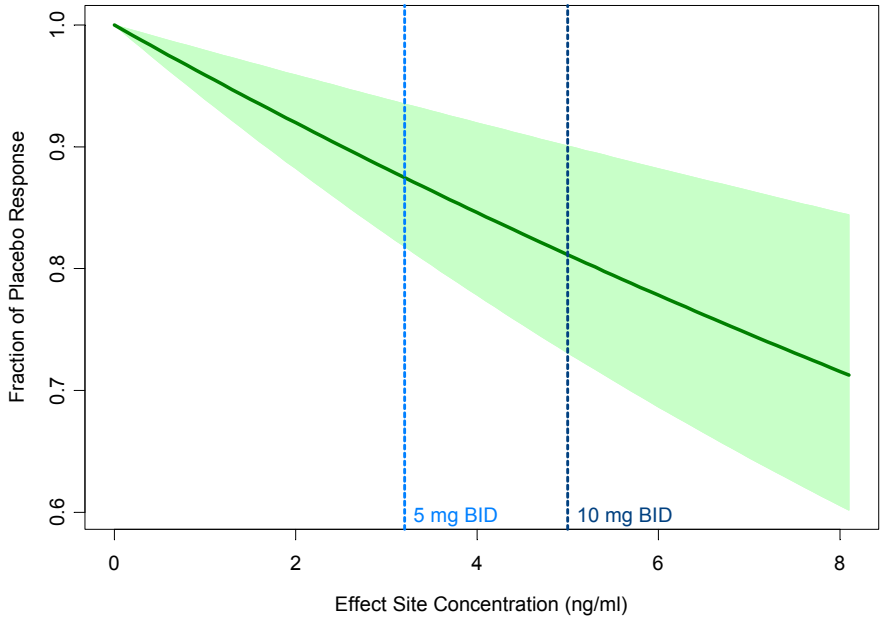
3.2.5.1. PK-PD modeling

A PK-PD analysis was performed to characterize the exposure response relationship for asenapine on the YMRS (Figure 10).

Data from the 2 short-term placebo-controlled efficacy trials in bipolar mania (dose range 5 – 10 mg twice daily) were used in an exposure response analysis. A population pharmacokinetic-pharmacodynamic model of YMRS score time course was developed using asenapine plasma concentrations as measure of exposure.

The asenapine exposure response was characterized by a model that related the response in a log-linear fashion to asenapine concentrations at a hypothetical effect site. This accounted for a short delay (half life estimated at 0.75 days) between accumulation of plasma concentrations and onset of the effect on YMRS. Despite the small dose range that was tested, the exposure response relationship was statistically significant.

Figure 10 Asenapine exposure response for YMRS score at Day 21



Note: Solid lines refer to median prediction. Shaded area denotes 90% prediction interval. Vertical lines refer to median predicted effect site concentrations at steady state of 5 mg BID or 10 mg BID.

BID = twice daily; PD = pharmacodynamic; PK = pharmacokinetic; YMRS = Young Mania Rating Scale

3.2.6. Summary

Asenapine was superior to placebo in the treatment of subjects with a manic or mixed bipolar episode in both trials.

3.2.7. Dosing recommendation for bipolar mania

The recommended starting dose of asenapine, and the dose maintained by 90% of the subjects studied, is 10 mg given twice daily. The dose can be decreased to 5 mg twice daily if there are adverse effects. In controlled trials, the starting dose for asenapine was 10 mg twice daily. On the second and subsequent days of the trials, the dose could be lowered to 5 mg twice daily, based on tolerability, but less than 10% of subjects had their dose reduced. The safety of doses above 10 mg twice daily has not been evaluated in clinical trials.

4. SUMMARY OF SAFETY

4.1. General Information and Background

The safety data presented in this briefing book are based on the asenapine NDA submitted to the FDA in August 2007 and the safety update submitted in February 2009. The primary focus of the safety presentation in this briefing book will be the NDA safety dataset. The February 2009 safety update will be used to provide the most extensive safety experience available on serious adverse events, deaths, suicidal and self-injurious behaviors, pregnancy, and overdose.

As of the NDA safety database cutoff of 15 January 2007, 63 trials in the asenapine schizophrenia and bipolar mania clinical development programs had been conducted with the sublingual formulation of asenapine. These trials included 38 completed clinical pharmacology studies, 14 completed phase 2/3 trials (11 in schizophrenia [Table 1] and 3 in bipolar mania [Table 14]) and 12 ongoing trials (9 in schizophrenia [Table 2] and 3 in bipolar mania [Table 15]). A total of 3359 subjects were treated with asenapine sublingual tablets in the completed trials: 1108 subjects from clinical pharmacology trials and 2251 subjects from phase 2/3 studies. Safety information from clinical pharmacology studies were submitted in the NDA; other than the discussion of orthostatic hypotension (section 4.4.4.2), safety information from clinical pharmacology studies will not be presented in this briefing book.

A safety update was submitted to the FDA in February 2009 that included data up to the cutoff date of 01 December 2008, plus serious adverse events and deaths as reported up to 01 February 2009. Per FDA request, the safety update was limited to adverse event, serious adverse event (including death), and discontinuation data. At the time of the safety update, six of the schizophrenia trials that had been ongoing at the time of the original NDA were completed (Table 2) as were the three trials in bipolar mania.

Safety data on the following subject groupings are presented in this briefing book:

- The combined subject population from the phase 2/3 studies completed at the time of the original NDA. This includes 2251 subjects treated with any dose of asenapine sublingual tablets in either the schizophrenia or bipolar mania indications, out of which 1953 were treated with doses between 5-10 mg twice daily.

- The subject population from the short-term (6-week) schizophrenia trials, Trials 041002, 041013, 041004, 041021, 041022, and 041023 (n = 870 treated with asenapine). This population includes 572 subjects who were treated with doses between 5-10 mg twice daily.

- The subject population from the short-term (3-week) bipolar mania trials, Trials A7501004 and A7501005 (n = 379 treated with asenapine, all in the dose range of 5-10 mg twice daily).

- The subject population of the long-term (52 week) safety trial in schizophrenia, Trial 25517 (n = 908 treated with asenapine, all in the dose range of 5-10 mg twice daily).

- The combined subject population from the phase 2/3 studies completed at the time of the February 2009 safety update. This includes 3457 subjects treated with any dose of asenapine sublingual tablets in either the schizophrenia or bipolar mania indications, out of which 3159 were treated with doses between 5-10 mg twice daily. This pool will be used in the discussion of serious adverse events, deaths, suicidal and self-injurious behaviors, pregnancy, and overdose.

For a number of safety parameters, the incidence per 100 exposure years has been calculated in order to allow for a more adequate comparison between asenapine and placebo or comparators.

Data on the oral formulation of asenapine were not integrated with sublingual data, but full clinical trial reports and a summary of safety data were included in the NDA. Data from the oral formulation will not be discussed in this briefing book.

4.2. Subject exposure and disposition

4.2.1. Subject exposure

Table 23 summarizes the descriptive statistics of exposure to asenapine as reported in the NDA.

Table 23 Summary of exposure to study medication in the combined phase 2/3 trials as of the 15 January 2007 NDA cutoff

Exposure	Placebo (N=706)	Asenapine BID			Risp 3 mg BID (N=120)	Halo 4 mg BID (N=115)	Olan 5-20 mg QD (N=899)
		<5 mg (N=298)	5-10 mg[a] (N=1953)	All (N=2251)			
Number of days exposed							
Mean	26.8	42.0	114.2	104.6	63.9	31.1	115.8
Standard deviation	23.24	79.28	133.34	129.82	103.55	14.86	134.65
Median	21.0	21.0	42.5	42.0	24.0	41.0	44.0
Range (min, max)	0.5, 266	1, 732	0.5, 414	0.5, 732	1, 575	2, 46	1, 406
Total (subject-years)	**51.9**	**34.3**	**610.6**	**644.9**	**21.0**	**9.8**	**284.9**
Total Daily Dose							
Mean		1.6	14.4	12.7	5.3	7.7	14.5
Standard deviation		1.28	4.96	6.35	0.93	0.44	3.69
Median		1.3	14.5	12.2	5.6	7.9	14.8
Modal		0.4	20.0	20.0	5.6	8.0	15.0
Range (min, max)		0.2, 4.9	0, 85.7	0, 85.7	1, 7.4	6, 9	0, 32.5

a fixed and flexible doses

BID = twice daily; Halo=haloperidol; NDA = New Drug Application; Olan=olanzapine; QD = once daily; Risp=risperidone

As of the February 2009 safety update data cutoff, 1206 additional subjects had been exposed to asenapine (including 107 placebo subjects from acute trials who were switched to asenapine) and 547 subjects had extended exposure to asenapine in long term trials. The total exposure to asenapine was 1351.9 subject-years, an increase of 741.3 subject-years from the original NDA (Table 24).

Table 24 Summary of exposure to study medication in the combined completed phase 2/3 trials, as of the February 2009 Safety Update cutoff

Exposure	Placebo (N=1064)	Asenapine BID <5 mg (N=298)	Asenapine BID 5-10 mg[a] (N=3159)	Asenapine BID All (N=3457)	Risp 3 mg BID (N=120)	Halo 4 mg BID (N=115)	Olan 5-20 mg QD (N=1139)
Number of days exposed							
Mean	49.65	42.04	156.31	146.46	63.9	110.07	183.22
Standard deviation	63.98	79.28	142.45	141.81	103.55	138.89	157.27
Median	25.5	21	97	82	24	42	140
Range (min, max)	1, 381	1, 732	1, 419	1, 732	1, 575	2, 413	1, 414
Total (subject-years)	**144.6**	**34.3**	**1351.9**	**1386.2**	**21.0**	**34.66**	**571.34**
Total Daily Dose							
Mean		1.64	15.28	14.1	5.31	8.13	14.39
Standard deviation		1.28	4.17	5.54	0.93	1.2	3.62
Median		1.31	16.67	15	5.57	8	15
Modal		0.4	20	20	6	8	10
Range (min, max)		0.2, 4.9	2, 20	0.2, 20	1, 7.35	5.39, 13.04	5.18, 20

Total daily dose for each subject is defined as total dose should have received minus (plus) any missed (extra) doses.
Modal is defined as mode of the mode.
a fixed and flexible doses
BID = twice daily; Halo=haloperidol; Olan=olanzapine; QD = once daily; Risp=risperidone

4.2.2. Subject Disposition

In the 6-week placebo-controlled schizophrenia trials, a higher percentage of subjects treated with asenapine 5-10 mg twice daily completed the trials (56%) compared with placebo (44%). The discontinuations due to adverse events/worsening of disease for asenapine (8%) were comparable to placebo (9.5%). The discontinuations due to lack of efficacy for asenapine (9%) were lower than placebo (22%, Table 25).

Table 25 Summary of subject disposition (6-week schizophrenia studies)

Subject Disposition n (%)	Placebo	Asenapine BID					Risperidone 3 mg BID	Haloperidol 4 mg BID	Olanzapine 10-20 mg QD
		< 5 mg	5 mg Fixed Dose	10 mg Fixed Dose	5-10 mg Flexible Dose	All 5-10 mg			
	(N=503)	(N=298)	(N=274)	(N=208)	(N=90)	(N=572)	(N=120)	(N=115)	(N=194)
Completed	224 (44.5)	87 (29.2)	157 (57.3)	122 (58.7)	42 (46.7)	321 (56.1)	48 (40.0)	68 (59.1)	101 (52.1)
Discontinued	229 (55.5)	211 (70.8)	117 (42.7)	86 (41.3)	48 (53.3)	251 (43.9)	72 (60.0)	47 (40.9)	93 (47.9)
Reason for discontinuation									
Adverse event/ worsening of disease[a]	48 (9.5)	27 (9.1)	20 (7.3)	20 (9.6)	6 (6.7)	46 (8.0)	9 (7.5)	12 (10.4)	21 (10.8)
Worsening of disease	*23 (4.6)*	*0*	*8 (2.9)*	*12 (5.8)*	*3 (3.3)*	*23 (4.0)*	*0*	*6 (5.2)*	*10 (5.2)*
Adverse event	*25 (5.0)*	*27 (9.1)*	*12 (4.4)*	*8 (3.8)*	*3 (3.3)*	*23 (4.0)*	*9 (7.5)*	*6 (5.2)*	*11 (5.7)*
Worsening of schizophrenia[b]	0	1 (0.3)	0	0	0	0	0	0	0
Lack of efficacy	109 (21.7)	96 (32.2)	30 (10.9)	20 (9.6)	4 (4.4)	54 (9.4)	28 (23.3)	4 (3.5)	23 (11.9)
Withdrew consent	77 (15.3)	62 (20.8)	42 (15.3)	28 (13.5)	26 (28.9)	96 (16.8)	23 (19.2)	26 (22.6)	28 (14.4)
Lost to follow-up	18 (3.6)	9 (3.0)	13 (4.7)	5 (2.4)	8 (8.9)	26 (4.5)	7 (5.8)	4 (3.5)	11 (5.7)
Other	27 (5.4)	16 (5.4)	12 (4.4)	13 (6.3)	4 (4.4)	29 (5.1)	5 (4.2)	1 (0.9)	10 (5.2)

a data obtained from End of Trial case report form

b Worsening of schizophrenia was not recorded as an adverse event for studies 041002, 041004, 041013

BID = twice daily; QD = once daily

In the 3-week bipolar mania trials, slightly more asenapine subjects (5-10 mg twice daily) completed the trials (65%) compared with placebo (60%). The discontinuations due to adverse events/worsening of disease for asenapine (10%) were greater than placebo (5%). The discontinuations due to lack of efficacy for asenapine (8%) were lower than placebo (16%, Table 26).

Table 26 Summary of subject disposition (3-week bipolar mania trials)

Subject Disposition **n (%)**	**Placebo** **(N=203)**	**Asenapine 5-10 mg BID flexible dose** **(N=379)**	**Olanzapine 5-20 mg QD flexible dose** **(N=394)**
Completed	121 (59.6)	246 (64.9)	313 (79.4)
Discontinued	82 (40.4)	133 (35.1)	81 (20.6)
Reason for discontinuation			
Adverse event/ worsening of disease[a]	11 (5.4)	37 (9.8)	15 (3.8)
Worsening of disease	*9 (4.4)*	*17 (4.5)*	*4 (1.0)*
Adverse event	*2 (1.0)*	*20 (5.3)*	*11 (2.8)*
Lack of efficacy	32 (15.8)	30 (7.9)	23 (5.8)
Withdrew consent	26 (13.8)	53 (14.0)	31 (7.9)
Lost to follow-up	6 (3.0)	6 (1.6)	8 (2.0)
Other	7 (3.4)	7 (1.8)	4 (1.0)

a data obtained from End of Trial case report form

BID = twice daily; QD = once daily

In the 52-week schizophrenia safety trial, 38.5% of asenapine treated subjects completed the trial. Most of the discontinuations were due to withdrawal of consent (22%), lack of efficacy (14%) and worsening of disease (11%, Table 27).

Table 27 Summary of subject disposition (long-term schizophrenia safety trial 25517)

Subject disposition **n (%)**	**Asenapine flexible dose 5-10 mg BID** **(N=908)**	**Olanzapine flexible dose 10-20 mg QD** **(N=311)**
Completed	350 (38.5)	178 (57.2)
Discontinued	558 (61.5)	133 (42.8)
Reason for discontinuation		
Adverse event/ worsening of disease[a]	155 (17.1)	38 (12.2)
Worsening of disease	*98 (10.8)*	*17 (5.5)*
Adverse event	*57 (6.3)*	*21 (6.8)*
Lack of efficacy	130 (14.3)	28 (9.0)
Withdrew consent	202 (22.2)	49 (15.8)
Lost to follow up	20 (2.2)	6 (1.9)
Other	51 (5.6)	12 (3.9)

a data obtained from End of Trial case report form

BID = twice daily; QD = once daily

4.3. General Safety

4.3.1. Overview

Most (68% to 88%) subjects in the phase 2/3 trials completed at the NDA cutoff, regardless of treatment group, experienced an adverse event. The lowest incidence of adverse events was in the placebo group (68%) and the highest incidence was in the risperidone group (88%). Overall 79% of subjects treated with asenapine experienced an adverse event, which was similar to the percentages for the other active comparators (haloperidol and olanzapine, 76% each). Most adverse events were mild to moderate in intensity; severe adverse events were experienced by 14% of subjects treated with asenapine. Serious adverse events were reported in 14% of asenapine-treated subjects (Table 28); 4% of subjects experienced serious adverse events considered related to treatment as judged by the investigator.

Table 28 Overview of adverse events (combined phase 2/3 studies)

Adverse Event Category n (%)	Placebo (N=706)	Asenapine BID <5 mg (N=298)	Asenapine BID 5-10 mg[a] (N=1953)	Asenapine BID All (N=2251)	Risperidone 3 mg BID (N=120)	Haloperidol 4 mg BID (N=115)	Olanzapine 5-20 mg QD (N=899)
Any adverse event	483 (68.4)	246 (82.6)	1523 (78.0)	1769 (78.6)	105 (87.5)	87 (75.7)	682 (75.9)
Related AEs	290 (39.7)	134 (45.0)	1099 (56.3)	1233 (54.8)	64 (53.3)	65 (56.5)	494 (54.9)
Severe AEs	52 (7.4)	59 (19.8)	260 (13.3)	319 (14.2)	21 (17.5)	7 (6.1)	105 (11.7)
Serious adverse events	61 (8.6)	50 (16.8)	275 (14.1)	325 (14.4)	21 (17.5)	8 (7.0)	87 (9.7)
Discontinuations due to AEs/SAEs[b]	69 (9.8)	57 (19.1)	285 (14.6)	342 (15.2)	28 (23.3)	12 (10.4)	103 (11.5)
D/C due to SAEs	36 (5.1)	16 (5.4)	125 (6.4)	141 (6.3)	12 (10.0)	5 (4.3)	40 (4.4)

AE = adverse event; BID = twice daily; D/C = discontinued; QD = once daily; SAE = serious adverse event

4.3.2. Adverse reactions

Adverse reactions are defined as adverse events judged by the investigator to be related to treatment. Adverse reactions during the short-term schizophrenia and bipolar mania trials are discussed below.

4.3.2.1. Adverse reactions in short-term schizophrenia trials

Adverse reactions reported in 2% or more of subjects in one of the asenapine dose groups that occurred at greater incidence than in the placebo group during the four short-term (6-week) placebo-controlled trials for schizophrenia, in which sublingual asenapine was administered in doses ranging from 5 mg to 10 mg twice daily (fixed dose trials: Trials 041004, 041023, 041021, and flexible dose trial: Trial 041022), are summarized below (Table 29). Of the adverse reactions observed during the short-term schizophrenia trials, the only apparent dose-related adverse reaction was akathisia.

Table 29 Adverse reactions in 6-week schizophrenia trials

System Organ Class / Preferred Term[a]	Placebo	Asenapine BID		
		5 mg	10 mg	All (5 mg or 10 mg)
% of subjects	N = 378	N = 274	N = 208	N = 572[b]
Gastrointestinal disorders				
Dry mouth	2%	2%	1%	2%
Oral hypoesthesia	1%	6%	6%	5%
Salivary hypersecretion	0%	<1%	3%	1%
Vomiting	3%	2%	3%	2%
General disorders				
Fatigue	2%	3%	1%	2%
Investigations				
Weight increased	<1%	2%	1%	2%
Metabolism disorders				
Increased appetite	1%	3%	0%	2%
Nervous system disorders				
Akathisia[c]	3%	3%	10%	6%
Other extrapyramidal symptoms (excluding akathisia)[d]	6%	8%	11%	9%
Somnolence[e]	7%	13%	11%	12%

a Adverse reactions reported in 2% or more of subjects in one of the asenapine dose groups that occurred at a greater incidence than in the placebo group

b Also includes the Flexible-dose trial (N=90)

c Akathisia includes: akathisia and hyperkinesia

d Extrapyramidal symptoms included dystonia, oculogyration, dyskinesia, tardive dyskinesia, muscle rigidity, parkinsonism, tremor, and extrapyramidal disorder (excluding akathisia)

e Somnolence includes the following events: somnolence, sedation, and hypersomnia

BID = twice daily

4.3.2.2. Adverse reactions in short-term bipolar mania trials

Adverse reactions reported in 2% or more of subjects in one of the asenapine dose groups that occurred at greater incidence than in the placebo group from the two short-term (3-week) placebo-controlled trials in bipolar mania, in which sublingual asenapine was administered in flexible doses of 5 mg or 10 mg twice daily (Trials A7501004 and A7501005), are summarized below (Table 30).

Table 30 Adverse reactions in 3-week bipolar mania trials

System Organ Class / Preferred Term[a] % of subjects	Placebo N = 203	Asenapine BID 5 mg or 10 mg[b] N = 379
Gastrointestinal disorders		
Constipation	2%	2%
Dry mouth	1%	3%
Dyspepsia	1%	2%
Nausea	3%	4%
Oral hypoesthesia	1%	5%
Vomiting	2%	3%
General disorders		
Fatigue	2%	3%
Investigations		
Weight increased	1%	5%
Metabolism disorders		
Increased appetite	1%	4%
Nervous system disorders		
Akathisia[c]	3%	3%
Other extrapyramidal symptoms (excluding akathisia)[d]	2%	7%
Dizziness	3%	10%
Dysgeusia	1%	3%
Headache	4%	6%
Somnolence[e]	5%	23%
Psychiatric disorders		
Anxiety	1%	2%

a adverse reactions reported in 2% or more of subjects in one of the asenapine dose groups that occurred at greater incidence than in the placebo group

b Flexible dosing

c Akathisia includes: akathisia and hyperkinesia

d Extrapyramidal symptoms included: dystonia, blepharospasm, torticollis, dyskinesia, tardive dyskinesia, muscle rigidity, parkinsonism, gait disturbance, masked facies, and tremor (excluding akathisia).

e Somnolence includes the following events: somnolence, sedation, and hypersomnia

BID = twice daily

4.3.3. Serious adverse events (including deaths)

In order to provide the most extensive safety experience available on serious adverse events (including deaths) the discussion that follows is based on the combined subject population from the phase 2/3 studies completed at the time of the February 2009 safety update. This includes 3457 subjects treated with any dose of asenapine sublingual tablets in either the schizophrenia or bipolar mania indications, out of which 3159 were treated with doses between 5-10 mg twice daily.

4.3.3.1. Serious adverse events

An adverse event was defined as serious if at any dose it resulted in death, was life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect or was an adverse event that may not have been immediately life-threatening or resulted in death or hospitalization, but may have jeopardized the subject or required intervention to prevent one of the outcomes above. All serious adverse events (including deaths) that occurred up to 30 days following the last dose of study drug or up to the last

follow-up visit, whichever was later, are summarized and listed. Serious adverse events and deaths occurring later than 30 days and considered treatment-related were also to be reported.

The incidence of serious adverse events was low across all treatment groups in the phase 2/3 trials completed by the February 2009 Safety Update cutoff, ranging from 10% of subjects in the placebo group to 18% of subjects in the risperidone group. Overall 15% of subjects treated with asenapine experienced serious adverse events, which was slightly higher than the percentages for the other active comparators (haloperidol and olanzapine, 11 and 12%, respectively). The most frequently occurring serious adverse events were schizophrenia and schizophrenia, paranoid type (i.e., worsening of disease, 5% and 3% for asenapine, respectively, Table 31).

Table 31 Serious adverse events in the combined completed phase 2/3 trials, as of the February 2009 Safety Update cutoff

Adverse Event (Preferred Term)[a] n (%)	Placebo (N=1064)	Asenapine BID <5 mg (N=298)	Asenapine BID 5-10 mg[b] (N=3159)	Asenapine BID All (N=3457)	Risperidone 3 mg BID (N=120)	Haloperidone 2-8 mg BID (N=115)	Olanzapine 5-20 mg QD (N=1139)
Any SAE	107 (10.1)	50 (16.8)	491 (15.5)	541 (15.6)	21 (17.5)	13 (11.3)	136 (11.9)
Schizophrenia	24 (2.3)	19 (6.4)	151 (4.8)	170 (4.9)	3 (2.5)	9 (7.8)	27 (2.4)
Schizophrenia, paranoid type	20 (1.9)	16 (5.4)	91 (2.9)	107 (3.1)	8 (6.7)	4 (3.5)	24 (2.1)
Depression	5 (0.5)	0	37 (1.2)	37 (1.1)	3 (2.5)	0	12 (1.1)
Mania	24 (2.3)	0	32 (1.0)	32 (0.9)	0	0	15 (1.3)
Suicidal ideation	2 (0.2)	3 (1.0)	25 (0.8)	28 (0.8)	1 (0.8)	0	7 (0.6)
Psychotic disorder	8 (0.8)	5 (1.7)	21 (0.7)	26 (0.8)	1 (0.8)	0	9 (0.8)
Schizoaffective disorder	0	0	16 (0.5)	16 (0.5)	0	0	2 (0.2)
Suicide attempt	2 (0.2)	0	15 (0.5)	15 (0.4)	1 (0.8)	1 (0.9)	8 (0.7)
Bipolar I disorder	3 (0.3)	0	12 (0.4)	12 (0.3)	0	0	5 (0.4)
Agitation	0	0	9 (0.3)	9 (0.3)	0	0	0
Schizophrenia, undifferentiated type	2 (0.2)	2 (0.7)	7 (0.2)	9 (0.3)	0	0	3 (0.3)
Anxiety	0	0	8 (0.3)	8 (0.2)	0	0	1 (0.1)
Completed suicide	0	0	8 (0.3)	8 (0.2)	0	0	4 (0.4)
Syncope	0	0	7 (0.2)	7 (0.2)	0	0	0
Drug during pregnancy	0	0	5 (0.2)	5 (0.1)	0	0	1 (0.1)
Abortion induced	0	0	4 (0.1)	4 (0.1)	0	0	0
Depressive symptom	0	0	4 (0.1)	4 (0.1)	0	0	0
Dystonia	0	1 (0.3)	3 (0.1)	4 (0.1)	0	0	0
Hyponatraemia	1 (0.1)	1 (0.3)	3 (0.1)	4 (0.1)	0	1 (0.9)	0
Hypertension	0	0	4 (0.1)	4 (0.1)	0	0	0
Mental disorder	0	1 (0.3)	3 (0.1)	4 (0.1)	0	0	0
Overdose	0	0	4 (0.1)[c]	4 (0.1)	0	0	2 (0.2)
Road traffic accident	0	0	4 (0.1)	4 (0.1)	0	0	0
Aggression	0	0	3 (0.1)	3 (0.1)	0	0	0
Alcohol poisoning	0	0	3 (0.1)	3 (0.1)	0	0	0
Fall	0	0	3 (0.1)	3 (0.1)	1 (0.8)	0	1 (0.1)
NMS	0	0	3 (0.1)	3 (0.1)	0	0	0
Non-cardiac chest pain	0	0	3 (0.1)	3 (0.1)	0	0	0
Pneumonia	1 (0.1)	1 (0.3)	2 (0.1)	3 (0.1)	3 (2.5)	0	0
Rhabdomyolysis	0	1 (0.3)	2 (0.1)	3 (0.1)	0	0	1 (0.1)

a With an incidence of n = 3 or greater in the All Asenapine group

b fixed and flexible doses

c Includes 2 cases of asenapine overdose

BID = twice daily; NMS = Neuroleptic malignant syndrome; SAE = serious adverse event

No substantial differences in the nature or the incidence of serious adverse events between the original NDA and the February 2009 safety update were observed. The proportion of subjects treated with 5-10 mg asenapine twice daily in the combined completed phase 2/3 studies experiencing a serious adverse event did not change substantially (original NDA 14.1% vs. February 2009 update 15.5%). The serious adverse events with an incidence greater than or equal to n = 3 that were presented in the original NDA occurred at similar percentages as observed in the February 2009 Safety Update. The updated profile shows few new serious adverse events that have reached the threshold, with incidences between n = 3 and n = 5: drug exposure during pregnancy, abortion induced, hypertension, road traffic accident, fall, non-cardiac chest pain, and pneumonia.

4.3.3.2. Deaths

Overall, there was no increased incidence of drug related mortality associated with asenapine therapy.

Deaths in the subject population from the completed phase 2/3 studies by the February 2009 safety update cutoff

As of 01 December 2008, a total of 26 deaths were reported in the phase 2/3 program. Of these, 19 were reported in the all asenapine group, 1 in the placebo group, 1 in the haloperidol group, and 5 in the olanzapine group. The incidence of death in the all asenapine group (0.5%) was comparable with the olanzapine group (0.4%). The incidence of death in the placebo group was 0.1%, most likely due to the longer exposure of subjects in the asenapine and olanzapine groups compared with placebo. The incidence of death per 100 exposure years was slightly higher in the asenapine 5-10 mg BID group (1.26 per 100 exposure years) compared with olanzapine (0.88 per 100 exposure years), but lower compared with the haloperidol group (2.89 per 100 exposure years, Table 32).

Table 32 Summary of deaths by patient years of exposure in the combined completed phase 2/3 trials as of the February 2009 Safety Update

	Placebo (N=1064)	Asenapine BID			Risp 3 mg BID (N=120)	Halo 2-8 mg BID (N=115)	Olan 5-20 mg QD[b] (N=1139)
		< 5 mg (N=298)	5-10 mg[a] (N=3159)	ALL (N=3457)			
Death n (%)	1 (0.1)	2 (0.7)	17 (0.5)[c]	19 (0.5)	0	1 (0.9)	5 (0.4)
Subject exposure years	144.6	34.3	1351.9	1386.2	21.0	34.7	571.3
Incidence per 100 exposure years	0.69	5.83	1.26	1.37	0	2.89	0.88

a fixed and flexible dosing

b flexible dosing

c includes a death of a preterm child from a woman treated with asenapine

BID = twice daily; Halo = haloperidol; QD = once daily; Olan = olanzapine; Risp = risperidone,

Seventeen of the 19 deaths in the all asenapine group were reported in subjects receiving 5-10 mg twice daily. Of these, 4 were considered by the investigator to be related to asenapine: 2 completed suicides, 1 concerning a newborn from a female subject exposed to asenapine during her pregnancy, and one overdose (not an overdose of asenapine). Brief narratives are provided below, except for the 2 completed suicides, which are provided in Section 4.4.3, Suicidality:

- 38-year-old woman with a history of bipolar I disorder started asenapine treatment for acute mania. At end of trial (one year after starting asenapine) pregnancy test was positive. She had a history of 4 pregnancies, of which three were spontaneous abortions at gestational ages 14, 12 and 20 weeks respectively. One pregnancy resulted in a live birth per Caesarean section due to fetal distress at gestational age of 34 weeks. Ultrasound confirmed the pregnancy and showed gestational age of 29 weeks plus 2 days. She gave birth to a daughter (gestational age 31 weeks plus 5 days) at home. The baby died 5 minutes after delivery from asphyxia. No further information concerning congenital anomalies was reported.

- 37-year-old man with no history of suicide attempts started asenapine for the treatment of bipolar mania. Five months after starting asenapine, he felt mildly depressed and had suicidal ideations. He thought he was worthless and decided to commit suicide by jumping from an expressway. He sustained a dislocation of the 5th and 6th cervical spine. He was hospitalized and underwent surgery for the C5-C6 dislocation. He recovered without sequelae and was discharged 2 weeks later. The subject continued to have depression from bipolar disorder. The subject could not come to his scheduled follow-up visit, so he requested to be withdrawn from the trial. Asenapine was discontinued and the subject dropped out of the trial. Six weeks after discontinuation of asenapine, he attempted to commit suicide by ingestion of bathroom cleaning liquid. He was hospitalized but he subsequently died as a result of the poisoning. No autopsy was performed.

The cause of death in the remaining 13 cases, all which were assessed by the investigator as not related to asenapine, were suicide (6 cases), cardiac failure (2 cases), and one case each of overdose (not an overdose of asenapine), lobar pneumonia, pulmonary embolism and arteriosclerosis, unspecified cause, and metastatic lung cancer.

Overall, the incidence of mortality in asenapine treated subjects was comparable with the incidence in the olanzapine group. A review of all fatal cases showed no evidence of drug associated mortality with asenapine treatment.

Deaths in trials ongoing at the February 2009 safety update cutoff

One death occurred in the trials that were ongoing as of the February 2009 safety update: a 76-year old woman died approximately one month after her last dose of asenapine. The cause of death was reported as cardio-respiratory arrest. The investigator did not consider the death related to asenapine.

4.3.4. Adverse events leading to discontinuation

In both the schizophrenia and bipolar mania short-term trials, adverse events leading to discontinuation were those related to worsening of disease (e.g., schizophrenia, psychotic disorder, mania) and the incidence of each (1%-3%) was comparable to placebo. This finding indicates that the safety profile of asenapine appeared favorable during the clinical development program, as treatment discontinuation was not related to safety or tolerability issues in the vast majority of cases (Table 33, Table 34).

Table 33 Adverse events that led to discontinuation (6-week schizophrenia studies)

Adverse Event (Preferred Term)[a] n (%)	Placebo	Asenapine BID					Risperidone 3 mg BID	Haloperidol 4 mg BID	Olanzapine 10-20 mg QD
		<5 mg	5 mg Fixed Dose	10 mg Fixed Dose	5-10 mg Flexible Dose	All 5-10 mg			
	(N=503)	(N=298)	(N=274)	(N=208)	(N=90)	(N=572)	(N=120)	(N=115)	(N=194)
Any adverse event[b]	51 (10.1)	43 (14.4)	21 (7.7)	22 (10.6)	8 (8.9)	51 (8.9)	14 (11.7)	12 (10.4)	21 (10.8)
Schizophrenia	18 (3.6)	19 (6.4)	5 (1.8)	6 (2.9)	1 (1.1)	12 (2.1)	3 (2.5)	5 (4.3)	0
Psychotic disorder	6 (1.2)	8 (2.7)	3 (1.1)	5 (2.4)	1 (1.1)	9 (1.6)	3 (2.5)	1 (0.9)	4 (2.1)
Schizophrenia, paranoid type	7 (1.4)	2 (0.7)	3 (1.1)	2 (1.0)	1 (1.1)	6 (1.0)	1 (0.8)	1 (0.9)	2 (1.0)
Agitation	3 (0.6)	2 (0.7)	5 (1.8)	0	0	5 (0.9)	0	0	2 (1.0)
Akathisia	0	0	1 (0.4)	4 (1.9)	0	5 (0.9)	0	1 (0.9)	0
Aggression	0	1 (0.3)	1 (0.4)	1 (0.5)	0	2 (0.3)	0	0	0
Anxiety	0	2 (0.7)	1 (0.4)	1 (0.5)	0	2 (0.3)	0	1 (0.9)	0
Dystonia	0	0	1 (0.4)	0	1 (1.1)	2 (0.3)	0	1 (0.9)	0
Tremor	0	0	0	2 (1.0)	0	2 (0.3)	0	0	0

a adverse events with an incidence of n = 2 or greater

b any adverse event leading to discontinuation; data obtained from adverse event CRF page as reason for discontinuation

BID = twice daily; CRF = case report form; QD = once daily

Table 34 Adverse events by preferred term that led to discontinuation with an incidence of n = 2 or greater (3-week bipolar mania trials)

Adverse Event (Preferred Term) n (%)	Placebo (N=203)	Asenapine 5-10 mg BID flexible dose (N=379)	Olanzapine 5-20 mg QD flexible dose (N=394)
Any adverse event[a]	12 (5.9)	38 (10.0)	22 (5.6)
Mania	6 (3.0)	10 (2.6)	4 (1.0)
Anxiety	0	4 (1.1)	1 (0.3)
Hypoaesthesia oral	0	4 (1.1)	0
Depression	2 (1.0)	3 (0.8)	0
Agitation	0	2 (0.5)	2 (0.5)
Dizziness	0	2 (0.5)	0
Dystonia	0	2 (0.5)	0
Irritability	0	2 (0.5)	0
Alcohol poisoning	0	2 (0.5)	1 (0.3)

a any adverse event leading to discontinuation; data obtained from adverse event CRF page as reason for discontinuation

BID = twice daily; CRF = case report form; QD = once daily

In the combined phase 2/3 trials the risperidone group had the highest incidence of discontinuations due to adverse events (23%), followed by asenapine 5-10 mg BID (15%), olanzapine (11%), and placebo (10%). Based on the subject years exposure analysis, the incidence rate of discontinuations due to adverse events for asenapine 5-10 mg BID (47 per 100 exposure years) was less than placebo (133 per 100 exposure years) and slightly higher than that seen for olanzapine (122 per 100 exposure years) (Table 35).

The incidence of discontinuations due to adverse events in the asenapine 5-10 mg BID group was highest for schizophrenia (2.6%), depression (1.1%), psychotic disorder (1.0%), and schizophrenia paranoid type (1.0%); the incidence of depression was slightly higher than placebo (0.3%) and the incidences of schizophrenia, psychotic disorder, and schizophrenia paranoid type were comparable to placebo.

Table 35 Adverse events by preferred term that led to discontinuation (combined phase 2/3 studies)

Adverse Event (Preferred Term)[a] n (%)	Placebo (N=706)	Asenapine BID <5 mg (N=298)	Asenapine BID 5-10 mg[b] (N=1953)	Asenapine BID All (N=2251)	Risperidone 3 mg BID (N=120)	Haloperidone 4 mg BID (N=115)	Olanzapine 5-20 mg QD (N=899)
Any adverse event[c]	69 (10)	57 (19)	285 (15)	342 (15)	28 (23)	12 (10.4)	103 (11.5)
Subject exposure years	51.9	34.3	610.6	644.9	21.0	9.8	284.9
Incidence[d]	132.95	166.18	46.68	53.03	133.33	36.15	122.45
Schizophrenia	19 (2.7)	24 (8.1)	51 (2.6)	75 (3.3)	5 (4.2)	5 (4.3)	11 (1.2)
Psychotic disorder	8 (1.1)	10 (3.4)	20 (1.0)	30 (1.3)	8 (6.7)	1 (0.9)	8 (0.9)
Depression	2 (0.3)	1 (0.3)	22 (1.1)	23 (1.0)	2 (1.7)	0	6 (0.7)
Schizophrenia, paranoid type	9 (1.3)	2 (0.7)	20 (1.0)	22 (1.0)	6 (5.0)	1 (0.9)	3 (0.3)
Akathisia	1 (0.1)	0	17 (0.9)	17 (0.8)	0	1 (0.9)	0
Mania	6 (0.8)	0	16 (0.8)	16 (0.7)	0	0	6 (0.7)
Agitation	5 (0.7)	3 (1.0)	12 (0.6)	15 (0.7)	1 (0.8)	0	5 (0.6)
Anxiety	1 (0.1)	3 (1.0)	11 (0.6)	14 (0.6)	0	1 (0.9)	1 (0.1)
Suicidal ideation	3 (0.4)	2 (0.7)	10 (0.5)	12 (0.5)	1 (0.8)	0	2 (0.2)
Paranoia	0	0	7 (0.4)	7 (0.3)	0	0	2 (0.2)
Sedation	0	0	7 (0.4)	7 (0.3)	0	0	5 (0.6)
Hypoaesthesia oral	0	0	7 (0.4)	7 (0.3)	0	0	0
Suicide attempt	1 (0.1)	0	6 (0.3)	6 (0.3)	1 (0.8)	0	5 (0.6)
Bipolar I disorder	0	0	5 (0.3)	5 (0.2)	0	0	2 (0.2)
Delusion	3 (0.4)	2 (0.7)	3 (0.2)	5 (0.2)	1 (0.8)	0	0
Insomnia	0	1 (0.3)	4 (0.2)	5 (0.2)	1 (0.8)	0	4 (0.4)
Schizoaffective disorder	0	0	5 (0.3)	5 (0.2)	0	0	0
Dystonia	0	0	5 (0.3)	5 (0.2)	0	1 (0.9)	0
Somnolence	0	0	5 (0.3)	5 (0.2)	0	0	2 (0.2)
Vomiting	1 (0.1)	1 (0.3)	4 (0.2)	5 (0.2)	1 (0.8)	0	3 (0.3)
Aggression	1 (0.1)	1 (0.3)	3 (0.2)	4 (0.2)	0	0	0
Dizziness	1 (0.1)	0	4 (0.2)	4 (0.2)	2 (1.7)	0	2 (0.2)
Nausea	2 (0.3)	0	4 (0.2)	4 (0.2)	1 (0.8)	1 (0.9)	4 (0.4)
ALT increased	0	0	4 (0.2)	4 (0.2)	0	0	1 (0.1)
Alcohol poisoning	0	0	4 (0.2)	4 (0.2)	0	0	1 (0.1)

a with an incidence of n = 4 or greater

b fixed and flexible doses

c any adverse event leading to discontinuation; data obtained from adverse event CRF page as reason for discontinuation

d incidence/100 exposure years

ALT = alanine aminotransferase; BID = twice daily; CRF = case report form; QD = once daily

4.4. Safety topics of interest

4.4.1. Metabolic effects

4.4.1.1. Body weight

Asenapine has limited effect on body weight, as was seen in the short-term and, most importantly, the long-term studies. Data from the long term schizophrenia trial show that mean weight gain stabilized after approximately 12 weeks of asenapine treatment in contrast to olanzapine treatment, which showed continued weight gain up till 52 weeks of treatment (asenapine 1.57 kg vs. olanzapine 5.59 kg in subjects treated for 52 weeks). Mean body weight gain was inversely correlated with baseline body mass index (BMI); obese subjects (BMI > 27 kg/m^2) treated with asenapine showed minimal mean weight gain.

Body weight in combined phase 2/3 trials

In the combined phase 2/3 trials the mean weight change from baseline to endpoint in subjects treated with asenapine 5-10 mg twice daily was 1.1 kg (Table 36), which was lower than for olanzapine treated subjects (3.4 kg) and risperidone treated subjects (2.0 kg). The proportion of subjects with a clinically relevant weight increase defined as an weight increase of >7% over baseline at endpoint was 10.5% in the asenapine 5-10 mg BID group which was lower than for olanzapine (25.8%) and comparable to risperidone (10.8%).

Table 36 Summary statistics of weight changes combined phase 2/3 studies

Body weight parameter	Placebo	Asenapine BID			Risp	Halo	Olan
		<5 mg	5-10 mg[a]	All	3 mg BID	4 mg BID	5-20 mg QD
	(N=706)	(N=298)	(N=1953)	(N=2251)	(N=120)	(N=115)	(N=899)
Body weight (kg)							
N	702	296	1938	2234	117	115	898
Baseline mean (SE)	81.7 (0.74)	85.1 (1.12)	77.5 (0.41)	78.5 (0.39)	86.8 (1.98)	76.5 (1.62)	78.4 (0.61)
N	607	235	1837	2072	89	107	849
Change from baseline (SE)[b]	0.1 (0.14)	0.9 (0.33)	1.1 (0.09)	1.0 (0.09)	2.0 (0.55)	0.3 (0.23)	3.4 (0.20)
>7% gain, n(%)	11 (1.6)	28 (9.4)	206 (10.5)	234 (10.4)	13 (10.8)	5 (4.3)	232 (25.8)
>7% loss, n(%)	16 (2.3)	8 (2.7)	73 (3.7)	81 (3.6)	3 (2.5)	0	17 (1.9)

a fixed and flexible doses

b change to endpoint

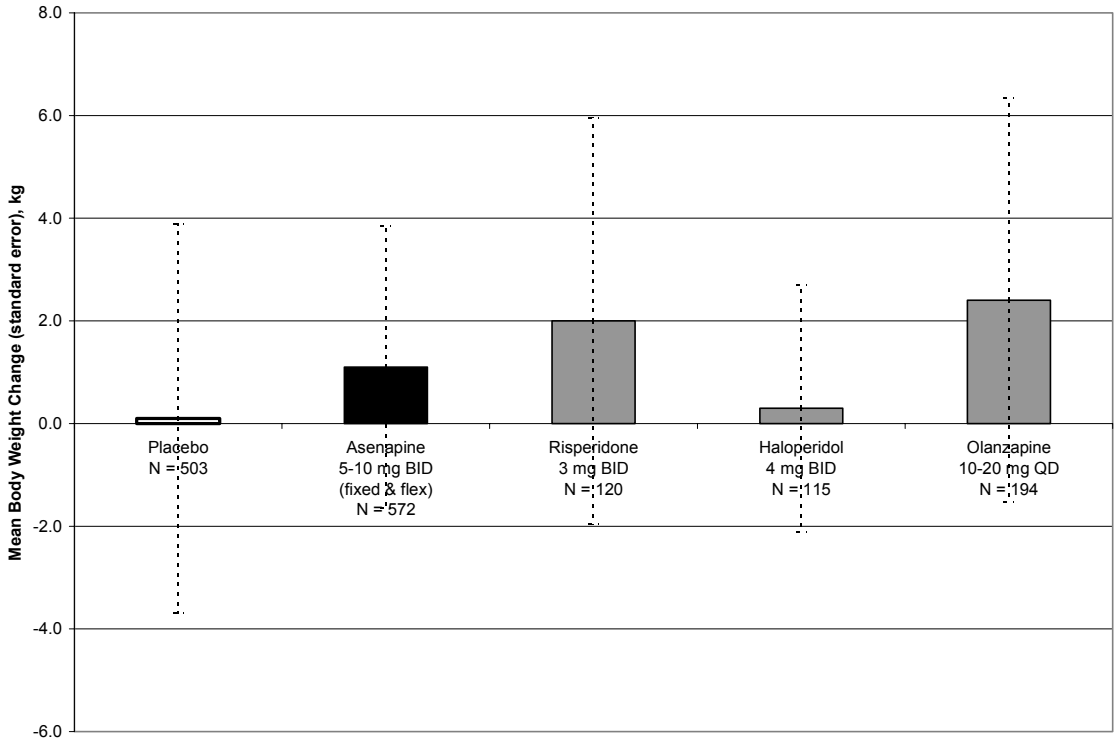
BID = twice daily; Halo = haloperidol; Olan = olanzapine; QD = once daily; Risp = risperidone; SE = standard error

Body weight in short-term schizophrenia trials

Figure 11 shows the mean weight change for the treatment groups in the short term schizophrenia studies (other than the asenapine <5 mg BID group). All treatment groups showed an increase in mean body weight at endpoint compared with placebo (0.1 kg) with the largest increase seen for olanzapine (2.4 kg), followed by risperidone (2.0 kg), and then the all asenapine 5-10 mg BID group (1.1 kg); the mean increase for

haloperidol was 0.3 kg. The change in weight for asenapine did not appear to be dose related. The proportion of subjects who had a ≥ 7% weight gain showed a similar trend: placebo (2.0%), haloperidol (4.3%), all asenapine 5-10 mg BID (4.9%), risperidone (9.2%), and olanzapine (14.4%).

Figure 11 Mean weight change, schizophrenia short-term trials

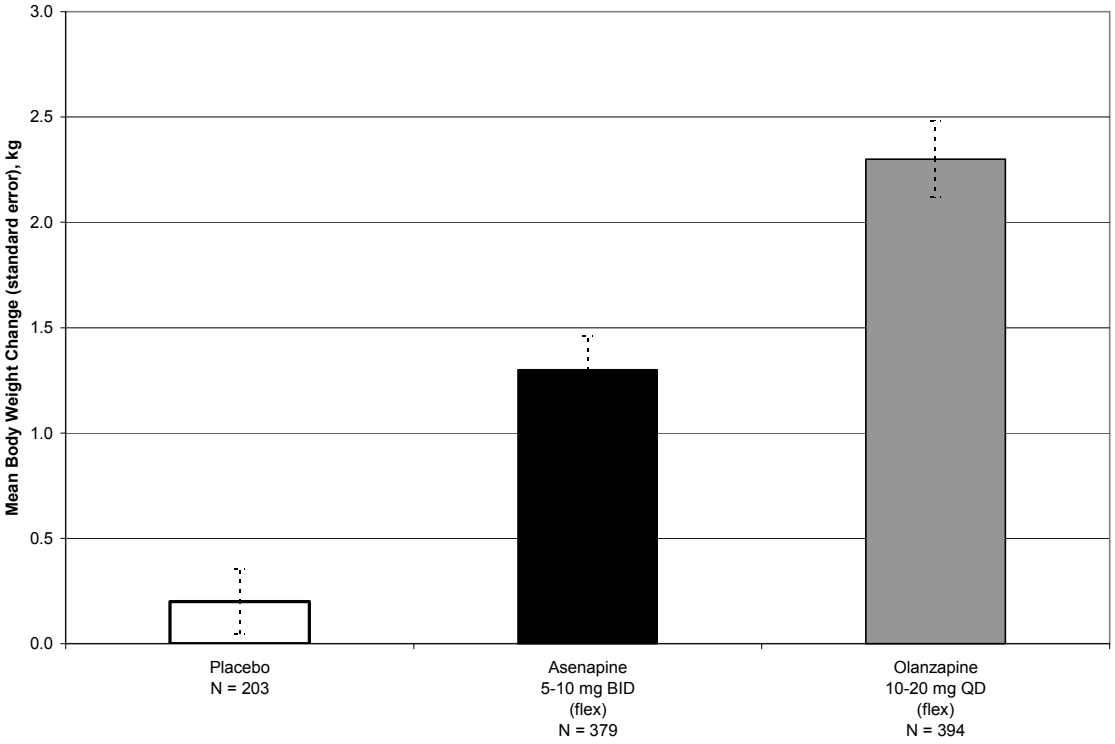


BID = twice daily; QD = once daily

Body weight in short-term bipolar mania trials

Figure 12 shows the mean weight changes for the three treatment groups, asenapine, olanzapine, and placebo, in the short-term bipolar mania trials. All treatment groups showed a small mean increase in mean body weight at endpoint with the lowest increase seen for placebo (0.2 kg), followed by asenapine 5-10 mg BID (1.3 kg) and olanzapine (2.3 kg). The proportion of subjects who had a ≥ 7% weight gain showed a similar trend: placebo (0.5%), asenapine 5-10 mg BID (5.8%), and olanzapine (14.7%).

Figure 12 Mean body weight change, short-term bipolar mania trials



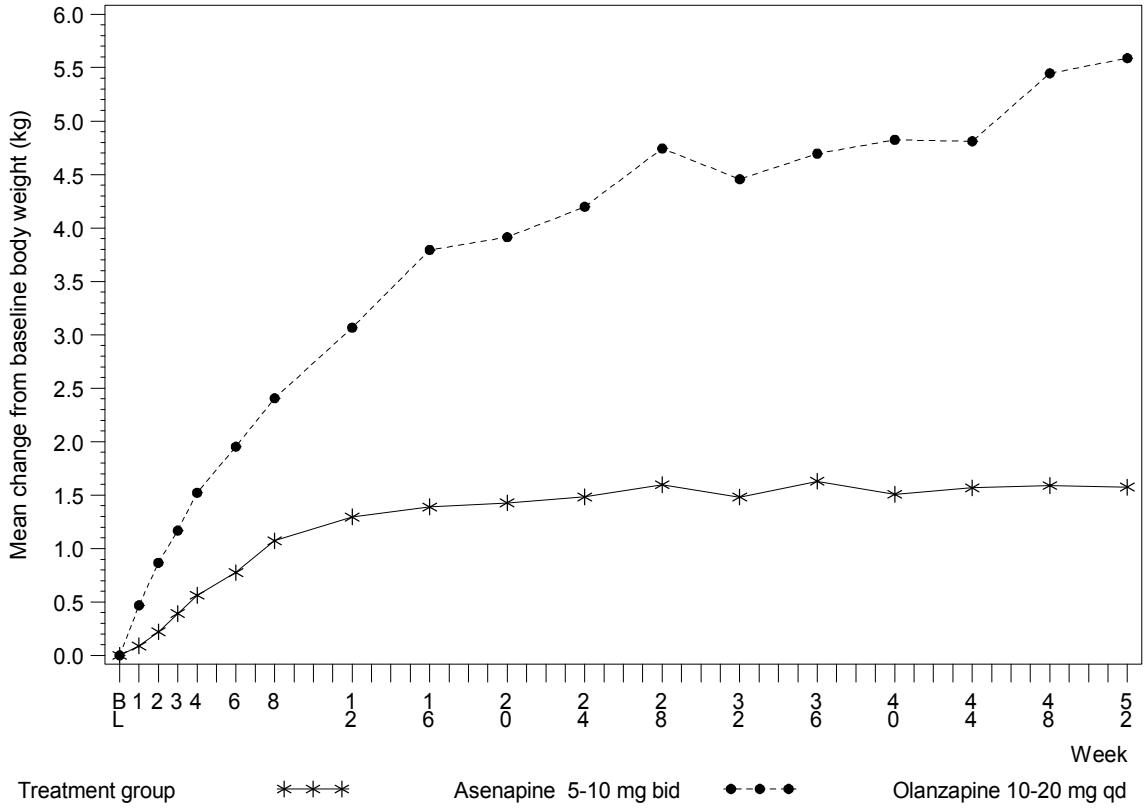
BID = twice daily; QD = once daily

Body weight in long-term schizophrenia trial

Figure 13 shows the mean change in body weight from baseline over time (OC analysis). At 12 weeks the mean weight gain stabilized for the asenapine 5-10 mg BID group in contrast to the olanzapine 10-20 mg QD group, which showed continued weight gain up till 52 weeks of treatment. At 52 weeks, the mean change from baseline in body weight was 1.57 kg in the asenapine group and 5.59 kg in the olanzapine group. Mean change from baseline in body weight at endpoint was 0.91 kg in the asenapine group and 4.18 kg in the olanzapine group.

At 52 weeks, the percentage of subjects having body weight increases of ≥ 7% was 22.5% in the asenapine group and 44.4% in the olanzapine group. At endpoint, the percentage of subjects having body weight increases of ≥ 7% was 14.7% in the asenapine group and 36.1% in the olanzapine group.

Figure 13 Mean change from baseline in body weight (kg), long-term schizophrenia trial (All-Subjects-Treated, OC)



BID = twice daily; BL = baseline; OC = observed cases; QD = once daily

The mean weight change from baseline to endpoint for asenapine was lower than for olanzapine in each baseline BMI category, as was the percentage of subjects with a ≥ 7% increase in body weight (Table 37).

Table 37 Weight Change to endpoint by baseline BMI category in long-term schizophrenia safety trial

	Asenapine 5-10 mg BID			Olanzapine 10-20 mg QD		
	BMI < 23 N=295	BMI 23 - ≤27 N=290	BMI > 27 N=302	BMI < 23 N=98	BMI 23 - ≤27 N=111	BMI > 27 N=96
Mean change (SE) from Baseline (kg)[a]	1.72 (0.24)	0.97 (0.26)	0.04 (0.32)	6.98 (0.84)	3.73 (0.54)	1.84 (0.81)
≥ 7% increase in body weight[b]	22.0	12.8	9.3	57.1	29.7	21.9

a Change to endpoint

b % of subjects

SE = standard error

BID = twice daily; BMI = body mass index; QD = once daily

Summary

Asenapine has limited effect on mean body weight, showing less weight gain (1.1 kg) than risperidone (2.0 kg) and olanzapine (3.4 kg) in the combined phase 2/3 trials. Data from the long term schizophrenia trial show that mean weight gain stabilized after approximately 12 weeks of treatment with asenapine, in contrast to olanzapine treatment, which showed continued weight gain up till 52 weeks of treatment. Mean body weight gain was inversely correlated with baseline BMI; obese subjects (BMI > 27 kg/m^2) treated with asenapine showed minimal mean weight gain.

4.4.1.2. Glucose control

Asenapine has shown limited effects on glucose-related laboratory parameters, such as fasting glucose, fasting insulin, and glycated hemoglobin (HbA1c). In the short-term bipolar trials, mean changes from baseline to endpoint were comparable with the placebo group (Table 40). In the short term schizophrenia trials, a mild increase in fasting glucose, comparable with increases seen in the olanzapine and risperidone groups, was observed (Table 38). Incidence of significantly elevated glucose parameters was similar across all treatment groups (Table 39, Table 41, Table 43). A mean increase in fasting glucose, which was lower than for olanzapine, was observed for asenapine in the long-term schizophrenia trial (Table 42). A review of adverse events related to glucose metabolism disorders did not raise a concern of an adverse effect of asenapine on glucose control. Overall, we conclude there are no clinically important glucose changes.

Short-term schizophrenia trials

Table 38 Mean difference from baseline in glucose control laboratory values, short-term schizophrenia trials

Test Name	Units	Placebo N = 503		Asenapine 5-10 mg BID[a] N = 572		Risperidone 3 mg BID N = 120		Haloperidol 4 mg BID N = 115		Olanzapine 10-20 mg QD[b] N = 194	
		n[c]	Mean (SD)	n[c]	Mean (SD)	n[c]	Mean (SD)	n[c]	Mean (SD)	n[c]	Mean (SD)
Insulin total fasting	ng/dL	232	-14.83 (106.602)	372	-0.51 (90.576)	--	--	84	1.26 (166.272)	136	11.99 (121.182)
Glucose fasting	mg/dL	350	-1.64 (26.544)	377	3.24 (26.250)	60	-0.83 (32.361)	87	2.20 (22.379)	138	4.00 (31.287)
HbA1c	%	276	-0.02 (0.281)	453	0.02 (0.349)	--	--	95	-0.05 (0.269)	180	0.05 (0.374)

a Fixed and flexible dosing

b Flexible dosing

c n = n assessed (denominator for the mean calculation)

HbA1c = glycated hemoglobin; SD = standard deviation

Table 39 Summary of subjects with post−baseline markedly abnormal glucose control laboratory changes/values short-term schizophrenia trials

Test Name	Criteria	Placebo N = 503		Asenapine 5-10 mg BID[a] N = 572		Risperidone 3 mg BID N = 120		Haloperidol 4 mg BID N = 115		Olanzapine 10-20 mg QD[b] N = 194	
		n[c]	n (%)	n[c]	n (%)	n[c]	n (%)	n[c]	n (%)	n[c]	n (%)
Glucose fasting	> 1.5 x ULN	357	10 (2.8)	397	12 (3.0)	60	2 (3.3)	89	3 (3.4)	148	5 (3.4)
Glucose fasting	> 2 x ULN	281	2 (0.7)	461	5 (1.1)	--	--	98	0 (0.0)	180	4 (2.2)
HbA1c	> 8.0%	357	4 (1.1)	397	4 (1.0)	60	1 (1.7)	89	2 (2.2)	148	3 (2.0)

a Fixed and flexible dosing

b Flexible dosing

c n = n assessed (denominator for the mean calculation)

BID = twice daily; HbA1c = glycated hemoglobin; QD = once daily; ULN = upper limit of normal

Short-term bipolar mania trials

Table 40 Mean difference from baseline in glucose control laboratory values, short-term bipolar mania trials

Test Name	Units	Placebo N = 203			Asenapine 5-10 mg BID N = 370			Olanzapine 5 – 20 mg QD N = 394		
		n[a]	Mean	SD	n[a]	Mean	SD	n[a]	Mean	SD
Insulin total fasting	ng/dL	105	6.73	160.308	207	5.13	118.938	233	17.64	144.906
Glucose fasting	mg/dL	89	-0.55	22.619	156	-0.62	19.237	176	1.16	21.857
HbA1c	%	157	0.02	0.374	315	0.08	0.420	339	0.10	0.475

a n = n assessed (denominator for the mean calculation)

BID = twice daily; HbA1c = glycated hemoglobin; QD = once daily; SD = standard deviation

Table 41 Summary of subjects with post−baseline markedly abnormal glucose control changes/values short-term bipolar mania trials

Test name	Criteria	Placebo N = 203		Asenapine 5-10 mg BID N = 379		Olanzapine 5-20 mg QD N = 394	
		n[a]	n (%)	n[a]	n (%)	n[a]	n (%)
Glucose fasting	> 1.5 x ULN	89	1 (1.1)	164	1 (0.6)	180	3 (1.7)
Glucose fasting	> 2 x ULN	89	1 (1.1)	164	0 (0.0)	180	1 (0.6)
HbA1c	> 8.0%	160	0 (0.0)	319	3 (0.9)	341	5 (1.5)

a n = n assessed

BID = twice daily; HbA1c = glycated hemoglobin; QD = once daily; ULN = upper limit of normal

Long-term schizophrenia trial

(HbA1c was not measured in the long-term schizophrenia trial).

Table 42 Mean difference from baseline in glucose control laboratory values, long-term schizophrenia trial

Test Name	Units	Asenapine 5−10 mg BID (Flex) N = 908			Olanzapine 5−20 mg QD (Flex) N =311		
		n[a]	Mean	SD	n[a]	Mean	SD
Glucose fasting	mg/dL	548	2.391	21.679	195	3.510	25.128

a n = n assessed (denominator for the mean calculation)

BID = twice daily; QD = once daily; SD = standard deviation

Table 43 Summary of subjects with post−baseline markedly abnormal glucose control laboratory changes/values, long-term schizophrenia trial

Test Name	Criteria	Asenapine 5−10 mg BID (Flex) N = 908		Olanzapine 5−20 mg QD (Flex) N =311	
		n[a]	n (%)	n[a]	n (%)
Glucose fasting	> 1.5 x ULN	548	7 (1.3)	196	3 (1.5)
Glucose fasting	> 2 x ULN	548	2 (0.4)	196	1 (0.5)

a n = n assessed

BID = twice daily; QD = once daily; ULN = upper limit of normal

4.4.1.3. Lipids (cholesterol, HDL, LDL, fasting triglyceride)

Asenapine has shown limited effects on total cholesterol, low density lipoprotein (LDL) cholesterol, and fasting triglycerides (Table 45, Table 47, Table 49). Mean decreases in total cholesterol and fasting triglyceride levels were seen at endpoint in the long-term schizophrenia trial (Table 48). In the short-term schizophrenia trials and short-term bipolar trials, minimal changes in lipid levels were observed (Table 44, Table 46). In contrast, olanzapine clearly showed increases in fasting triglycerides, total cholesterol, and LDL cholesterol across all subject groupings (Table 44, Table 46, Table 48). Overall, and particularly from the long-term data in subjects with schizophrenia, there are no clinically important lipid changes with asenapine treatment.

Short-term schizophrenia trials

Table 44 Mean difference from baseline in lipid laboratory values, short-term schizophrenia trials

Test Name	Units	Placebo N = 503		Asenapine 5-10 mg BID[a] N = 572		Risperidone 3 mg BID N = 120		Haloperidol 4 mg BID N = 115		Olanzapine 10-20 mg QD[b] N = 194	
		n[c]	Mean (SD)	n[c]	Mean (SD)	n[c]	Mean (SD)	n[c]	Mean (SD_	n[c]	Mean (SD)
Cholesterol total	mg/dL	469	-3.61 (31.619)	539	0.37 (30.464)	116	0.75 (34.192)	106	-1.60 (26.829)	181	6.98 (34.351)
HDL-Cholesterol		290	0.51 (9.330)	480	0.55 (9.940)	--		106	0.38 (10.793)	181	1.03 (10.619)
LDL-Cholesterol	mg/dL	285	0.13 (27.774)	465	1.34 (26.738)	--		105	-0.86 (25.223)	169	2.04 (31.306)
Triglycerides fasting	mg/dL	295	-13.47 (79.464)	380	3.85 (104.257)	--		88	-8.85 (76.194)	139	19.80 (94.262)

mg/dL

a Fixed and flexible dosing

b Flexible dosing

c n = n assessed (denominator for the mean calculation)

BID = twice daily; HDL = high density lipoprotein; LDL = low density lipoprotein; QD = once daily; SD = standard deviation

Table 45 Summary of subjects with post−baseline markedly abnormal lipid laboratory changes/values, short-term schizophrenia trials

Test Name	Criteria	Placebo N = 503		Asenapine 5-10 mg BID[a] N = 572		Risperidone 3 mg BID N = 120		Haloperidol 4 mg BID N = 115		Olanzapine 10-20 mg QD[b] N = 194	
		n[c]	n (%)	n[c]	n (%)	n[c]	n (%)	n[c]	n (%)	n[c]	n (%)
Cholesterol total	>50% above ULN	470	1 (0.2)	541	0 (0.0)	116	0 (0.0)	106	0 (0.0)	182	1 (0.5)
LDL−Cholesterol	> 50% above ULN	288	0 (0.0)	468	2 (0.4)	--		105	0 (0.0)	174	1 (0.6)
Triglycerides fasting	> 5.65 mmol/L in a fasting state	302	4 (1.3)	400	7 (1.8)	--		89	1 (1.1)	148	6 (4.1)

a Fixed and flexible dosing

b Flexible dosing

c n = n assessed

BID = twice daily; LDL = low density lipoprotein; QD = once daily; ULN = upper limit of normal

Short-term bipolar mania trials

Table 46 Mean difference from baseline in lipid laboratory values, short-term bipolar mania trials

Test Name	Units	Placebo N = 203			Asenapine 5-10 mg BID N = 370			Olanzapine 5 – 20 mg QD N = 394		
		n[a]	Mean	SD	n[a]	Mean	SD	n[a]	Mean	SD
Cholesterol total	mg/dL	163	-1.54	29.780	322	1.05	33.285	347	12.59	33.584
HDL-Cholesterol	mg/dL	163	-0.03	9.099	322	0.93	9.513	346	1.02	10.587
LDL-Cholesterol	mg/dL	158	1.90	25.594	304	1.65	29.475	335	6.32	30.387
Triglycerides fasting	mg/dL	129	-17.86	101.033	237	-3.54	104.949	278	29.36	93.285

a n = n assessed (denominator for the mean calculation)

BID = twice daily; HDL = high density lipoprotein; LDL = low density lipoprotein; QD = once daily; SD = standard deviation

Table 47 Summary of subjects with post−baseline markedly abnormal lipid laboratory changes/values short-term bipolar mania trials

Test name	Criteria	Placebo N = 203		Asenapine 5-10 mg BID N = 379		Olanzapine 5-20 mg QD N = 394	
		n[a]	n (%)	n[a]	n (%)	n[a]	n (%)
Cholesterol total	> 50% above ULN	164	2 (1.2)	323	1 (0.3)	348	1 (0.3)
LDL−Cholesterol	> 50% above ULN	164	3 (1.8)	322	4 (1.2)	348	4 (1.1)
Triglycerides fasting	> 5.65 mmol/L in a fasting state	132	1 (0.8)	252	2 (0.8)	285	6 (2.1)

BID = twice daily; LDL = low density lipoprotein; ULN = upper limit of normal

Long-term schizophrenia trial

Table 48 Mean difference from baseline in lipid laboratory values, long-term schizophrenia trial

Test Name	Units	Asenapine 5−10 mg BID (Flex) N = 908			Olanzapine 5−20 mg QD (Flex) N =311		
		n[a]	Mean	SD	n[a]	Mean	SD
Cholesterol total	mg/dL	887	-6.023	35.942	304	3.216	38.359
Triglycerides fasting	mg/dL	546	-9.823	92.248	196	30.407	202.611

a n = n assessed (denominator for the mean calculation)

BID = twice daily ; QD = once daily ; SD = standard deviation

Table 49 Summary of subjects with post−baseline markedly abnormal lipid laboratory changes/values, long-term schizophrenia trial

Test Name	Criteria	Asenapine 5−10 mg BID (Flex) N = 908		Olanzapine 5−20 mg QD (Flex) N =311	
		n[a]	n (%)	n[a]	n (%)
Cholesterol total	> 50% above ULN	888	17 (1.9)	304	8 (2.6)
Triglycerides fasting	> 5.65 mmol/L in a fasting state	546	18 (3.3)	196	8 (4.1)

a n = n assessed

ULN = upper limit of normal

4.4.2. Extrapyramidal symptoms (EPS)

The data demonstrate that asenapine has a lower incidence of EPS effects than that seen with first generation (typical) antipsychotics, such as haloperidol. The EPS profile of asenapine was more comparable to other second generation (atypical) antipsychotic treatments used in the clinical program, such as risperidone and olanzapine.

In the short term schizophrenia trials the incidence of adverse events related to EPS was 13.6% in the asenapine 5-10 mg BID group vs. 7.8% in the placebo group, 39.1% for haloperidol, 8.8% for olanzapine and 7.5% for risperidone (Table 50). There was an apparent dose-relationship observed for EPS, which is not unusual with the use of antipsychotics in general. Using rating scales, Abnormal Involuntary Movement Scale (AIMS) for dyskinesia, Barnes Akathisia Rating Scale (BARS) for akathisia, and Simpson-Angus Rating Scale (SARS) for parkinsonism, the proportion of asenapine 5-10 mg BID subjects meeting clinically relevant threshold values for these scales was comparable with placebo (Figure 14) and considerably lower than with haloperidol in terms of akathisia and dyskinesia.

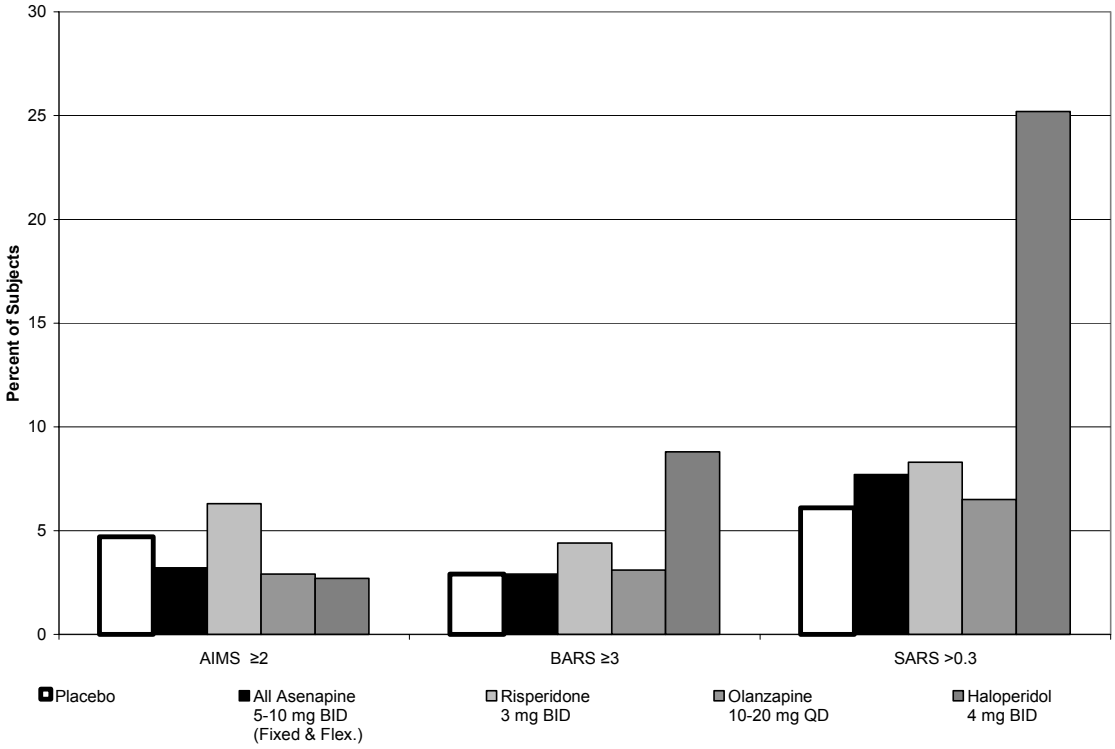
In the short term bipolar trials the incidence of EPS was comparable to olanzapine (10.0% vs. 9.4%) and higher than placebo (4.4%, Table 51). EPS rating scales showed only a small proportion of asenapine treated subjects reaching the threshold for AIMS, BARS and SARS (all below 6%) comparable to placebo and olanzapine with the exception of dyskinesia (SARS, Figure 15) which was higher than the placebo group.

Table 50 Adverse events by EPS category (6-week schizophrenia trials)

Adverse Event EPS Category N (%)	Placebo (N=503)	Asenapine BID <5 mg (N=298)	Asenapine BID 5 mg Fixed Dose (N=274)	Asenapine BID 10 mg Fixed Dose (N=208)	Asenapine BID 5–10 mg Flexible Dose (N=90)	Asenapine BID All 5-10 mg (N=572)	Risperidone 3 mg BID (N=120)	Haloperidol 4 mg BID (N=115)	Olanzapine 10-20 mg QD (N=194)
Any adverse event	39 (7.8)	19 (6.4)	30 (10.9)	38 (18.3)	10 (11.1)	78 (13.6)	9 (7.5)	45 (39.1)	17 (8.8)
EPS categories									
Akathisia	13 (2.6)	2 (0.7)	11 (4.0)	22 (10.6)	3 (3.3)	36 (6.3)	5 (4.2)	17 (14.8)	9 (4.6)
Dyskinesia	5 (1.0)	4 (1.3)	1 (0.4)	4 (1.9)	1 (1.1)	6 (1.0)	1 (0.8)	3 (2.6)	0
Dystonia	4 (0.8)	2 (0.7)	6 (2.2)	4 (1.9)	5 (5.6)	15 (2.6)	1 (0.8)	11 (9.6)	2 (1.0)
Parkinsonism	14 (2.8)	6 (2.0)	14 (5.1)	16 (7.7)	2 (2.2)	32 (5.6)	0	22 (19.1)	6 (3.1)
Unspecified	6 (1.2)	6 (2.0)	2 (0.7)	0	0	2 (0.3)	3 (2.5)	1 (0.9)	1 (0.5)

BID = twice daily; EPS = extrapyramidal symptoms; QD = once daily

Figure 14 EPS rating scale results, short-term schizophrenia trials



AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; BID = twice daily; EPS = extrapyramidal symptoms; QD = once daily; SARS = Simpson-Angus Rating Scale

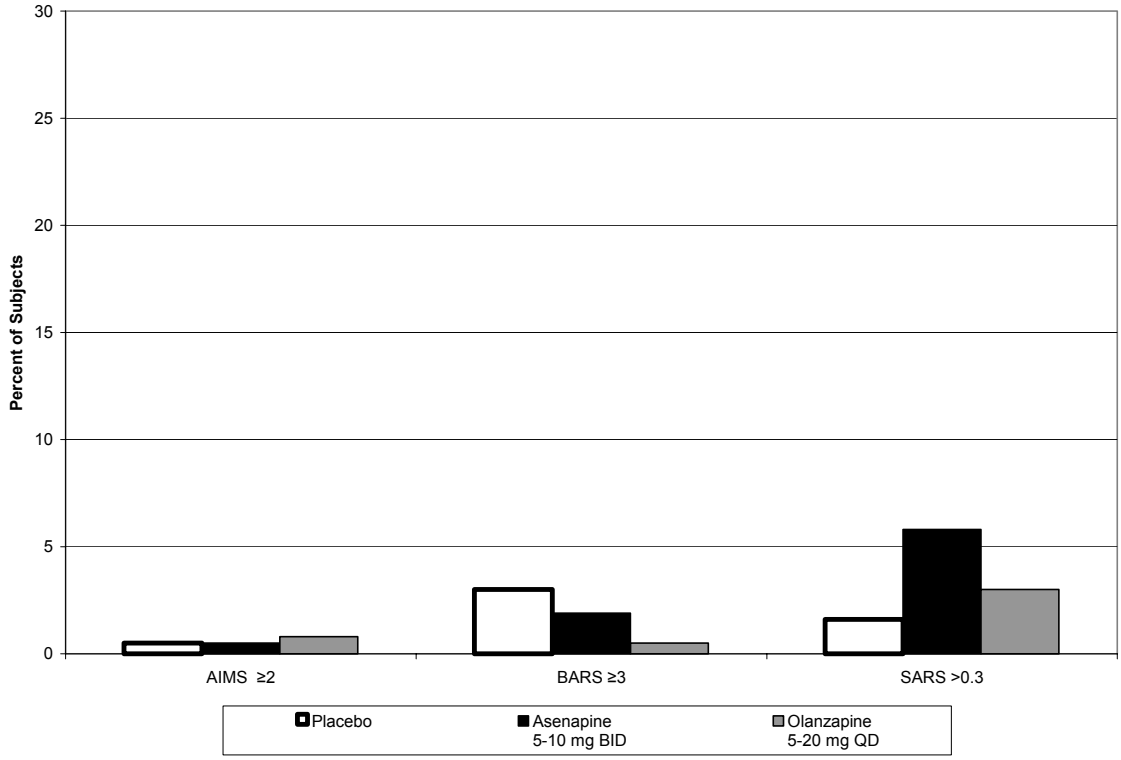
Short-term bipolar mania trials

Table 51 Adverse events by EPS category (3-week bipolar mania trials)

Adverse Event EPS Category N (%)	Placebo (N=203)	Asenapine 5-10 mg BID flexible dose (N=379)	Olanzapine 5-20 mg QD flexible dose (N=394)
Any adverse event	9 (4.4)	38 (10.0)	37 (9.4)
EPS categories			
Akathisia	5 (2.5)	15 (4.0)	21 (5.3)
Dyskinesia	0	4 (1.1)	0
Dystonia	2 (1.0)	12 (3.2)	4 (1.0)
Parkinsonism	3 (1.5)	16 (4.2)	17 (4.3)

BID = twice daily; EPS = extrapyramidal symptoms; QD = once daily

Figure 15 EPS rating scale results, short-term bipolar mania trials



AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; BID = twice daily; EPS = extrapyramidal symptoms; QD = once daily; SARS = Simpson-Angus Rating Scale

4.4.3. Suicidality

Overall, asenapine 5-10 mg twice daily does not show an increased risk of suicidal ideation and behavior compared with placebo or olanzapine.

4.4.3.1. Adverse events associated with suicidality

The incidence of adverse events associated with suicide and self-injurious behavior in the combined completed phase 2/3 trials as of the February 2009 Safety Update cutoff is presented in Table 52. There were eight completed suicides in the asenapine 5-10 mg BID group (0.3%) and 4 in the olanzapine group (0.4%). Brief narratives for the 12 cases of completed suicides are provided below:

Asenapine-treated subjects

- 49-year-old man with a history of bipolar I disorder, diabetes mellitus and hypertension was self-admitted to the clinic due to a manic episode. He was started on asenapine on Day 3 of hospitalization and was discharged 12 days later. At time of discharge, he reported feeling well without signs of suicidality.

Two days after discharge, the investigator was notified that subject had committed suicide by jumping off a bridge. There was no history of suicide attempts. Before committing suicide, he told his girlfriend of his plan. There were possible relationship problems, since his girlfriend was married to someone else. Autopsy report states drowning as cause of death. The investigator assessed the event as possibly related to asenapine.

- 65-year-old man with a history of schizophrenia was started on asenapine treatment. Subject was rated as chronically suicidal without being at high risk of suicide. Approximately 3 weeks later, asenapine dosage was increased due to persistent schizophrenia symptoms (lack of organization). At that time there was no indication of suicidal behavior. Two days later, he was found dead in a forest. He committed suicide by hanging. No autopsy was performed. The investigator assessed the event as possibly related to asenapine.

- 32-year-old man with a history of schizophrenia with hospitalization started asenapine for the treatment of schizophrenia. The subject did not have history of suicidal behavior or other psychiatric disorders. The patient had not suffered from depressive illness in the past, but the schizophrenic disease had been accompanied by negative symptoms. Approximately 5 months after initiating asenapine treatment, he experienced an exacerbation of schizophrenia and committed suicide by hanging. Subject had left a suicide note for his father. Autopsy reported strangulation as the cause of death. The investigator assessed this event as not related to asenapine.

- 25-year-old man with a history of paranoid schizophrenia diagnosed since he was 17, positive family history for suicide (father), and previous suicide attempts was treated with asenapine. The subject also had multiple hospital admissions for the treatment of schizophrenia. Seventeen days after starting asenapine treatment, he experienced an exacerbation of schizophrenia and committed suicide by hanging. No autopsy report was available. The investigator assessed this event as not related to asenapine.

- 25-year-old man with a history of schizophrenia was treated with asenapine. The subject did not have a history of suicidal behavior. Approximately 1 month after starting asenapine treatment, he committed suicide by hanging. There were no warning signs of depression or worsening of his schizophrenia prior to the event. The autopsy report confirmed the cause of death as suffocation by hanging. The investigator assessed this event as unlikely related to asenapine.

- 21-year-old man with a history of schizophrenia was treated with asenapine. One week after starting asenapine treatment, he committed suicide by jumping off a high building. The subject had a history of suicide attempts, suicidal ideation, and

automutilation. There is no information if an autopsy was performed. The investigator assessed this event as unlikely related to asenapine.

- 32-year-old man with a history of schizophrenia was treated with asenapine. Approximately 9 months after starting asenapine treatment, he had an exacerbation of schizophrenia and committed suicide by hanging. Subject had a history of suicidal behavior (cutting his wrists in 1995). There is no information if autopsy was performed. The investigator assessed this event as unlikely related to asenapine.

- 24-year-old man with a history of schizophrenia and suicidal behavior (suicide attempt in 2004) was treated with asenapine. Approximately 5 months after starting asenapine treatment, he was found dead at home by his parents. An empty package of clozapine (50 tabs, 100mg each) was found and suicide was suspected. The subject took the last dose of asenapine one day before he committed suicide. Autopsy showed lethal doses of clozapine in the kidney. The cause of death was reported as acute poisoning with clozapine. The investigator assessed this event as unlikely related to asenapine.

Olanzapine-treated subjects

- 52-year-old man with no history of suicidal ideations or suicide attempts was treated with olanzapine. Two months later, the dose of olanzapine was increased by one titration step. The dose was again increased 2 weeks after the last dose increase. Approximately 3 months after starting olanzapine, he experienced increased tiredness and "oral propensity for addiction". He decided to stop taking olanzapine 6 months after starting olanzapine. He continued to feel tired but felt better concerning his thought disorders. At the end of trial visit, 7 months after starting olanzapine, he denied having any suicidal thoughts. One week after the last trial visit, he committed suicide by standing on the rail tracks of a city train. The investigator assessed this event as not related to olanzapine.

- 40-year-old woman with a history of bipolar affective disorder was treated with olanzapine. The subject did not report to the site for a scheduled visit 12 days after the start of olanzapine. A bystander (not specified) reported that the subject had an argument with her husband and she committed suicide by consuming organophosphates a day prior to the scheduled visit. No autopsy was performed. The investigator assessed this event as not related to olanzapine.

- 42-year-old man with a history of schizophrenia, undifferentiated type since 2004 and no history of suicide attempts was treated with olanzapine. Approximately 7 months after starting olanzapine, the investigator hospitalized the subject in a psychiatric rehabilitation ward to increase the improvement of the subject. There was no worsening of symptoms that would necessitate the hospitalization. No

depression or psychotic symptoms were reported during the hospitalization. Approximately 1 year after starting olanzapine, while the subject was still in the hospital, he committed suicide by hanging himself. No autopsy was performed. The investigator assessed this event as not related to olanzapine.

- 24-year-old man with a history of bipolar mania or mixed episodes, suicidal gesture (cord around his neck), occasional suicidal ideation, and depression was treated with olanzapine. Three months after participating in the extension trial, the site was notified by the subject's mother that her son had passed away due to a self-inflicted gunshot wound to the head. Subject had talked to his mother earlier that day and he had asked money from her to buy medication for his shoulder pain. Subject's mother was not able to help him financially during this time. The autopsy report confirmed the cause of death as self-inflicted gunshot wound to the head. The investigator considered the suicide as not related to olanzapine.

Most events related to suicidality (78/115, 68%) were considered serious adverse events, 52 (45%) of the events led to discontinuation. The incidence of suicidal behaviors that led to discontinuation was comparable between asenapine 5-10 mg BID (1.0%) and olanzapine (0.8%). The incidence of suicidal behaviors that were considered serious adverse events was similar between asenapine 5-10 mg BID and olanzapine (both 1.8%).

Table 52 Adverse events related to suicidality (combined completed phase 2/3 trials, February 2009 Safety Update cutoff)

Adverse Event SOC/ Preferred Term n (%)	Placebo (N=1064)	Asenapine			Risperidone 3 mg BID (N=120)	Haloperidone 2-8 mg BID (N=115)	Olanzapine 5-20 mg QD (N=1139)
		<5 mg BID (N=298)	5-10 mg[a] BID (N=3159)	All (N=3457)			
Psychiatric disorders							
HLGT Suicidal and self-injurious behaviours	13 (1.2)	9 (3.0)	65 (2.1)	74 (2.1)	3 (2.5)	1 (0.9)	24 (2.1)
SAEs	4 (0.4)	3 (1.0)	47 (1.5)	50 (1.4)	2 (1.7)	1 (0.9)	21 (1.8)
Discontinuations	7 (0.7)	2 (0.7)	31 (1.0)	33 (1.0)	2 (1.7)	1 (0.9)	9 (0.8)
Completed suicide	0	0	8 (0.3)	8 (0.2)	0	0	4 (0.4)
Intentional self injury	2 (0.2)	1 (0.3)	3 (0.1)	4 (0.1)	0	0	1 (0.1)
Self injurious ideation	0	0	1 (0.0)	1 (0.0)	0	0	0
Suicidal behaviour	1 (0.1)	1 (0.3)	0	1 (0.0)	0	0	1 (0.1)
Suicidal ideation	9 (0.8)	8 (2.7)	40 (1.3)	48 (1.4)	2 (1.7)	0	10 (0.9)
Suicide attempt	2 (0.2)	0	16 (0.5)	16 (0.5)	1 (0.8)	1 (0.9)	8 (0.7)
Subject exposure years	145	34	1352	1386	21	35	571
HLGT Suicidal and self-injurious behaviours	13	9	65	74	3	1	24
Incidence[b]	8.99	26.24	4.81	5.34	14.29	2.89	4.20
Completed suicide	0	0	8	8	0	0	4
Incidence[b]	0	0	0.59	0.58	0	0	0.70
Suicide attempt	2	0	16	16	1	1	8
Incidence[b]	1.38	0	1.18	1.15	4.76	2.89	1.40
Suicidal ideation	9	8	40	48	2	0	10
Incidence[b]	6.22	23.3	2.96	3.46	9.53	0	1.75

a fixed and flexible doses

b incidence /100 exposure years

BID = twice daily; MedDRA = Medical Dictionary for Regulatory Affairs; QD = once daily; SAE = serious adverse event; SOC HLGT = MedDRA high level group term

4.4.3.2. Suicidality by exposure years

An analysis of suicidality per 100 subject exposure years shows that for the effective dose of asenapine (5-10 mg twice daily), the incidence for suicidal ideation was 2.96 per 100 exposure years and the incidence of events in the Medical Dictionary for Regulatory Affairs (MedDRA) high level group term (HLGT) of suicidal and self-injurious behaviors was 4.81 per 100 exposure years, both are lower than placebo (6.22 and 8.99 per 100 exposure years, respectively) and comparable with olanzapine (1.75 and 4.20 per 100 exposure years, respectively). The incidence of suicide attempt with asenapine 5-10 mg twice daily was 1.18 per 100 exposure years, which is comparable to placebo (1.38 per 100 exposure years) and olanzapine (1.40 per 100 exposure years). The incidence of completed suicides was 0.59 per 100 exposure years for the asenapine 5-10 mg BID group, which is comparable to olanzapine (0.70 per 100 exposure years). There were no cases of completed suicides in the placebo, asenapine < 5 mg BID, haloperidol, and risperidone groups; this observation is possibly a result of the much shorter exposure time in these treatment groups.

4.4.3.3. Intersept Scale for Suicidal Thinking

An analysis of the InterSePT Scale for Suicidal Thinking (ISST) was conducted in some trials. The InterSePT scale is a 12-item instrument for the assessment of current suicidal ideation with a maximum score of two points per item (Lindenmayer et al, 2003).

For the combined phase 3 trials completed by the NDA cutoff, the mean total score and change from baseline at each time point and endpoint showed a decrease in the mean total score across all treatment groups throughout the trials and at endpoint (-0.1 placebo, -0.1 asenapine 5-10 mg BID, 0.2 haloperidol, and -0.2 olanzapine). No differences among the treatment groups were observed.

An analysis of the ISST was conducted in the phase 3 short-term schizophrenia trials, Trials 041021, 041022, and 041023. The results of the mean total score and change from baseline at Day 42 and endpoint showed a small increase in the mean total score at endpoint, with essentially no differences among the treatment groups (0.4 for placebo, 0.5 for all asenapine 5-10 mg BID, 0.2 for haloperidol, and 0.6 for olanzapine).

4.4.3.4. Summary

Based on subject-years exposure, asenapine 5-10 mg twice daily does not show an increased risk of suicidal ideation and behavior compared with placebo or olanzapine. An analysis of the ISST showed no differences in scores among treatment groups.

4.4.4. Cardiovascular safety

4.4.4.1. QTc prolongation

In a dedicated QT trial, asenapine was shown to produce a mild QT prolongation. Additionally, based on an investigation of adverse events that may be indicative of QT prolongation as well as an evaluation of electrocardiogram (ECG) outliers, there is no suggestion that asenapine is associated with clinically relevant QT prolongation.

Dedicated QT trial

A dedicated QT trial (A7501001) was conducted to assess the effect of asenapine, compared with placebo, on the QT interval. Subjects with schizophrenia were assigned to either placebo (n = 35), asenapine 5/10 mg BID (n = 38), asenapine 15/20 mg BID (n = 38), or quetiapine 375 mg BID (n = 37). For the asenapine groups, 38 subjects received asenapine 5 mg BID (Days 1 to 10), 29 continued to receive asenapine 10 mg BID (Days 11 to 16), 38 subjects received asenapine 15 mg BID (Days 1 to 10), and 32 continued to receive asenapine 20 mg BID (Days 11 to 16). Serial ECGs were performed in triplicate at predose and 1, 2, 3, 4, 6, 8, and 12 hours following the morning dose of study medication on Days 1, 10, and 16.

Analysis of the primary endpoint (the difference from placebo in time-matched change from baseline in QTcF [dQTcF] at t_{max}, Table 53) indicated a potential for asenapine to prolong the QTc interval. The QTc prolongation at t_{max} was statistically significant only for the 10 mg twice daily dose regimen of asenapine and for quetiapine on Day 16. A dose-response relationship for asenapine was not apparent. Overall, estimates of QTc prolongation at this single time point were relatively imprecise, as denoted by the large confidence intervals.

Table 53 Dedicated QT trial: Summary of mean estimates of QTcF prolongation at t_{max} compared with placebo

Treatment	Day	Time matched dQTcF from placebo at t_{max}	
		Mean (msec)	95% CI
Asenapine 5 mg BID	10	2.6	-4.5, 9.7
Asenapine 10 mg BID	16	10.5	2.6, 18.3
Asenapine 15 mg BID	10	6.4	-0.5, 13.4
Asenapine 20 mg BID	16	5.2	-2.5, 12.9
Quetiapine 375 mg BID	10	6.7	-0.4, 13.8
Quetiapine 375 mg BID	16	9.9	2.1, 17.8

BID = twice daily; CI = confidence interval dQTcF = change from baseline in QTcF; QTcF = QT interval corrected for heart rate, Fridericia correction; tmax = time of maximal concentration

PK-PD modeling was a prespecified secondary analysis in this trial. As this method allowed all QTc data to be analyzed simultaneously, it resulted in a more precise estimation of the drug-related QTc prolongation for asenapine and quetiapine. In line with the primary analysis results, PK-PD modeling showed a significant, but mild,

positive effect of both asenapine and quetiapine on the QTc interval, which was linearly related to plasma concentrations of both drugs. The point estimates of QTc prolongation associated with mean steady state asenapine C_{max} values ranged from 2 to 5 msec across the doses studied and were smaller than those for quetiapine at the tested dose (7-8 msec). At the therapeutic doses of 5 and 10 mg twice daily the upper bound of the 95% confidence interval of the mean asenapine effect was less than 5 msec.

None of the asenapine-treated subjects in this trial experienced a QTc increase from baseline ≥60 msec at any dose, whereas 1 subject in the quetiapine group and 4 subjects in the placebo group experienced such an increase. None of the subjects in any treatment group had a QTcF value ≥ 480 msec.

In conclusion, results from this trial indicate that asenapine has a mild effect on QTc but not more than that seen with quetiapine.

Evaluation of QT data in Phase 3 program

In the long-term phase 3 schizophrenia trial (Trial 25517) ECGs were performed at Screening, Weeks 3, 6, 24, and Endpoint, and the tracings were read by a central laboratory. No subjects on asenapine 5–10 mg twice daily or olanzapine 10-20 mg once daily had a QTc interval > 500 msec (Fridericia corrected). Three subjects on asenapine (0.3%) and one subject on olanzapine (0.3%) had a QTc prolongation from baseline >60 msec.

The PK-PD model from the dedicated QT trial was used to create unconditional prediction intervals to check the consistency in distribution of the QTc data from Trial 25517 and that predicted by the model. The observed phase 3 dQTcF versus concentration data were in line with the prediction intervals with a tendency of a larger percentage of dQTcF observations below the median predicted dQTcF. These results further corroborated the mild prolonging effect of asenapine on QTc.

Adverse events potentially related to QT prolongation in phase 2/3 population

The incidence of adverse events associated with QT prolongation in the combined Phase 2/3 trial population is summarized in Table 54. No serious adverse events associated with QT prolongation (sudden death, cardiac arrest, ventricular fibrillation, or torsade des pointes) were observed.

Table 54 Adverse events potentially related to QT prolongation (combined phase 2/3 trials)

Adverse Event SOC/ Preferred Term n (%)	Placebo (N=706)	Asenapine 5-10 mg BID (N=1953)	Risperidone 3 mg BID (N=120)	Haloperidol 4 mg BID (N=115)	Olanzapine 5-20 mg QD (N=899)
Cardiac disorders					
Ventricular tachycardia	1 (0.1)	0	0	0	0
Investigations					
ECG QTc interval prolonged	1 (0.1)	15 (0.8)	0	0	3 (0.3)
ECG QT prolonged	2 (0.3)	2 (0.1)	0	0	0
Nervous system disorders					
Syncope	1 (0.1)	10 (0.5)	0	0	4 (0.4)
Syncope vasovagal	0	1 (0.1)	0	0	0
Vascular disorders					
Circulatory collapse	0	1 (0.1)	0	0	0

There were no episodes of sudden death, cardiac arrest, ventricular fibrillation, or torsade des pointes

BID = twice daily; dQTcF = change from baseline in QTcF; ECG = electrocardiogram; QTcF = QT interval corrected for heart rate, Fridericia correction; SOC = system organ class

The incidence of QTc interval prolonged, reported as an adverse event, was slightly greater in the asenapine 5-10 mg BID dose group (0.8%) compared with placebo (0.1%) and olanzapine (0.3%); however, the incidence of any QT interval prolongation adverse event was low (< 1%). The one case of circulatory collapse in the 5-10 mg BID asenapine group was in a subject who switched from placebo to asenapine (Trial A7501006); no ECG findings had been evident the day before and the day after the event; the event led to discontinuation but was not considered to be a serious event; the subject recovered.

It should be noted that syncope may be due to other more common pathophysiological mechanisms such as decreases in blood pressure or vasovagal mechanisms rather than QT prolongation. The data on syncope are discussed in section 4.4.4.2, Orthostatic hypotension (including syncope).

In summary, a dedicated QT trial showed asenapine to produce a mild QTc prolongation. Additionally, based on an investigation of adverse events that may be indicative of QT prolongation as well as an evaluation of ECG outliers, there is no suggestion that asenapine is associated with clinically relevant QT prolongation.

4.4.4.2. Orthostatic hypotension including syncope

In the combined phase 2/3 trials asenapine showed a limited effect on orthostasis based on the low incidence of reports of adverse events related to orthostatic hypotension.

Healthy volunteers in the clinical pharmacology trials had a higher incidence of syncope (4%), postural dizziness (24%) and orthostatic hypotension (2%) compared with the subjects in the combined phase 2/3 schizophrenia and bipolar mania trials (0.5 % syncope, 0.1% dizziness postural, 0.3% orthostatic hypotension).

The incidence of syncope in the asenapine 5-10 mg BID dose group in the schizophrenia and bipolar mania trials was comparable to the olanzapine group (0.5% vs. 0.4%).

As a result of the α1-adrenergic antagonistic activity of the drug, the hypotensive effects of asenapine are not unexpected and were seen particularly in healthy volunteers with a high resting vagal tone.

4.4.5. Other safety topics of interest

4.4.5.1. Liver-related parameters

Asenapine did not show clinically relevant effects on liver parameters. Asenapine may produce some transient changes in liver transaminases (primarily alanine aminotransferase [ALT]) in certain subjects; however, it is not associated with clinically relevant abnormal liver changes or elevated bilirubin levels. In the combined phase 2/3 trials there was a small increase in ALT from baseline to endpoint in the asenapine group (2.2 U/L), which was lower than for olanzapine (3.8 U/L, Table 55). The proportions of subjects with ALT elevations > 3 times the upper limits of the normal reference range in the short-term, placebo-controlled trials of asenapine at therapeutic doses (5-10 mg twice daily) in subjects with schizophrenia or bipolar mania were 3.3% and 2.5% for subjects treated with asenapine and 1.9% and 0.6% for subjects treated with placebo, respectively. In the complete clinical program, no subject had laboratory values indicating drug induced liver injury, i.e., a combined elevation of ALT >3 times the upper limit of normal and bilirubin >2 times the upper limit of normal (Hy's law), nor were there any serious or non-serious adverse event reports indicating clinically relevant liver injury due to asenapine treatment (Table 56).

Table 55 Summary statistics for liver-related parameters (combined phase 2/3 studies)

Chemistry Test		Placebo (N=706)	Asenapine BID			Risperidone 3 mg BID (N = 120)	Haloperidol 4 mg BID (N = 115)	Olanzapine 5-20 mg QD (N = 899)
			<5 mg (N = 298)	5-10 mg[a] (N = 1953)	All (N = 2251)			
Total Bilirubin (µmol/L)	**N**	617	279	1825	2104	111	98	830
Baseline mean		7.2	7.3	7.5	7.5	6.9	7.7	7.6
Change from baseline[b]		1.2	0.5	0.4	0.4	-0.1	0.6	-0.2
ALT (U/L)	**N**	632	284	1844	2128	116	106	840
Baseline mean		29.8	30.1	26.3	26.8	27.7	23.2	24.2
Change from baseline[b]		-1.5	3.3	2.2	2.3	1.4	-1.7	3.8
AST (U/L)	**N**	629	284	1843	2127	116	106	839
Baseline mean		24.4	24.7	22.4	22.7	22.7	22.2	24.2
Change from baseline[b]		-0.1	1.6	2.0	1.9	1.2	-2.1	3.8

a fixed and flexible doses
b at last assessment on study drug
ALT = alanine aminotransferase; AST = aspartate aminotransferase; BID = twice daily; QD = once daily

Table 56 Liver related adverse events (combined phase 2/3 studies)

Adverse Event SOC/ Preferred Term n (%)	Placebo (N=706)	Asenapine BID <5 mg (N=298)	Asenapine BID 5-10 mg[a] (N=1953)	Asenapine BID All (N=2251)	Risp 3 mg BID (N=120)	Halo 4 mg BID (N=115)	Olan 5-20 mg QD (N=899)
Investigations							
ALT increased	2 (0.3)	2 (0.7)	31 (1.6)	33 (1.5)	0	1 (0.9)	45 (5.0)
AST increased	0	2 (0.7)	12 (0.6)	14 (0.6)	0	1 (0.9)	26 (2.9)
Blood bilirubin increased	0	0	3 (0.2)	3 (0.1)	0	1 (0.9)	6 (6.7)
GGT increased	2 (0.3)	2 (0.7)	5 (0.3)	7 (0.3)	0	1 (0.9)	0
Hepatic enzyme abn	0	0	0	0	0	0	8 (0.9)
Hepatic enzyme incr	4 (0.6)	3 (0.1)	11 (0.6)	14 (0.6)	0	0	11 (1.2)
Liver function test abn	2 (0.3)	0	3 (0.2)	3 (0.1)	2 (1.7)	1 (0.9)	2 (0.2)
Transaminases incr	0	0	1 (0.1)	1 (0.04)	0	0	2 (0.2)
Hepato-biliary disorders							
Chronic hepatitis	0	0	1 (0.1)	1 (0.04)	0	0	0
Hepatic function abn	0	0	0	0	0	0	1 (0.1)
Hepatic pain	0	0	1 (0.1)	1 (0.04)	0	0	0
Hepatitis	0	1 (0.3)	0	1 (0.04)	0	0	0
Liver disorder	0	0	2 (0.1)	2 (0.1)	0	0	0

[a] fixed and flexible doses

[b] at last assessment on study drug

[c] value changed at any time point during treatment

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BID = twice daily; Halo=haloperidol; GGT = gamma-glutamyl transferase; Olan = olanzapine; Risp = risperidone; SOC = system organ class

4.4.5.2. Hyperprolactinemia

Asenapine has a limited effect on prolactin levels. In the combined phase 2/3 trials there was a mean decrease of prolactin from baseline to endpoint comparable to placebo (Table 57). In the asenapine 5-10 mg BID group the proportion of subjects with increased prolactin values of 4xULN was lower than the risperidone and haloperidol groups. Few adverse events (<1%) and no serious adverse events related to abnormal prolactin levels were reported by subjects treated with asenapine.

Table 57 Summary statistics for prolactin values (combined phase 2/3 studies)

Prolactin	Placebo (N=706)	Asenapine BID			Risperidone 3 mg BID (N=120)	Haloperidone 4 mg BID (N=115)	Olanzapine 5-20 mg QD (N=899)
		<5 mg (N=298)	5-10 mg[a] (N=1953)	All (N=2251)			
Prolactin (µg/L) N	465	283	535	818	116	106	180
Baseline median	14.3	16.4	15.8	15.9	12.8	25.3	13.3
Change from baseline[b]	-3.4	-5.9	-2.3	-3.2	21.2	2.5	0.4
Prolactin (U/L) N	151			1280			
Baseline median	0.3			0.4			
Change from baseline[b]				-0.1			

Values reported in U/L were collected for 11 placebo, 899 asenapine 5-10 mg BID, and 318 olanzapine subjects and not included in the table

[a] fixed and flexible doses

[b] median value at last assessment on study drug

BID = twice daily; QD = once daily

1280
0.4
-0.1

648
0.4
0.0

-0.0

4.5. Safety in special groups and situations

4.5.1. Elderly

In the original NDA, a total of 25 subjects 65 years of age or older were enrolled in the asenapine treatment groups, 7 in placebo, 10 in olanzapine, and 1 each in the risperidone and haloperidol groups. Overall, the safety profile for these subjects was similar to subjects below the age of 65.

4.5.2. Pediatric/Adolescent

Safety in pediatric/adolescent subjects has not been established.

4.5.3. Gender/Race/Geographic region

No effect of gender on the overall distribution of adverse events or on the incidence of adverse events leading to discontinuation has been observed. No clinically relevant effect of race on the overall distribution of adverse events was observed although it should be noted that exposure to racial groups, other than Caucasian, was considerably lower than exposure to Caucasians. Other than the observation that a greater proportion of subjects receiving placebo in the US region had adverse events (73%) compared with the non-US region (54%), no relevant regional effects on the overall distribution of adverse events were observed

4.5.4. Use in pregnancy and lactation

Trials to assess the effects of asenapine on human reproduction and development have not been conducted. Subjects with reproductive potential participating in a clinical trial were required to use a medically acceptable method of birth control. Despite these measures, a total of 10 subjects became pregnant in trials completed for the sublingual and oral asenapine program (as of the February 2009 safety update cutoff). Of the 10 pregnancies, 7 subjects (5 reported as serious adverse event, 2 as non-serious) received asenapine and 3 received olanzapine. Of the 7 asenapine-treated subjects, the pregnancy outcomes were induced abortion in four subjects, one subject had a pre-term neonatal death (female infant died due to asphyxia within 5 minutes of birth, see also section 4.3.3.2), and two subjects had healthy full term infants (not considered serious adverse events). Of the three olanzapine-treated subjects, one subject had a therapeutic abortion (reported as a serious adverse event), one delivered a healthy full-term infant, and the outcome is unknown in one subject who was lost to follow-up (both not considered serious adverse events). No congenital abnormalities were reported in any of the cases.

One additional subject from a trial ongoing at the February 2009 Safety Update cutoff became pregnant. This subject is not included in the 10 pregnancies noted above. Outcome for this pregnancy is unknown (subject was lost to follow up).

Teratology trials conducted in rats and rabbits dosed at 10 and 21 times the maximum recommended human dose of 20 mg/day based on mg/m^2 showed that asenapine was not teratogenic. Maternal and embryotoxic effects were only seen at this high dose. This drug has a Pregnancy Category C designation and is not recommended for use during pregnancy unless it is clearly needed. Women receiving asenapine should not breast-feed.

4.5.5. Asenapine Overdoses

A total of six reports of accidental or intentional acute overdosage with asenapine, involving overdoses with the sublingual formulation in the range from 15 to 400 mg—up to 20 times the maximum tolerated dose (20 mg BID) used—were reported in the asenapine clinical trial program (as of the February 2009 safety update cutoff). All cases were reported as serious adverse events, except one case of accidental overdosage with 50 mg asenapine that was not considered serious due to the absence of symptoms.

Symptoms that were considered at least possibly related to asenapine by the investigators were agitation and confusion (400 mg); akathisia, orofacial dystonia and sedation (50 mg); asymptomatic ECG findings (bradycardia, supraventricular complexes, intraventricular conduction delay, 15 mg). In one case of overdose, unresponsiveness to verbal stimuli was reported, which probably indicated a certain degree of sedation (25-30 mg). All of the subjects recovered, including 3 who recovered on the same or next day.

In most cases it was not known if the tablets were kept sublingually before swallowing. The oral bioavailability of asenapine is less than 2% due to an extensive first pass effect in the liver, compared with 35% bioavailability when tablets are taken sublingually. Within the therapeutic dose range (5-10 mg twice daily), AUC and C_{max} increase is less than linear with dose. In the supratherapeutic dose range (>10 mg twice daily), AUC and C_{max} increase considerably less than proportionally with dose. This less than proportional increase of C_{max} and AUC with dose may be attributed to limitations in the absorption capacity of the oral mucosa following sublingual administration. As a result, with high sublingual doses a larger portion of the dose may be swallowed. In addition, it is possible that in case of an intentional overdose, tablets will be swallowed directly, which would result in relatively lower exposure to asenapine.

4.5.6. Abuse liability, withdrawal and rebound

Asenapine was not systematically studied in humans for its potential for abuse, tolerance, or physical dependence. A review of the adverse events associated with abuse potential was conducted. Clinical trials did not reveal any tendency for any drug-seeking behavior. There does not appear to be any clinically relevant adverse effect of asenapine when therapy is stopped. Asenapine is not a controlled substance.

4.5.7. Cognitive and motor performance

Somnolence was reported in subjects treated with asenapine. It was usually transient with the highest incidence reported during the first week of treatment. In short-term, fixed-dose, placebo-controlled schizophrenia trials, somnolence was reported in 13.1% (36/274) of subjects receiving asenapine 5 mg twice daily and in 11.1% (23/208) of subjects receiving asenapine 10 mg twice daily compared with 7.1% (27/378) of subjects receiving placebo (Table 29). In short-term, placebo-controlled bipolar mania trials of therapeutic doses (5-10 mg twice daily), somnolence was reported in 22.7% (86/379) of subjects receiving asenapine compared with 5.4% (11/203) of subjects receiving placebo (Table 30). During clinical trials with asenapine, including long-term trials without comparison to placebo, somnolence was reported in 17% (334/1953) of subjects treated with asenapine. Somnolence (including sedation) led to discontinuation in 0.6% (11/1953) of subjects in short-term, placebo-controlled trials.

Despite the relatively modest increased incidence of these events compared with placebo, patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that asenapine therapy does not affect them adversely.

5. BENEFIT-TO-RISK PROFILE SUMMARY

Asenapine sublingual tablets were demonstrated to be effective in the acute treatment of schizophrenia and the treatment of acute manic or mixed episodes associated with bipolar I disorder, as shown by two well controlled and adequately powered trials in each indication.

Asenapine delivers its efficacy with minimal impact on metabolic parameters, including weight gain, glucose, and lipids, as well as with minimal impact on prolactin levels, both of which have been highlighted as concerns with some currently available therapies. Additionally, asenapine is not associated with clinically relevant effects on QTc interval and has a limited effect on orthostasis. It has a low propensity to induce EPS, and has no clinically relevant effect on liver parameters.

Asenapine balances demonstrated efficacy with limited impact on weight gain, lipids and prolactin. Therefore, asenapine is an important treatment option for patients with schizophrenia and bipolar I disorder.

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