Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Asenapine

Proprietary Product Name: Saphris

Sponsor: Schering-Plough Pty Limited

April 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	New Chemical Entity
Decision:	Approved
Date of Decision:	7 March 2011
Active ingredient(s):	Asenapine (as the 1:1 maleate salt)
Product Name(s):	Saphris
Sponsor's Name and Address:	Schering-Plough Pty Limited 66 Waterloo Road North Ryde NSW 2113
Dose form(s):	Sublingual tablets
Strength(s):	5 mg and 10 mg
Container(s):	Blister pack
Pack size(s):	20, 60 and 100 (both strengths)
Approved Therapeutic use:	Treatment of schizophrenia in adults Treatment of acute manic or mixed episodes associated with Bipolar 1 Disorder in adults as monotherapy or in combination with lithium or sodium valproate Prevention of relapse of manic or mixed episodes in Bipolar 1 Disorder in adults as monotherapy or in combination with lithium or sodium valproate
Route(s) of administration:	Sublingual
Dosage:	10-20 mg daily
ARTG Number (s):	166561, 166562

Product Background

This AusPAR describes the evaluation of a submission by Schering-Plough Pty Limited to register a new chemical entity, asenapine (Saphris) sublingual tablets, for the following indications:

Treatment of schizophrenia including prevention of relapse and maintenance of clinical improvement during continuation therapy,

Treatment of acute mania or mixed episodes associated with bipolar disorder and maintenance of clinical improvement during the manic episode as monotherapy or in combination with lithium or sodium valproate.

Asenapine is a novel antipsychotic belonging to the dibenzo-oxepino pyrroles class. Based on its receptor pharmacology it is proposed that its efficacy is mediated by its antagonist activity on dopamine (D)-2 and serotonin (5-HT) – 2A receptors. Asenapine has also been shown to have activities on 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2C}, 5-HT_6, 5-HT_7, D_3 and alpha-2 adrenergic receptors which may be associated with improvements in cognition and negative

and affective symptoms. Asenapine has been demonstrated to have the highest affinity for blocking serotonin receptors, followed by dopamine and alpha-adrenergic receptors with minimal affinity for muscarinic receptors.

The proposed dosages were as follows:

Schizophrenia: 5 to 10 mg twice daily (bd) administered at an initial daily dose of 5 mg bd. An increase in dose to 10 mg bd is recommended only after clinical assessment.

Bipolar 1 disorder: 10 mg bd. The dose can be reduced to 5 mg bd according to clinical assessment. For combination therapy a starting dose of 5 mg bd is recommended. Depending on the clinical response and tolerability in the individual patient, the dose can be increased to 10 mg bd.

Regulatory Status

Asenapine was given marketing authorisation in the USA in September 2009 and in the European Union (EU) in September 2010. The initial indication in the USA was:

Acute treatment of schizophrenia in adults; for acute treatment of manic or mixed episodes associated with bipolar 1 disorder with or without psychotic features in adults.

This was extended in September 2010 to include maintenance treatment of schizophrenia in adults and the indication of adjunctive therapy with either lithium or valproate for the acute treatment of manic or mixed episodes associated with bipolar I disorder. The schizophrenia indication was not accepted by the European Medicines Agency (EMA) because the studies on schizophrenia were not considered to have shown sufficient evidence of effectiveness. In the EU the indication is for the treatment of moderate to severe manic episodes associated with bipolar I disorder in adults.

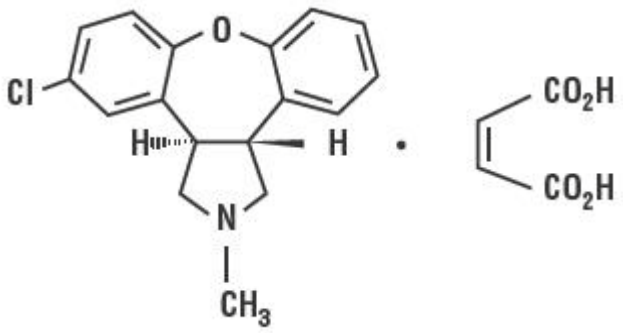
Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

Asenapine maleate (1:1 salt) is a racemate that is composed of the following compound plus its enantiomer.



It is manufactured by chemical synthesis.

Asenapine maleate is a crystalline powder that exists in two polymorphic forms.[1] Its aqueous solubility is 0.37% and it has a pKa value of 8.6. Its log P values (octanol/water) are 4.9 (neutral species) and 1.4 (protonated species).

The drug substance specifications include identified impurities. The Medicines Toxicology Evaluation Section was asked for advice as to whether those impurities have been adequately qualified at the proposed limit.[2]

Drug Product

Asenapine 5 mg and 10 mg sublingual tablets are circular tablets manufactured by freeze-drying an aqueous suspension of asenapine, gelatin and mannitol in pre-formed aluminium blister pockets. These are sealed to give aluminium/aluminium blister packs of ten tablets.

The British Pharmacopoeia refers to this type of product as an 'oral lyophilisate', while similar products in Australia have been called 'wafers'.

The finished product specifications include a requirement for disintegration of the tablets.

The finished product specifications include a limit for a specified impurity. The Medicines Toxicology Evaluation Section was asked for advice as to whether this impurity has been adequately qualified at the proposed limit. All other identified degradants are limited at the relevant International Council on Harmonisation (ICH) qualification threshold (0.5%).

Bioavailability

Asenapine has very low oral bioavailability (less than 2%) due to a high first pass effect but its absolute bioavailability by the sublingual route has been estimated as 35% based on cross study comparisons.

The pharmacological activity of the drug is claimed to be primarily due to unchanged asenapine. Nevertheless, one of its metabolites, desmethyl asenapine, was also measured in most studies.

Twelve bioavailability studies were submitted. The most relevant studies showed that:

- Consumption of water within 10 minutes of taking a sublingual tablet led to decreased bioavailability
- There appears to be some small variation in sublingual, supralingual and buccal absorption of the drug, although the effect is not consistent (Studies 041030 and 25512)
- Food decreases the bioavailability of the drug, presumably as a result of increased clearance due to increased liver blood flow (Study 041029)

Some questions have been raised concerning the pivotal bioavailability studies. Satisfactory responses were required before the results of those studies can be accepted.

Pharmaceutical Subcommittee Consideration

The application was considered by the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM). It had no objection on pharmaceutic and biopharmaceutic grounds to the approval of the application provided all outstanding issues are addressed to the satisfaction of the TGA.

The PSC endorses all the questions raised by the TGA in relation to pharmaceutic and biopharmaceutic issues.

[1] Asenapine maleate will be referred to as simply asenapine for the remainder of this AusPAR.
[2] Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.

The Committee considered that the sponsor should be asked to provide three recent consecutive batch analysis data for the drug substance.

The PSC considered that the attention of the Delegate should be drawn to the following issues:

- The observed cardiac side-effects. The Committee considered that the metabolites of asenapine should be characterised in order to identify which of the metabolite(s) is/are responsible for these cardiac events.
- The conflicting results obtained with the two models used to analyse the population pharmacokinetic data. The Committee considered that the sponsor should be asked to clarify this issue.
- Effect of "dry mouth" on absorption of asenapine. Many of the patients taking asenapine would also be taking anti-cholinergic agents which cause dry mouth. The PSC agreed that the "dry mouth" effect should be investigated in view of the fact that the drug is absorbed sublingually.

The Delegate did not require further information on the issues raised by the PSC.

Quality Summary and Conclusions

A number of questions were raised concerning chemistry, quality control and bioavailability aspects. Registration approval was not recommended until satisfactory responses were received to those issues.

III. Nonclinical Findings

Introduction

Overall, the nonclinical submission was adequate, although many studies were dated and were not of the standard expected for current studies, including safety pharmacological studies that were generally not Good Laboratory Practice (GLP) compliant. Notable shortcomings in the toxicity studies included histopathology results that were sometimes not tabulated, less than comprehensive toxicokinetics (often with sampling of too short a duration) and sometimes poor documentation of doses (that is, whether they applied to the salt or base).

Pharmacology

Primary pharmacodynamics

The pharmacodynamics of asenapine were extensively investigated, especially in terms of *in vitro* receptor binding and functional activities but also in terms of *in vivo* activity in a number of animal models. However, its exact mechanism of action is not clear, although antagonism at the dopamine D_2 and 5-HT_{2A} receptors is likely to be involved as this is thought to be associated with antipsychotic/anti-schizophrenic activity (Kapur and Mamo, 2003; Meltzer, 1999; Meltzer, 2003).[3,4,5] Studies with cloned human receptors showed high affinities for all dopamine receptors, for many 5-HT receptor subtypes, for H_1 receptors and for α adrenergic receptors. Rank order of affinities was: 5-HT_{2C}> 5-HT_{2A}> 5-HT_7> 5-HT_{2B}>

[3] Kapur S, Mamo D. Half a century of antipsychotics and still a central role for dopamine D2 receptors. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2003; 27: 1081-1090.

[4] Meltzer HY. The role of serotonin in antipsychotic drug action. Neuropsychopharmacol 1999; 21: 106S-115S.

[5] Meltzer HY et al. Serotonin receptors: their key role in drugs to treat schizophrenia. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2003; 27: 1159-1172.

5-HT_6> α_{2B}, > D_3 (all with subnanomolar binding affinities) >H_1> D_4> α_{2A}> α_1> α_{2C}> D_{2L}> D_1> 5-HT_{5A}= D_{2S}> 5-HT_{1A}> 5-HT_{1B}> H_2. (all with binding affinities in the nanomolar range). No affinity for H_3, β adrenergic or muscarinic receptors was observed nor was there affinity for sigma receptors (only guinea pig investigated) and rat and human data were broadly consistent, with asenapine showing antagonist activity at dopamine, 5-HT, α adrenergic and H_1 receptors from rat brain.

Comparison with other antipsychotic drugs (aripiprazole, ziprasidone, quetiapine, olanzapine, risperidone, clozapine and haloperidol) at cloned human receptors (INT00002643) showed that asenapine shares broadly similar receptor binding characteristics with all the other atypical antipsychotic drugs tested with most having strong affinity at dopamine (particularly D_2), 5-HT (particularly 5-HT_{2C}, 5-HT_{2A} and 5-HT_6) and α adrenergic receptors. However, the rank order of receptor binding affinity was different for asenapine and the other antipsychotics tested and it is noteworthy that at the dopamine, 5-HT and α adrenergic receptor subtypes, asenapine generally showed the highest binding affinity. Exceptions were D_2 receptors at which aripiprazole had higher affinity, 5-HT_{1A} receptors at which ziprasidone had a higher affinity and 5-HT_{2B} receptors at which ziprasidone and aripiprazole had higher affinity. A notable difference between asenapine and other atypical antipsychotics was its stronger interaction with a broader set of 5-HT receptors with asenapine having pK_i values of ≥8.4 at all 5-HT receptor subtypes while other antipsychotics had values of <6.6 at one or more 5-HT receptor subtypes. In contrast to quetiapine, olanzapine and clozapine, asenapine has no appreciable affinity for muscarinic receptors. Of all the drugs tested, only asenapine had measurable affinity for H_2 receptors.

Assessment of functional effects at receptors *in vitro* (in particular inhibitions of calcium flux, agonist-stimulated cAMP production and accumulation of inositol phosphates) also showed asenapine antagonistic activity at dopamine, α adrenergic and H_1 receptors and at many 5-HT receptor subtypes. Specifically, antagonist activity at D_2, D_3, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_6 and 5-HT_7, α_{2A}, α_{2B} and α_{2C} adrenergic and H_1 cloned human receptors was demonstrated, although activity at α_{2C} receptors was weak. Little or no agonist or antagonist activity was observed at rat metabotropic glutamate receptors (mGluR1, mGluR2, mGluR4 and mGluR5) or at human mGluR4. Asenapine enantiomers showed comparable binding affinities ((-) asenapine showed slightly higher affinity at D_4 receptors than (+) asenapine) and functional activity at the receptors investigated.

In vivo studies also showed asenapine to be active in animal behaviour models thought to be predictive of antipsychotic activity in humans (for example, inhibition of apomorphine-induced climbing, inhibition of shuttle box avoidance and reversal of apomorphine-induced disruption of prepulse inhibition of the acoustic startle response). The median effective dose (ED_{50}) of asenapine for impairment of conditioned avoidance behaviour in the shuttle box test in rats was 0.6 mg/kg subcutaneously (SC) but asenapine restored apomorphine-induced disruption of prepulse inhibition of the acoustic startle response in rats and inhibited apomorphine induced climbing in mice at lower doses (≤0.03 mg/kg SC and 0.02 -0.04 mg/kg SC, respectively). In both rats and mice, these lower doses would be expected to result in drug exposures (area under the plasma concentration time curve [AUC] or maximal plasma concentration [C_{max}]) that were below those in humans treated with the minimum recommended dose. Inhibition of amphetamine- and MK801-induced hyperlocomotion in mice and of amphetamine-induced hyperlocomotion in rats (models predictive of antipsychotic/antimanic activity) was observed at similar (or even lower) doses.

As judged by binding density of ligands to their receptors, repeated dosing with asenapine altered the levels of dopamine (D_1, D_2 and D_4) receptors and 5-HT (5-HT_{1A} and 5-HT_{2A})

receptors in rat brain in a regional specific and dose dependent manner (with some of the changes occurring at clinically relevant doses). However, no effects were observed at D_3 or 5-HT_{2C} receptors, for which asenapine had strong binding affinity. Changes in levels of glutamate receptors caused by repeated dosing of asenapine were probably indirectly related to drug interactions with other neurotransmitters such as serotonin and dopamine, both of which may modulate glutamatergic transmission. The alterations in levels of dopamine and 5-HT receptors may have implications for efficacy over prolonged treatment periods, although there appears to be no evidence currently for changed efficacy with such treatment.

Overall, the nonclinical results suggest that asenapine should show antipsychotic activity, mediated mainly by antagonism at D_2 and HT_{2A} receptors with antagonism of other 5-HT receptor subtypes (particularly 5-HT_{2C}) and α_2 adrenergic receptors probably playing a secondary role. When registered typical or atypical antipsychotic drugs were used as comparators, both similarities and differences between these and asenapine were observed and asenapine may exhibit a stronger effect on central serotonergic function.

Safety and secondary pharmacology

Most of the safety pharmacology studies were conducted in the early to mid 1990s and were below the standards expected in current studies, with only three (two using dog Purkinje fibres *in vitro*, one investigating *in vivo* respiratory effects) being GLP compliant. Studies emphasised cardiovascular effects, which is appropriate but effects on renal function were not examined while central nervous system (CNS) effects are covered under primary pharmacology. There were no studies of potential effects on platelet function, although prothrombin (PT) and activated partial thromboplastin time (APTT) values were unaffected by treatment in the repeat dose toxicity studies.

Cardiovascular effects

In vitro studies revealed effects on action potential duration and hERG current. Reductions in action potential duration were observed in isolated guinea pig ventricular papillary muscle at concentrations ≥ 30 µM (salt; about 12.1 µg/mL, equivalent to 8.6 µg/mL of the base) and in dog Purkinje fibres at≥ 0.3 µM (base; about 86 ng/mL), indicative mainly of Ca^{2+} channel blockade as the reductions occurred largely during the plateau phase. These concentrations are high relative to the mean C_{max} at the maximum recommended human dose (MRHD) of 8.5 ng/mL in elderly patients (respectively about 1000x and 10x). In dog Purkinje fibres, the corresponding ratio for the prominent plasma metabolite, N-desmethylasenapine, was higher than for the parent drug (about 190x a C_{max} value of 4.3 ng/mL). hERG current was blocked by asenapine (salt) with an median inhibitory concentration (IC_{50}) of 0.3 µM (about 10 x C_{max}). However, tests were conducted in protein free salt solution and both asenapine and its N-desmethyl metabolite are highly protein bound which would result in markedly higher safety margins for free rather than total drug concentrations. N-desmethylasenapine, with its higher IC_{50} in the hERG assay and lower plasma concentrations in patients (see *Pharmacokinetics: metabolites*) would be expected to have a lower potential than asenapine for interaction with hERG channels in patients.

The main cardiovascular effect observed in *in vivo* studies in dogs with intravenous (IV), oral (PO) and sublingual administration, and rabbits and cats with IV administration, was a decrease in arterial blood pressure associated with a reduction in peripheral resistance and probably due to inhibition at α_1 receptors. In dogs, tachycardia and a negative inotropic effect were also observed, as well as potentiation of the hypotension and tachycardia induced by tilt. The hypotensive response to tilt, as well as a response to carotid occlusion (also in dogs) and reductions in vasopressor responses to noradrenaline in dogs, rabbits and cats can probably also be attributed to α_1 adrenergic antagonist activity. In some (but not all) studies

in dogs, electrocardiogram (ECG) changes were observed, most notably increases in the QTc interval and reductions in the PR interval.

After sublingual administration in dogs, the No Observed Effect Level (NOEL) was 0.01 mg/kg, with moderate tachycardia observed at 0.1 mg/kg (C_{max} values 1 and 29 ng/mL, respectively). In the initial study, transient QTc prolongation (calculated using the Bazett formula) was also observed at 0.1 mg/kg, however, recalculation of QTc values using the Fridericia and Van de Water formulae did not show an increase in QTc at sublingual doses up to 1 mg/kg. Further, sublingual administration of the individual enantiomers at 0.1 mg/kg did not show an increase in the QTc interval (Bazett formula) for either enantiomer except at the 60 minute time point for (-) asenapine but tachycardia was again observed with both enantiomers. The safety margin for tachycardia calculated from C_{max} values and based on a NOEL of 0.01 mg/kg is 0.1 (safety margin 3.4 at 0.1 mg/kg). These results suggest that tachycardia may be observed clinically. However, tachycardia, as well as QTc prolongation were minimal in the dog toxicity studies and clinical trials (*General toxicity*). The data on response to tilt predict a potential for asenapine to cause orthostatic (postural) tachycardia and possibly, orthostatic hypotension (noted in the draft Product Information). The NOEL (sublingual route) was 0.01 mg/kg for potentiation of tachycardia and 0.1 mg/kg for potentiation of hypotension (respective safety margins of 0.1 and 3.4). Results from *in vitro* studies with isolated dog Purkinje fibres indicated that neither asenapine nor its N-desmethyl metabolite possess intrinsic positive chronotropic activity, suggesting that the tachycardia induced by asenapine *in vivo* in the dog is due to an indirect mechanism.

Other activities

Gastrointestinal activity, in terms of effects on motility and propensity to induce gastrointestinal ulcers of any severity was not observed in rats with a 10 mg/kg PO dose, which would give an expected drug exposure (AUC) about 10 times that in patients at the MRHD. Some activity was seen in a GLP rat respiratory study, with 5 mg/kg SC asenapine eliciting a transient (20-45 minute post dose) central respiratory depressor effect (increases in tidal volume, expired volume, enhanced pause). However, the C_{max} at the NOEL of 1.5 mg/kg SC would be in the range of 90 ng/mL or about 10 times the corresponding human value with the MRHD, suggesting little potential for clinical respiratory effects.

It is well established that D_2 receptor blockade is predictive of plasma prolactin elevation and this was observed in male rats at 1 hour following single doses of 0.1-1 mg/kg SC and 0.032-0.5 mg/kg PO in 2 secondary pharmacological studies. This was also apparent over 0.75-3 hours post-dosing with both SC asenapine and PO risperidone after single and repeat dosing (*Genotoxicity and Carcinogenicity*) but not in a 13 week rat toxicity study with later sampling (*General toxicity*). By contrast, PO asenapine showed no appreciable hormonal activity in a general hormonal screening test and tests for progestational and anti-progestational activity in rabbits, and mineralocorticoid and anti-oestrogenic activity in rats were negative, although doses tested were low, in some studies below the MRHD on a mg/m^2 basis.

Asenapine induced sedation but at relatively high doses, with this being a notable clinical sign at the high doses used in the acute toxicity studies and being observed in the clinical trials (clinical overview). Although a reduction in spontaneous locomotor activity following a single dose of asenapine was consistently observed in a number of studies, effects on locomotor activity after repeated dosing showed a more complex pattern (decreased activity was a consistent clinical sign in the repeat dose toxicity studies), with substantial increases observed following cessation of 4 weeks of treatment in rats.

There were no positive findings likely to be of clinical relevance in an *in vitro* bio-receptor screening using asenapine, its individual enantiomers and the N-desmethyl and N-oxide metabolites (all 1 µM), with the exception of the expected interactions with primary pharmacological targets. Asenapine was inactive in tests for subjective effects (mice) or addiction potential (rats) although studies of the latter used low SC doses (to 0.3 mg/kg) or intraperitoneal (IP) administration (2 mg/kg), while single doses of up to 1 mg/kg (in excess of the pharmacologically active dose) did not elicit perioral movements in rats. This was observed, however, following asenapine treatment via the drinking water but this occurred after a longer duration of treatment than with haloperidol (respectively 4 and 2 weeks), although atypical antipsychotic comparators were not tested.

Catalepsy, which may be predictive of extrapyramidal symptoms, was induced by asenapine but at a higher dose than required for primary pharmacological effects (ED_{50} about 1 mg/kg SC vs 0.001-1 mg/kg SC (IP in some studies)). It was also less potent in this respect than haloperidol but atypical antipsychotics were not used as comparators. Asenapine showed appreciable local anaesthetic activity in an isolated toad nerve preparation (2.5-fold greater activity than the positive control, lignocaine), a finding likely to be related to the observation of oral hypoaesthesia in some clinical trials (sponsor's *Clinical Overview*). Sleeping patterns in rats, as assessed by electroencephalogram (EEG), were altered in studies using IP dosing but this was not included as an adverse event in the clinical overview or proposed product information.

Pharmacokinetics

Plasma asenapine clearance values were high in rats and dogs (respectively 4.6 and 3.7 L/h/kg at doses of about 1.5 mg/kg) and to a lesser extent rabbits (1.6 L/h/kg with a dose of 0.45 mg/kg) after single IV administration. There were no IV data for mice and only very limited data for humans (not included in the clinical summaries). Corresponding half-life ($t_{1/2}$) values were low (respectively 1.2, 0.9 and 2.4 hours) and this was also the case after sublingual administration in dogs (about 0.5 hours with a dose of 0.1 mg/kg twice daily [bd]) the only species for which there were pharmacokinetic data with this route. Although the assay used was relatively insensitive, this contrasts with asenapine plasma $t_{1/2}$ values in humans after multiple sublingual administrations with the proposed doses of 19-20 hours in one study.

Drug exposure data for the toxicity studies were not complete but available data showed high-dose drug exposures in excess of those expected in humans for the main studies, with the exception of the 52 week PO study in dogs. The often short duration of sampling would have resulted in under-estimates of exposure in mice and rats. The human area under the plasma concentration time curve from time zero to 12 hours ($AUC_{0\text{-}12\ h}$) value used for calculation of drug exposure ratios in the general toxicity and carcinogenicity studies was for elderly (65 years and over) patients who showed a higher exposure than younger patients (sponsor' *Clinical Summary*, proposed product information). The value for younger patients was used for the reproductive toxicity studies, as this was more appropriate.

Sampling in the SC mouse and rat carcinogenicity studies was particularly limited (0.25, 0.5 and 1.0 hours), precluding a proper determination of relative drug exposure, although data from the corresponding 13 week studies suggested respective high-dose exposure ratio (ER) values of at least 3.9 and 3.4. Additionally, drug exposure was demonstrated in the carcinogenicity studies, with C_{max} values well in excess of the elderly human value of 8.5 ng/mL ($\geq$ 20x). There were no toxicokinetic data for the rat fertility and early embryonic development study and embryofetal toxicity studies in rats and rabbit, all using the same PO doses (1, 5, 30 mg/kg/day given bd). However, the high-dose would have been expected to

have achieved an ER value of about 11 in rats, based on data from the separate 52 week PO toxicokinetic study (also see discussion under *Reproductive toxicity* below). In this toxicokinetic study, multiple treatment with 10.8 mg/kg bd gave an AUC from time zero to 7 hours ($AUC_{0\text{-}7\ h}$) value of 355 ng.h/mL in males (females data were only available for single dosing), or an $AUC_{0\text{-}24\ h}$ value of at least 710 ng.h/mL. By extrapolation, 15 mg/kg bd would produce expected exposure of 710 x 30/21.6 = 986 ng.h/mL / 86 = ER of 11.5. Asenapine was largely plasma protein bound in the experimental species and humans, based on *in vitro* data, and corrections for relative free drug concentrations are not needed.

Table 1: Exposure Ratios

Species	Duration (weeks)	Dose (mg/kg/day) and route	AUC (ng.h/mL), sample day/week	Cmax (ng/mL)	AUC exposure ratio (ER)[&]
General toxicity					
Mouse	13	3.0, 4.0, 5.0/7.5[†] SC	396, 471, 895 (wk 13, $AUC_{0\text{-}2.5\ h}$)	323, 366, 822	3.2, 3.9, 7.3
Mouse	88-99[#]	0.5, 1.5, 5/4 (m) SC 7/5 (f) SC	nd	28.7, 79.5, 201 (m) 166 (f)[x] (week 27)	
Rat	4	25, 50, 75 PO	nd		
Rat	13	6.5, 22.5, 75 PO	nd		
Rat	52	0.6, 3.6, 21.6 PO*	38.3, 93.3, 355 (wk 52, $AUC_{0\text{-}7\ h}$)[§]	15, 26, 110	0.6, 1.5, 5.8
Rat	13	0.5, 1.0, 2.0 SC	138, 166, 297 (d 84, $AUC_{0\text{-}\infty}$)	35, 82, 115	1.1, 1.4, 2.4
Rat	13	3.0, 4.0, 5.0 SC	231, 295, 410 (wk 13, $AUC_{0\text{-}2.5\ h}$)	195, 183, 263	1.9, 2.4, 3.4
Rat	100-107[#]	0.3, 1.2, 3.0/5.0 SC	nd	29.6, 117, 335 (week 97)	
Rat	2	0.1, 0.5, 3.0 IV	nd		
Dog	4	20, 40, 80 PO	nd		
Dog	13	1.25, 7.5, 20 PO	nd		
Dog	52	0.2, 1.2, 7.2 PO*	nd, 3.4, 51.7 (wk 52, $AUC_{0\text{-}8\ h}$)	0.4, 1.8, 39.2	nd, <0.1, 0.8
Dog	13	0.1, 0.5, 2.5 IV	20.4, 94, 556 (d 71, $AUC_{0\text{-}24\ h}$)	14.6, 64.3, 397 ($C_{5\ min}$)	0.2, 0.8, 4.6
Dog	39	0.1, 0.4, 1.6 IV	25, 122, 676 (d 261, $AUC_{0\text{-}\infty}$)	25.5, 68, 311 (C_0)	0.2, 1.0, 5.5
Reproductive and developmental toxicity					
Rat	GD 6-17	0.3, 0.9, 1.5 IV[§] (Study INT00039620)	92.3, 226, 413 (d 14, $AUC_{0\text{-}24\ h}$)	86, 147, 314 (C_0)	1.1, 2.6, 4.8
Rabbit	GD 6-18	0.025, 0.125, 0.625 IV (Study XP018)	4.9, 41.5, 179 (GD 10-15, $AUC_{0\text{-}\infty}$)	7.8, 48.6, 232 ($C_{5\ min}$)	<0.1, 0.5, 2.1
Rat juvenile	8	0.4, 1.2, 3.2 SC[$]	109, 298, 868 (d 1-56, $AUC_{0\text{-}7\ h}$)	36.7, 98.5, 251	1.3, 3.5, 10.1

[†] High-dose (HD) dose increase from Week 6
[#] carcinogenicity studies, HD dose reduction in Week 25 (mouse) and HD dose increase after 6 weeks (rat)
* given bd, [$] active moiety, [x] may be underestimated as this value was at the last sample time of 1 hour
[§] separate toxicokinetic studies
[&] AUC (x2 for bd dosing) relative to human $AUC_{0\text{-}24\ h}$ values of 2 x 61 ng.h/mL (general toxicity) or 2x 43 ng.h/mL (reproductive toxicity) with a dose of 10 mg bd (Section 6.2.6)
nd = no data

Metabolites

Asenapine was extensively metabolised in the experimental species, as in humans, with some species differences. Two *in vitro* studies using human microsomal preparations and insect

supersomes expressing recombinant cytochrome P450 (CYP) showed metabolism was mediated via CYP1A2 and to a lesser extent (based on the Michaelis constant [K_m] and maximum elimination rate [V_{max}] determinations with recombinant isoforms) CYP3A4. Metabolism by other recombinant CYP isoforms was measurable, including 2D6, which exhibited a low K_m value (0.3 µM vs 24.5 µM for CYP1A2) but also a low V_{max} value (0.18 vs 10.2 pmol/min/pmol CYP for CYP1A2) and 2C19. Asenapine was a competitive inhibitor of CYP2D6 with a relatively low IC_{50} value in a pooled human microsomal preparation (44 nM = 12.6 ng/mL).

Circulating human plasma metabolites (data from 4 individuals) were asenapine N+-glucuronide and to a lesser extent N-desmethylasenapine N-carbamoyl glucuronide and sometimes 11-hydroxyasenapine sulphate. Other human plasma metabolites identified from pooled samples included N-desmethylasenapine and asenapine N-oxide and overall these compounds were generally present to varying extents in mouse, rat or dog plasma, although differences in metabolite profiles were often pronounced. For example, the N-oxide derivative was a prominent plasma metabolite in rats after PO and IV administration unlike humans (clinical summary). 11-Hydroxyasenapine sulphate was not a common metabolite in experimental species, being seen only in mouse plasma at low levels and as minimal or in trace amounts in rat bile and rabbit urine, although substantial amounts in plasma were measured in one clinical trial in which selected metabolites were assayed quantitatively. $AUC_{0\text{-}12\ h}$ values were 22.1 (asenapine), 11.8 (N-desmethylasenapine), 17 (11-hydroxyasenapine sulphate) and 129 (asenapine N+-glucuronide) ng.h/mL, with asenapine N-oxide generally below the limit of measurement.

The main human plasma metabolite asenapine N+-glucuronide was not identified in the experimental species (except for low levels in rabbit plasma and as a minor rat bile component) and this difference was the subject of a position paper. This stated that samples from animal absorption/distribution/metabolism/excretion (ADME) studies were specifically monitored for this conjugate with traces being seen in mouse and dog excreta and 0.2% and 5% of the doses being recovered in rat bile and rabbit urine, respectively. This contrasts with human plasma AUC values of 93-106 ng.h/mL for asenapine glucuronide compared with 31-36 ng.h/mL for asenapine in 2 single dose (5 mg) clinical trials. C_{max} values were 6.5-7.9 ng/mL, which are equivalent to 14-17 nM (mol. wt. = 462.9). It was also noted that asenapine resembled other drugs such as olanzapine which was not appreciably metabolised by experimental animals (in this case mice, dogs and monkeys) to the main human metabolite, the 10-N+-glucuronide (Mattiuz el al., 1997).[6] Additionally, as noted within this report (see *Pharmacodynamics*), asenapine N+-glucuronide showed little or no activity. Overall, it was argued that this conjugate need not be investigated further, which is accepted as it is considered unlikely to exhibit toxicity.

Asenapine is a racemate of (+) and (-) enantiomers and enantioselectivity of metabolism to the N-desmethyl derivative was demonstrated in mouse (SC), rat (SC) and rabbit (IV) but not dog (IV), as shown by higher AUC values for the (+) enantiomer and low ratios of unlabelled to labelled metabolites (the (-) enantiomer was labelled). A similar effect was also seen in humans.

Toxicology

The repeat dose toxicity studies were conducted using PO, SC and IV administration, with the intended sublingual route being restricted to dog 7 day local tolerance studies with bd

[6] Mattiuz E. Disposition and metabolism of olanzapine in mice, dogs and rhesus monkeys. Drug Metab Dispos 1997; 25: 573-583.

dosing, which is acceptable. The main studies were characterised by clinical signs, indicative of pharmacological activity, impaired or enhanced body weight gains and premature deaths of unknown cause(s) but there were few indications of target organ toxicity. Findings affecting the mammary glands (acinar development and secretion), ovaries (prominent/enlarged corpora lutea, decreased relative weights), uterus (decreased relative weights, atrophy) and seminal vesicles (secretion) and altered oestrus cycles (for example increased dioestrus in rats) were probably related to elevated prolactin. This was demonstrated in male rats, in which increases in this hormone were measured at short intervals (to 3 hours) after SC or PO dosing (see *Secondary pharmacology*). Additionally, high activity of pituitary prolactin secreting cells was demonstrated in 2 PO dog studies (adrenocorticotropic hormone (ACTH) cells were also affected in one study) and elevated prolactin is an expected effect of dopamine receptor antagonists, which also include haloperidol and risperidone. Paradoxically, significant *decreases* in plasma prolactin were seen in the only toxicity study in which it was measured (13 week rat PO), despite mammary gland acinar development suggestive of elevated levels. This may be related to plasma sampling at the scheduled necropsy, following an overnight fast and it would have been useful to have determined prolactin at intervals over 24 hours post dosing.

The pituitary was otherwise unaffected, with relative weight changes in one 13 week SC rat study not being replicated in a second 13 week SC study using a higher dose range. By contrast, relative adrenal weights were generally increased in rats and tended to be higher in males in one dog study, sometimes associated with cortical hypertrophy, which may be related to generalised stress or effects on the pituitary. However, lymphoid atrophy was only occasionally observed (for example in the mouse SC 13 week study). The pathogenesis of occasional thyroid changes (increased relative weight, follicular hypertrophy) was not clear but they may have reflected effects on the pituitary or resulted indirectly from hepatic enzyme induction and enhanced thyroxine clearance. Thyroid stimulating hormone (TSH) was measured in one 13 week SC rat study with no effect of drug treatment being seen. Increased incidences of follicular hypertrophy were pronounced with long-term treatment in the rat carcinogenicity study (for example 29/60 high dose females vs 4-8/60 controls) but this was associated with reduced incidences of C-cell hyperplasia. Thyroids were unaffected by treatment in the mouse and dog studies, suggesting that effects on this organ may be specific to rats.

Relative liver weights were slightly increased in many mouse, rat and dog studies, often associated with modest elevations in plasma enzyme activities (transaminases, alkaline phosphatase) but with histological findings absent or restricted to hepatocytic vacuolation/swelling. These results are suggestive of an adaptive response and a slight induction of CYP 1A1/1A2 and CYP 2B1/2B2 was demonstrated in a 13 week rat SC study. It is noteworthy that although there were no drug-related histological findings in the liver in this particular study, thyroid follicular cell hypertrophy was seen in both sexes. There were additional findings in 2 dog studies suggestive of a potential for hepatotoxicity with high PO doses, 80 mg/kg/day x 4 weeks and 20 mg/kg/day x 13 weeks, although whether these would also be seen with the proposed sublingual route is not known. Elevated plasma bilirubin was observed and hepatocytic necrosis or multiple liver changes including peliosis, fibroplasia, biliary epithelial proliferation and perivasculitis, in addition to hepatocytic swelling/hypertrophy/vacuolation, was seen at initial histological examination. Liver slides from all the PO dog toxicity studies were re-examined in a later assessment and hepatocytic necrosis/degeneration was recorded for both of these studies. However, there were no indications of hepatotoxicity in rodents, or in dogs after IV dosing and this may be related to PO administration. Transient elevations in serum transaminases (mainly alanine

transaminase [ALT]) have been seen in humans during asenapine treatment but this was apparently not associated with clinically relevant signs of liver injury (sponsor's *Clinical Overview*).

Nephrotoxicity was not generally a feature of the repeat dose toxicity studies, although modest elevations in plasma creatinine and/or urea were observed in several rodent studies and there were instances of reduced urinary volume or the presence of urinary blood. Histological kidney changes (renal tubular basophilia/dilation) were seen in 2 dog studies with high PO doses (40-160 mg/kg/day) associated with glucosuria, although these were not apparent with PO doses of 21.6 mg/kg/day (given bd) x 4 weeks or 20 mg/kg/day x 13 weeks. There were no data to allow estimates of drug exposures at the higher PO doses but 21.6 mg/kg/day resulted in a drug exposure ratio of at least 3.9 (2 x $AUC_{0\text{-}8\ h}$ value of 239 ng.h/mL relative to a human value of 2 x 61 ng.h/mL). The *Clinical Overview* did not mention any evidence for nephrotoxicity or altered renal function in humans.

Other clinical pathology changes in the toxicity studies included decreased erythroid values, although haemoglobin or erythrocytes were sometimes increased and decreased leukocytes and lymphocytes in rodents, although haematological values were unaffected in the repeat-dose dog studies. There were, however, tendencies for increased leukocytes and neutrophils and decreased lymphocytes in a dog single dose study (50-200 mg/kg). Plasma glucose was consistently reduced in rats, tended to be increased in mice and was unaffected in dogs but the significance of these findings and reason for this species difference are not clear. Glucose tolerance tests were conducted in some dog studies, with no effect of drug treatment being apparent.

Veterinary examinations, which included pulse and respiration rates, were included in the dog studies and quantitative ECGs were conducted in the 13 and 39 week IV studies. Increased pulse or heart rates were often observed but there were limited effects on ECG intervals or waveforms, that is, occasional negative T-wave polarity and tendency for minimally increased QTc and JTc values. ECG examinations in the longer term IV study were at 1-2 hours post-dosing and mean plasma asenapine concentrations were 100 ng/mL at 1 hour and 40 ng/mL at 3 hours (2 hour sampling was not carried out), which compare with an expected human C_{max} value of 8.5 ng/mL. A mild positive effect for QTc was reported in a clinical trial but clinically relevant QT prolongation was apparently not seen (*Clinical Overview*). As in the dog studies, slight increases in heart rates were also observed.

Overall, there were no findings in the toxicity studies which would preclude approval of registration, although it should be noted that combination studies with lithium or sodium valproate were not conducted. These two agents are proposed to be used concurrently with asenapine in the treatment of bipolar disorder. Drug exposures were particularly low in the longest duration PO study in dogs, resulting from a combination of low doses (0.2-7.2 mg/kg/day), which could have been increased in the absence of overt toxicity and low oral bioavailability in this species (<10%). An IV study of sufficient duration was conducted, however, which achieved a modest exposure ratio with the high-dose (5.5). Although as noted above, plasma asenapine clearance was high after IV administration, with a mean $t_{1/2}$ value of only 0.9 hours in this particular study, the drug was measurable at least to the last sample time of 8 hours at a high-dose concentration (8.8 ng/mL) in excess of the human steady state minimum plasma concentration (C_{min}) value of 0.84 ng/mL with a sublingual dose of 10 mg bd.

Genotoxicity and Carcinogenicity

An appropriate range of GLP-compliant genotoxicity studies were conducted and these were generally adequate although the highest concentration scored (75 µg/mL) in the *tk* forward

gene mutation test in the absence of S9 metabolic activation resulted in a reduction in relative survival of only 37% and this could have been increased. Additionally, the highest concentration tested in the presence of S9 (44 hour harvest) in the chromosome aberration test had no effect on the mitotic index. The highest dose used in the rat micronucleus study (75 mg/kg) was acceptable and compares with oral median lethal dose (LD_{50}) values in rats of 110-176 mg/kg.

Some positive results were recorded in the chromosome aberration test, with significant increases being observed at the highest two concentrations tested in the absence of S9 (20 hour harvest). However, these were not concentration related, did not reach the laboratory criteria for a positive test and incidences of cells with aberrations were not consistently outside the laboratory historical control range and overall the study gave a negative result. The protocol for this test was unusual in that drug exposure was for 20 or 44 hours as opposed to 3 or 20 hours. In the *tk* forward gene mutation assay, a significant increase in mutant frequency at the highest concentration tested in the presence of S9 (75 µg/mL) in an initial experiment was not reproducible in a second experiment (40, 46, 52, 58, 64, 70 and 76 µg/mL).

Adequate long-term carcinogenicity studies did not show any oncogenic responses, although high-doses were sufficient to decrease survivals and male body weight gain (mouse) or substantially impair body weight gain (rat). As noted above (see *Pharmacokinetics*), estimated high-dose asenapine exposures were >3x that expected in humans and this negative oncogenic finding contrasts with those for two other common antipsychotic drugs, risperidone and haloperidol. These also elevated prolactin levels and respectively elicited female pituitary adenomas and mammary gland adenocarcinomas in mice and male endocrine pancreas adenomas and male and female mammary gland adenocarcinomas in rats, or mammary gland and pituitary tumours in female mice (Risperdal and Serenace Product Information documents).

Two repeated dose pharmacological studies were conducted to investigate whether differences between the effects of asenapine and risperidone on plasma prolactin concentrations might explain the difference in incidences of prolactin-related tumours seen in carcinogenicity studies. Doses (respectively 2.8 mg/kg/day SC and 5.0 mg/kg/day PO) were selected to achieve comparable pharmacological effects for the two drugs (including elevation of prolactin concentrations) but only male rats were investigated, with no differences between drugs being observed.

Reproductive toxicity

Effects of asenapine on reproductive toxicity were extensively investigated, with a summary of submitted studies given in Table 2.

Table 2: Overview of reproductive toxicity studies submitted:

Study type	*Species (strain)*	*Route*	*Doses (mg/kg/day)*	*Dose range finding study (dose mg/kg/day; strain[#])*
Fertility and early embryofetal development*	Rat (Wistar)	PO	0, 1, 5, 30[&]	0 and 30; Sprague Dawley
Embryofetal development*	Rat (Wistar)	PO	0, 1, 5, 30[&]	0 and 30; Sprague Dawley
Embryofetal development	Rat (Sprague Dawley)	IV	0, 0.3, 0.9, 1.5	-

Embryofetal development	Rabbit (Chinchilla)	PO	0, 1, 5, 30[&]	0 and 30; Dutch
Embryofetal development	Rabbit (NZW)	IV	0, 0.025, 0.125, 0.625	-
Pre-postnatal	Rat (Sprague Dawley)	IV	0, 0.3, 0.9, 1.5	0, 0.3 and 3; Sprague Dawley
Pre-postnatal (cross fostering)	Rat (Sprague Dawley)	IV	0, 1.5	30 PO[&] ; Sprague-Dawley[†]

* comprising Caesarean and littering subgroups, [#] dose range finding studies (oral route) were not done using the same strains as the main studies in either rats or rabbits, [&] all doses given bd
[†] a full study with PO dosing was not carried out, - = not conducted

Clinical signs were evident at all doses in all the main reproductive toxicity studies in both rats and rabbits (for both routes) and doses in these studies were considered adequate. However, a paucity of toxicokinetic data for the reproductive toxicity studies was a notable deficiency with no data for PO dosing in rabbits to allow drug exposure estimates for the embryofetal development study with this route. Drug exposure ratios would be 0.8, 4.1 and 24 based on body surface area[7] (BSA; 1, 5 and 30 mg/kg/day x 15 *vs* 0.56 mg/kg/day for a 50 kg person x 33). The maximum human dose is 28.12 mg/day of the salt and it is assumed that doses in the rabbit study also refer to the salt, although this was not clear.

Although plasma drug was measured in the IV rabbit embryofetal development study, data for rats was either obtained from a separate 2 week IV study in normal (non pregnant, non-lactating) females or from a 52 week PO toxicokinetic study. The latter only used males for repeat dosing, compared with both sexes after single dosing and there was a large discrepancy between high-dose male $AUC_{0\text{-}7\ h}$ values after single and multiple dosing. Estimates of drug exposure ratios with the PO high-dose used in rats (30 mg/kg/day) were therefore variable. Values could be considered to be 11.5, 37 or 18, respectively, based on the male 52 week value of 355 ng.h/mL x 2 (extrapolated from 21.6 to 30 mg/kg/day), the female single high dose value of 1600 ng.h/mL x 2, or the mid dose male 52 week value of 93.3 ng.h/mL x 2 extrapolated from 3.6 mg/kg/day to 30 mg/kg/day. The most valid (and conservative) estimate would appear to be the extrapolation from the male 52 week value (ER about 11).[8] Despite this uncertainty, it is likely that achieved exposure comfortably exceeded anticipated clinical exposure.

In the rat fertility study, pre-coital intervals were increased with all doses, although this may have reflected lethargy induced by the drug. Results from the dose range finding study suggested that both treated males and females were affected (when these were mated with untreated rats). In the main study, there was little effect of treatment on mating performance or pregnancies and the NOEL for effects on fertility was 2 x 15 mg/kg/day, although both mating and pregnancies were reduced in the dose range finding study at 30 mg/kg/day PO (given as a single daily dose vs bd in the main study). Pre-implantation losses were significantly increased with 5-30 mg/kg/day in the main study with an associated reduction in implantations/litter and live fetuses/litter and similar findings were observed in the rat oral embryofetal development study but not in the corresponding IV study. At the Lowest Observed Effective Dose (LOEL) (5 mg/kg/day PO), the drug exposure ratio was estimated to be 3 (93.3 x 2.5/1.8 = 130 ng.h/mL x 2/86 = 3). The NOEL for increased pre-implantation

[7] BSA doses can be compared across species for drugs given by the same route, as a substitute for actual exposure data. In this case, rabbit PO doses have been compared with the maximal human sublingual dose to obtain an ER estimate, despite the acknowledged difference in administration routes.
[8] Gender AUC differences were not pronounced but repeat high dose AUC values were << single high dose values.

loss was the low dose in the fertility study, giving a drug exposure ratio of about 1.0 (38.3 ng.h/mL x 0.5/0.3 x 2/86), while effects on post implantation losses were less marked and not consistent across all studies. However, increases in post implantation losses in rats were observed in the fertility study (littering section), the Caesarean subgroup of the embryofetal development study (associated with an increase in early resorptions) and the IV pre-postnatal studies.

In the rabbit, no embryotoxicity was evident with IV administration and the only findings after oral administration were a reduction in fetal weight and an increase in runts with the high dose (fetal/pup weights were generally not affected in the rat studies). NOEL values for embryotoxicity in rabbits were the high dose in the IV study and the mid dose in the oral study (respective exposure ratios of 2.1 and 4.1, the latter based on BSA). There was no clear evidence of a teratogenic effect in either rats or rabbits. Increases in fetuses with abnormal skeletal findings were observed in some rat studies but were quantitatively small, not clearly dose related and not consistently observed across the studies. The NOEL for teratogenicity was therefore the high dose in all studies, giving respective drug exposure ratios of 11.5 (PO) and 4.8 (IV) in rats, with corresponding values in the rabbit of 24 (based on BSA) and 2.1.

In the three IV postnatal studies (rats), as well as the rat fertility study (littering subgroup, with treatment throughout lactation), asenapine treatment of F_0 females resulted in reduced pup viability (mainly over post-partum Days 0-4) and small reductions in pup growth over the lactation period were observed in some studies. NOEL values for reduced pup viability in both the fertility study (oral) and the main IV pre-postnatal study were the low doses, achieving drug exposure ratios of about 1.0 in both studies. In the IV cross-fostering study, high postnatal pup losses (post-partum Days 0/1-4) were observed in the treated group, the treated group with within-group cross fostering and the vehicle group fostering pups from dams treated during gestation, suggesting that the neonatal mortality, which resulted from lack of suckling and/or cannibalisation of the pups, was caused by impairment of the pups rather than changes in nursing behaviour of the dams.

There was little evidence of an effect of treatment of F_0 females on the neurobehaviour of the F_2 generation in the fertility study and the main IV pre-postnatal study.

Use in children

Asenapine is not recommended for use in patients below 18 years of age, although a juvenile rat study was conducted in which SC treatment was over the age range 14-69 days and development, including reproductive performance was assessed. Doses achieved drug exposure ratios (based on AUC) of 1.3-10.1 and apart from body weight gain impairment, which was reversible in females by the time of pairing, little or no adverse effects of treatment were identified. All doses elicited increases in ambulation and rearing scores which were measured after cessation of treatment and similar post-treatment increases were noted in older rats (initially 57 days old and treated for 4 weeks) in a pharmacology study. In the juvenile rat study, fertility was slightly reduced with the mid-dose (MD) and HD (both 86% vs 100% for the controls) and this was slightly lower than the minimum historical control value of 89%, although this was based only on 9 studies. The biological significance of this observation is not clear. Overall, this study supports the use of asenapine in younger patients but this would require additional studies and may need re-assessment of effects on fertility.

Local tolerance

Sublingual administration was not used for the toxicity studies, although asenapine pharmacokinetics was assessed with this route in dogs and two GLP sublingual local

tolerance studies were conducted in female dogs. The later (2004) local tolerance study used a clinically relevant dose of 15 mg bd (vs 0.8 mg bd in an initial study) for 7 days, with little local effect of application being observed (unremarkable gross pathology and minor histological findings). The tablet composition and excipients were not given and were presumably the same as those proposed for registration.

Impurities

Toxicity studies with the impurities were conducted and on a BSA basis intakes of all doses were greatly in excess of that in humans at the maximum recommended dose.

Degradation products

Toxicity studies were not conducted but genotoxicity studies revealed that specific degradation compounds were clearly positive, in the presence and absence of S9, in a chromosome aberration test with human blood lymphocytes, although both were negative in bacterial reverse gene mutation assays and in two *in vivo* tests (rat micronucleus test, DNA damage in liver/stomach/duodenum). Assurance of safety can be gained from the negative findings for these compounds in the bacterial assays and the *in vivo* studies, in which doses of the purified degradants were very high (up to 70 or 100 mg/kg SC in the micronucleus test). Overall, the limits for the specified impurities and degradants are acceptable.

Nonclinical Summary and Conclusions

The exact mechanism of action is not clear but pharmacodynamic studies indicated that asenapine showed high affinity for dopamine receptors, various 5-HT receptor subtypes, α adrenergic receptors and histamine H_1 receptors *in vitro*. The (+) and (-) enantiomers were comparable but the N-desmethyl metabolite showed lower affinities while asenapine N+-glucuronide showed no appreciable affinity. *In vivo* studies showed asenapine to be active in animal models thought to be predictive of human anti-psychotic activity, with effects being seen with SC doses as low as 0.02-0.04 mg/kg in some tests. Secondary pharmacological activities included decreased activity, catalepsy and elevated plasma prolactin.

Safety pharmacology studies showed that relatively high concentrations of asenapine decreased action potential durations and hERG currents (IC_{50} = 0.3 µM or 86 ng/mL for the latter) *in vitro* and elicited cardiovascular changes *in vivo*. Dogs were mainly investigated and effects of treatment included decreased blood pressure and tachycardia, negative inotropic effect, potentiation of tilt-induced hypotension and tachycardia and in some studies ECG changes (QTc prolongation, decreased PR interval). Respiratory function in rats was affected (transient depressor effect) only at a high SC dose (NOEL = 1.5 mg base/kg SC), while GI motility was unaffected but potential renal effects were not investigated. There were no studies on potential effects on platelet function.

Plasma asenapine clearance values in rats and dogs were high after single IV administration (about 4 L/h/kg with a dose of 1.5 mg/kg), with corresponding low $t_{1/2}$ values (about 1 hour). Oral bioavailability values were 21-64% (rats) or <10% (dogs) and both asenapine and its N-desmethyl metabolite were highly bound to human and experimental species plasma proteins *in vitro* (>95%). Asenapine and its N-desmethyl metabolite did not act as p-glycoprotein substrates *in vitro*. Radioactivity was widely distributed in rats after PO [^{3}H]asenapine administration. Brain concentrations of parent drug and to a lesser extent, N-desmethylasenapine (but not asenapine N-oxide), were higher than those in plasma over 3 h after PO dosing in rats. There was evidence for melanin binding of parent drug and/or metabolites. Radioactivity was also widely distributed in dogs after sublingual administration of [^{14}C]asenapine.

Excretion of drug related material in experimental species (mouse, rat, rabbit, dog) was via faeces and to a lesser extent urine, while urinary excretion was slightly more prominent in humans. Asenapine was extensively metabolised, with some species differences being apparent, including prominent plasma asenapine N-oxide in rats but not in humans and the reverse for 11-O-asenapine sulphate. The major human plasma metabolite asenapine N+-glucuronide was generally not present in experimental species. *In vitro* experiments showed asenapine was mainly metabolised by CYP1A2 in human microsomal preparations and it inhibited this isoform and to a greater extent CYP2D6 (respective IC_{50} values of 0.61 µM = 174 ng/mL and 44 nM = 12.5 ng/mL). Inhibition of these 2 (recombinant) isoforms was also seen with the N-desmethyl metabolite.

Adverse neurological signs were seen in single dose toxicity studies and rat PO LD_{50} values were 110-176 mg/kg. Clinical pathology changes in dogs were suggestive of hepatotoxicity and nephrotoxicity. There was little irritation in a 7 day local tolerance study in dogs using sublingual application. Asenapine was not antigenic in guinea pigs and phototoxicity was not observed in an *in vitro* assay.

Repeat-dose toxicity studies were conducted in mice (PO, SC), rats (PO, SC, IV) and dogs (PO, IV). The longest duration studies were for 52 weeks in rats and dogs (PO) and 39 weeks in dogs (IV) and the high-doses used resulted in respective drug exposure ratios (based on AUC compared with the expected human value) of 5.8, 0.8 and 5.5. Findings included clinical signs indicative of pharmacological activity, impaired or enhanced weight gains and premature deaths of unknown cause(s) but there were few indications of target organ toxicity. Increased pulse/heart rates were often seen in dogs but ECG changes were minimal.

Several changes, including mammary gland development and secretion, appeared to be related to elevated prolactin. Other findings in rats included increased relative adrenal and thyroid weights, and thyroid follicular hypertrophy, while increased relative liver weights and elevated serum enzyme activities (transaminases, alkaline phosphatase) occurred in all species. Hepatotoxicity was not generally seen but high PO doses in dogs elicited elevated plasma bilirubin and hepatic necrosis. Modest elevations of plasma urea and creatinine were seen in some rodent studies, while renal tubular basophilia/dilation associated with glucosuria were seen with high PO doses in dogs in 2 short term studies.

Adequate toxicity studies were conducted and characterised by observations consistent with pharmacological activity but with little target organ toxicity being identified and there were no findings to preclude approval of registration. It should be noted, however, that no studies were conducted with asenapine in combination with lithium or sodium valproate, which may be used together with asenapine for the bipolar indication.

Asenapine was not genotoxic in generally adequate *in vitro* (bacterial reverse mutation, mammalian cell forward mutation at the *tk* locus, chromosomal aberration, sister chromatid exchange) and *in vivo* (rat PO micronucleus) tests. No oncogenic responses were observed in long-term carcinogenicity studies in mice and rats, with the high-doses used achieving estimated drug exposure ratios of 3.9 and 3.4, respectively. Survivals were decreased in mice and body weight gain was substantially impaired in male mice and male and female rats.

Reproductive toxicity studies were extensive and included the use of both PO and IV administration in the rat and rabbit embryofetal development studies and an additional rat pre-/post-natal study with pup cross-fostering. Littering phases were included in fertility and early embryonic development and embryofetal development studies in rats. Substantial placental transfer of parent drug and/or its metabolites to embryos and fetuses was demonstrated in rats and rabbits after IV administration of [^{14}C]asenapine, while radioactivity

was concentrated in rat milk (milk/maternal plasma ratios of up to 3.8). There were no plasma drug concentration data for rabbits with PO administration.

Asenapine was not teratogenic in rats or rabbits, with high-doses resulting in drug exposure ratios (actual or estimated) of 5 (rat IV), 11 (rat PO), 2 (rabbit IV) or 24 (rabbit PO, based on body surface area (BSA)). Decreased fetal weights and increased incidence of runts were observed in the latter study, with a drug exposure ratio of 4 (based on BSA) at the NOEL. Other adverse findings in the reproductive studies included increases in pre-implantation and post-implantation losses in some studies, post-natal loss over days 0-4 post-partum and reduced pup weight gain to weaning. The post-natal loss reflected fetal exposure rather than reduced maternal nursing. Fertility was unaffected by doses of up to 30 mg/kg/day in a rat study (estimated drug exposure ratio of 11).

An 8 week SC study was conducted in juvenile rats, with SC treatment at ages 14-69 days and doses of 0.4-3.2 mg base/kg/day resulted in drug exposure ratios of about 1-10. Indices of behaviour and development, including reproductive performance, were assessed. Findings included impaired body weight gain (reversible in females), clinical signs indicative of pharmacological activity and increased locomotor activity for at least 4 weeks after the cessation of dosing. Fertility was slightly reduced with the mid- and high-doses but reproductive indices were otherwise unaffected. There were no histological effects of high dose treatment in the brain.

No oncogenic responses were observed in the long-term rodent carcinogenicity studies, despite a potential for prolactin elevation being demonstrated in male rats consistent with dopamine receptor binding. Although intended for use in adults, results from a juvenile rat study suggested that asenapine could be used in younger patients but additional studies would be required to support treatment in this patient population.

Asenapine demonstrated binding to multiple receptors *in vitro* but, as with other antipsychotic agents, its exact mechanism of action is not known and efficacy in comparison to other registered medicines will have to be assessed from the clinical results. Safety pharmacology studies indicated a potential for adverse cardiovascular effects, including orthostatic hypotension and prolonged QTc intervals, as noted in the proposed product information and these should receive particular attention in the clinical evaluation.

IV. Clinical Findings

Introduction

The submission met the requirements for a new innovator medicine containing a new chemical entity except that a relative bioavailability study was not performed. Study 25506 looked at oral absolute bioavailability in two healthy volunteers.

A total of 841 healthy volunteers and 5895 patients were included in studies in the clinical development program for asenapine. Of healthy volunteers 96 males were randomised to receive placebo and 745 to asenapine (661 males/84 females). Among the patients, 1064 were randomised to receive placebo (659 M/405 F), 3457 to asenapine (2103 M/1354 F) and 1374 to an active comparator (876 M/498 F).

The submission states all studies in the asenapine clinical development program were conducted in accordance with Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki and in compliance with the FDA regulations.

Pharmacokinetics

Asenapine is a racemic mix of R and S enantiomers that are not significantly different from racemic asenapine with respect to antidopaminergic, antiserotonergic, adrenolytic and antihistaminic properties.

The submission included 5 bioavailability studies, 6 comparative bioavailability and bioequivalence studies, 7 healthy subject pharmacokinetic (PK) and initial tolerability studies, 3 patient PK and initial tolerability studies, 6 intrinsic factor PK studies, 6 extrinsic factor PK studies, 5 other PK studies and 7 other PK or PK/pharmacodynamic (PD) studies.

Absorption

Study 25540 was an open label, randomized, single dose, explorative study in healthy volunteers to investigate the pharmacokinetics of sublingual and oral administered asenapine with and without charcoal to prevent gastrointestinal absorption. It showed faster absorption of the sublingual (SL) formulation (t_{max} 0.53 [0.33-2.00] hours) versus the oral formulation (t_{max} 3.00 [1.00-4.00] hours) despite the results supporting that a part of the SL dose is swallowed. There is considerable first pass metabolism as shown in the same study with SL C_{max} 2.58 ± 1.88ng/mL versus oral C_{max} 0.138 ± 0.0627ng/mL.

This may be complicated by an entero-hepatic circulation.

Bioavailability

There were two studies conducted on absolute bioavailability. In Study 25533, an absolute bioavailability study with sublingually and intravenously administered asenapine in healthy males, no reliable C^{14}-asenapine and C^{14}-N-desmethylasenapine concentrations were obtained from the bioanalysis after the use of IV C^{14}- asenapine. Thus absolute bioavailability could not be determined. Study 041036, a single dose two-way crossover study to assess the absolute bioavailability of sublingually administered asenapine in healthy males was stopped after only 3 subjects had the 0.5 mg infusion due to concentrations of asenapine in plasma too low for measurement.

A PK report based on Study 041036 and Study 25506 was submitted. For this report, the IV PK results of both trials were combined. An overall mean $t_{½}$ from a series of 13 sublingual PK trials was used to calculate the area under the plasma concentration time curve [with IV dosing] ($AUC_{0-\infty,IV}$) for these combined IV data. From these same trials, an overall estimate of $AUC_{0-\infty,SL}$ was obtained to calculate the absolute bioavailability. For a 5 mg dose this was calculated at 34.8%.

Another study (25506), an open pilot pharmacokinetic study concerning IV administration at four different doses followed by a pilot bioavailability study of oral 30 mg in the two healthy volunteers receiving the highest tolerated IV dose of asenapine was abandoned after 1 of 2 subjects went into asystole after a 0.7 mg infusion.

Relative bioavailability (with that of an oral solution or suspension of defined particle size) where the absolute bioavailability of the new finished product has not been determined but that of a solution or suspension has been determined; was not performed.

Study 25540 had the primary objective of determining the amount of SL asenapine swallowed and as discussed above, the results support that a part of the SL dose is swallowed. However a comparison of the results for asenapine without charcoal show oral (n=8) C_{max} is 6.8% of the sublingual (n=7) C_{max}, while oral $AUC_{0-\infty}$ is 8.8% of the sublingual $AUC_{0-\infty}$.

Bioequivalence

Three formulations as follows were used in the trials, with some confusion in the summaries:

- Old formulation.

- New formulation, also known as Phase 3 (used in clinical trials)
- Commercial formulation.

The old formulation and the new formulation were compared in Study 041009 Block I - a single centre, two-way crossover relative bioavailability and safety study with differing formulated tablets of sublingually administered asenapine in subjects with schizophrenia or schizoaffective disorder. No statistically significant treatment effect was found.

The commercial formulation (N = 33) and the new formulation (N = 36) were compared in Study A7501015, a bioequivalence study of sublingual asenapine tablets (5 mg) in healthy volunteers. The formulations were considered bioequivalent based on 90% confidence intervals (CIs) for ratios of treatment mean C_{max} and area under the curve to the last quantifiable value (AUC_{0-tlqc}) values completely within the bioequivalence interval of 80% to 125%.

Influence of water

In Study 25537, an open label, randomized, relative bioavailability trial in healthy volunteers to study the effect of water administration at different time points after dosing on the pharmacokinetics of sublingually administered asenapine found that after 10 mg of asenapine SL followed by 150 mL water at 2, 5, 10 and 30 minutes later, bioequivalence was not shown between the time periods, except for 10 versus 30 minutes. That is, ideally a patient should wait 10 minutes after dosing before drinking water, however even at 2 minutes the reduction in C_{max} (17%) and AUC (18%) were less than the intra and inter patient variability.

Distribution

Volume of distribution during the terminal phase (Vz) was determined from Study 041036 (n = 3), a single dose two-way crossover study to assess the absolute bioavailability of sublingually administered asenapine in healthy males to be 1719 ± 238L, while from Study 25506 (n = 2), referred to under *Bioavailability* above, it was 1748 ± 107L.

Study 25522, an open label, single dose, study to assess the effect of hepatic impairment on the pharmacokinetics of asenapine and its metabolite demethyl asenapine in healthy subjects (n=8) found the bound fractions of asenapine in plasma after of 0.3 mg asenapine SL at 5 hours was 98.7 ± 0.12% and at12 hours was 98.7 ± 0.20%. Study 25521, an open label, single dose, study to assess the effect of renal impairment on the pharmacokinetics of asenapine and its metabolite demethyl asenapine had similar results.

Study A7501018, a Phase 1, open label, parallel group, single-dose study to evaluate the pharmacokinetics, safety and tolerability of asenapine in subjects with various degrees of hepatic function (Normal group n = 8) found that after 5 mg SL at 4 hours, the fraction unbound (fu) was 0.047 ± 0.005 in plasma (or 95.3% bound), while for Study A7501017, a Phase 1, open label, parallel group, single-dose study to evaluate the pharmacokinetics, safety and tolerability of asenapine in subjects with various degrees of renal function (Normal group n = 9) it was 0.037 ± 0.008. This high protein binding (by 1-α – acid glycoprotein [77%] and albumin [53.9%]) was supported by the results of *in vitro* studies.

There is low binding to erythrocytes (fraction = 0.18).

Elimination

Excretion

In Study 25532, an open, nonrandomized, single centre trial to determine the excretion balance, metabolic profile and pharmacokinetics of asenapine after a sub-lingual dose of [14c]-labelled asenapine, > 80% of the radioactive dose was excreted within 96 hours. Figure 1 shows the cumulative excretion of total radioactivity. The main faecal drug component was

asenapine as 5-16% of the dose. While in the urine it was asenapine-glucuronide as 10-20% of the dose. A comparison of the unchanged parent compound following a single dose and steady state urinary excretion is shown in Table 3.

Figure 1: Mean excretion of radioactive material per route and overall (Study 25532)

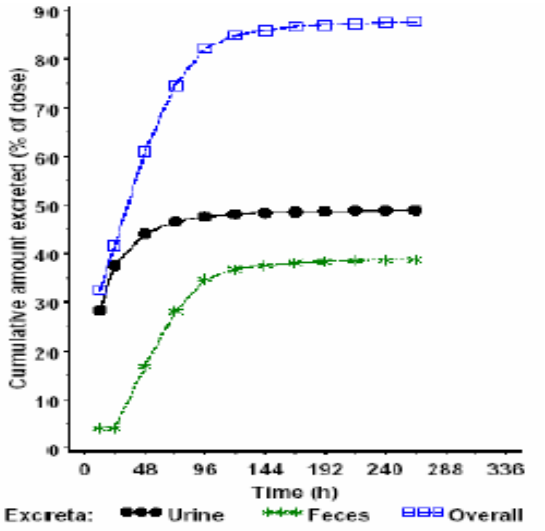


Table 3: Fraction excreted unchanged in urine(fe).

Single dose n = 6		**1 mg**	**3 mg**	**5 mg**
fe_{sd}	Mean ± SD	0.000167 ± 0.000409	0.000169 ± 0.000154	0.000173 ± 0.000222
	CV%	245	91.2	128
Steady state		3 mg bd n = 6	5 mg bd n = 6	10 mg bd n = 4
fe_{ss}	Mean ± SD	0.00655 ±0.000313	0.000392 ± 0.000236	0.000434 ± 0.000227
	CV%	47.8	60.1	52.3

Renal Excretion

In Study 25532, 48.9 ± 9.0% of the10 mg C^{14} asenapine dose was recovered in urine.

Hepatic excretion

In Study 25532, 38.8 ± 5.6% of the10 mg C^{14} asenapine dose was recovered in faeces.

Hepatic extraction ratio (E_H)

Asenapine is a high extraction ratio drug. Excretory product half lives range from 5 to 54 hours depending on dose.

Metabolism

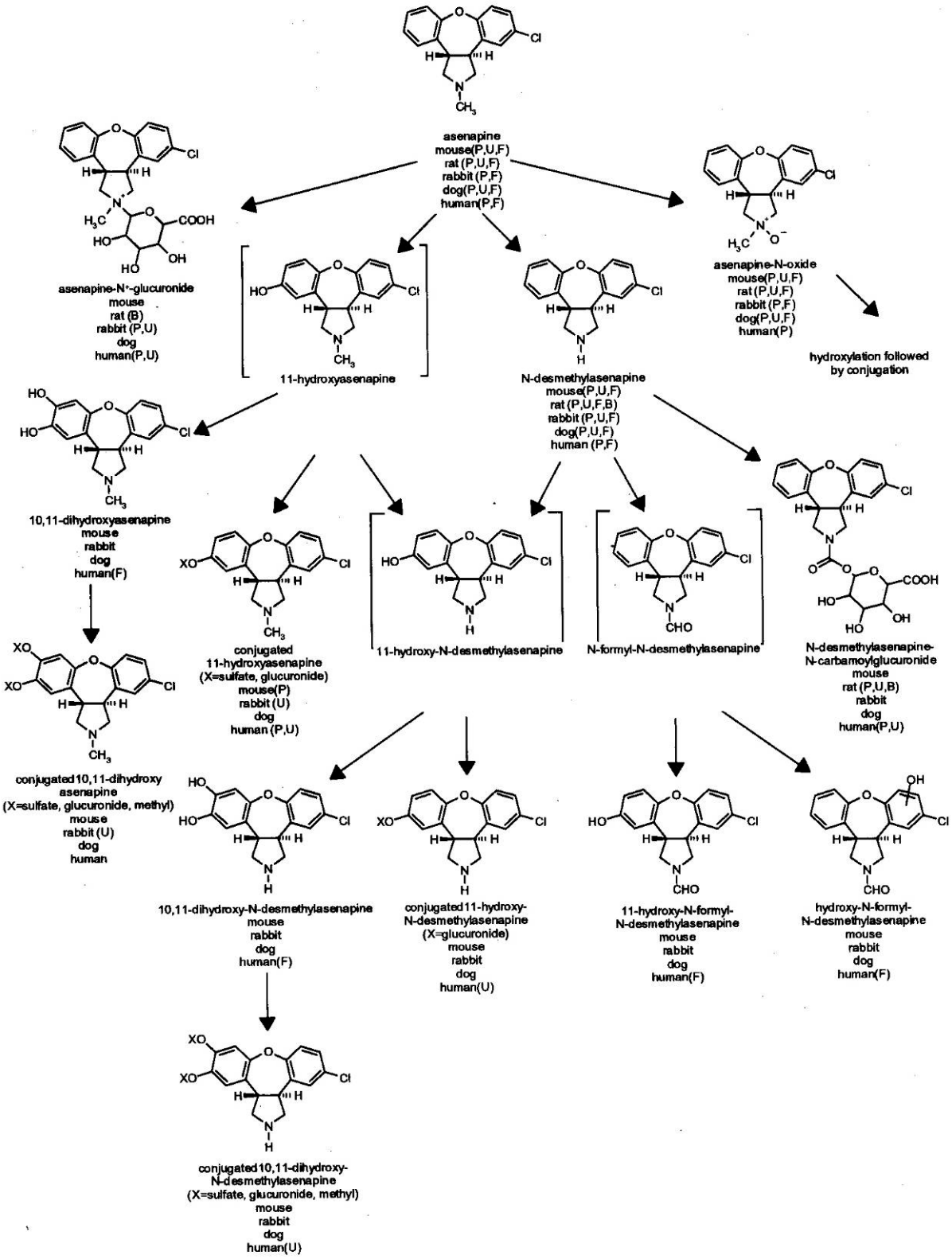
In vitro studies of asenapine yielded N-desmethylasenapine, asenapine N-oxide, 11-hydroxyasenapine and, if supplemented with cofactors and conditions required for activity of uridine diphosphoglucuronyl transferase (UGT), asenapine N+-glucuronide. For oxidative metabolism, *in vitro* studies using human microsomes show conversion by N-demethylation and N-oxidation with CYP1A2 the main human P450 involved in the formation of the N-oxide metabolite and, at a low concentration of asenapine, in the formation of N-desmethylasenapine. At a high concentration of asenapine both CYP1A2 and CYP3A4 are responsible for the formation of N-desmethylasenapine *in vitro*.

Asenapine has inhibitory activity (K_i) highest for CYP2D6 (K_i = 0.00675 µM, 0.016 µM) followed by CYP1A2 (K_i = 1.5 µM, 2.06 µM), CYP2C19 (K_i = 2 µM) and CYP3A4 (K_i = 33.2 µM).

N-desmethylasenapine and asenapine N-oxide were not expected to contribute to CYP450 inhibition in clinical use. The formation of asenapine N+-glucuronide appears to be mediated by only UGT1A4.

Proposed metabolic pathways for asenapine are shown in Figure 2.

Figure 2: Proposed metabolic pathways for asenapine

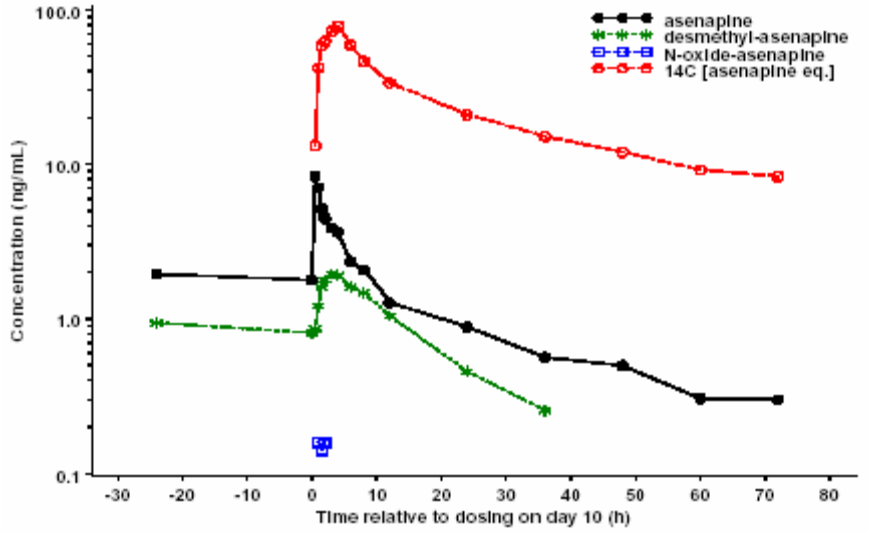


P= plasma, U = urine, F = faeces, B = bile

Sublingual administration of [14C]-asenapine to male healthy volunteers, resulted in extensive metabolism as indicated by the number of peaks found in the chromatograms.

The majority of human metabolites were identified using mass spectral characterization. The major peaks were assigned to asenapine, N-desmethylasenapine, asenapine N+-glucuronide and N-desmethylasenapine-N-carbamoylglucuronide. In single (non-pooled) plasma samples, the asenapine N+-glucuronide and unchanged asenapine (at one time point, 1 hour post dosing) were the major drug-related entities. Plasma concentrations of total radioactivity greatly exceeded those of asenapine and its desmethyl and N-oxide metabolites at any time point, indicating that asenapine is metabolized rapidly and that these two metabolites constitute only a small fraction of the total metabolites in plasma (Figure 3). The remainder of the peaks were associated with more polar compounds, most probably conjugates. Only N-desmethylasenapine and asenapine-11-O-sulfate showed receptor binding but neither is expected to contribute to the pharmacological activity due to lower affinity, low plasma concentrations and, for the sulphate, the inability to cross the blood brain barrier.

Figure 3: Mean concentration-vs-time plots of total radioactivity (expressed in asenapine equivalents), asenapine, desmethyl-asenapine and N-oxide-asenapine in plasma



Interconversion

The R and S enantiomers are not significantly different from the racemic asenapine with respect to anti-dopaminergic, anti-serotonergic, adrenolytic and antihistaminic properties.

In Study 041028, a single dose, open label trial to investigate the pharmacokinetics of the enantiomers of asenapine healthy male subjects, the plasma concentrations of the (S,S)- and (R,R)-enantiomers of asenapine were similar after simultaneous single SL doses of 2.5 mg of the (S,S)-enantiomer and 2.5 mg of the (R,R)-enantiomers of asenapine. Formation of the N-desmethyl metabolite seems to be enantioselective, with the exposure to (S,S)- enantiomer more than two-fold higher than the (R,R)- N-desmethyl-asenapine

Since N-desmethyl-asenapine shows a much lower binding affinity for therapeutically relevant receptors than asenapine and the level of exposure to N-desmethyl-asenapine is lower, the difference in AUC between the N-desmethyl-(R,R)-asenapine and the N-desmethyl-(S,S)-asenapine is considered to be of no clinical relevance.

Pharmacokinetics of Metabolites

From Study 25546, a placebo controlled, double blind, randomised, parallel groups, single and multiple dose study with asenapine in healthy Japanese and Caucasian subjects, to evaluate safety and pharmacokinetic parameters in a Japanese population in comparison to a Caucasian population the results are shown in Tables 4, 5 and 6.

Table 4: Summary of plasma PK parameters of desmethyl-asenapine after single dosing and at steady state - Caucasian

Parameter (unit) mean (%CV)	Single dose n = 6			Steady state n = 6		
	1 mg	3 mg	5 mg	3 mg bd	5 mg bd	10 mg bd
t_{max} (h)	6.00 (6.00-12.0)	7.00 (2.00-8.00)	6.00 6.00-8.00	6.00 (2.00-6.02)	4.03 (2.00-6.05)	5.01 (0.33-8.00)
C_{max} (ng/mL)	0.0942 (46.1)	0.269 (21.6)	0.599 (36.8)	0.789 (34.0)	1.23 (27.5)	3.29 (65.2)
dn-C_{max} (ng/mL/mg)	0.0942 (46.1)	0.0898 (21.6)	0.120 (36.8)	0.263 (34.0)	0.245 (27.5)	0.329 (65.2)
AUC_{0-last}[1] (ng.h/mL)	0.684 (65.0)	4.11 (29.8)	10.7 (47.1)	7.61 (36.0)	11.8 (24.6)	27.7 (51.7)
dn-AUC_{0-last}[1] (ng.h/mL)	0.684 (65.0)	1.37 (29.8)	2.14 (47.1)	2.54 (36.0)	2.36 (24.6)	2.77 (51.7)
$AUC_{0-\infty}$ (ng·h/mL)	6.79 (23.1)	5.27 (25.2)	13.5 (50.6)			
dn-$AUC_{0-\infty}$ (ng·h/mL/mg)	6.79 (23.1)	1.76 (25.2)	2.70 (50.6)			
$t_{1/2}$ (h)	54.1 (78.3)	12.7 (21.0)	17.1 (42.4)	16.5 (44.1)	19.0 (26.2)	17.2 (12.6)

Table 5: Summary of plasma PK parameters of asenapine-glucuronide after single dosing and at steady state - Caucasian

Parameter (unit) mean (%CV)	Single dose n = 6			Steady state n = 6		
	1 mg	3 mg	5 mg	3 mg bd	5 mg bd	10 mg bd
t_{max} (h)[a]	6.00 (4.00-6.00)	6.00 (4.00-6.00)	4.00 (4.00-8.00)	4.00 (3.00-4.00)	4.00 (3.00-4.00)	3.50 (3.00-4.00)
C_{max} (ng/mL)	1.49 (43.7)	4.41 (25.4)	6.53 (24.3)	9.40 (38.5)	16.5 (25.9)	33.7 (30.4)
dn-C_{max} (ng/mL/mg)	1.49 (43.7)	1.47 (25.4)	1.31 (24.3)	3.13 (38.5)	3.29 (25.9)	3.37 (30.4)
AUC_{0-last}[1] (ng.h/mL)	11.4 (46.7)	46.6 (26.9)	71.1(36.6)	76.8 (37.6)	129 (20.4)	261 (20.4)
dn-AUC_{0-last}[1] (ng.h/mL)	11.4 (46.7)	15.5 (26.9)	14.2 (36.6)	25.6 (37.6)	25.7 (20.4)	26.1 (20.4)
$AUC_{0-\infty}$ (ng·h/mL)	15.1 (34.4)	52.1 (28.5)	77.2 (35.0)			
dn-$AUC_{0-\infty}$ (ng·h/mL/mg)	15.1 (34.4)	17.4 (28.5)	15.4 (35.0)			
$t_{1/2}$ (h)	5.24 (27.1)	10.5 (79.2)	13.4 (74.3)	13.6 (27.5)	15.8 (12.4)	18.6 (19.4)

Table 6: Summary of plasma PK parameters of asenapine 11-O-sulfate after a single asenapine 5 mg and at steady state at 5 mg bd – Caucasian.

Parameter (unit) mean (%CV)	Single dose n = 5	Steady state n = 5
	5 mg	5 mg bd
t_{max} (h)	3.02 (1.50-4.03)	3.00 (2.00-4.00)
C_{max} (ng/mL)	2.78 (66.0)	2.96 (34.9)
AUC_{0-last}[1] (ng.h/mL)	17.7 (73.9)	2.14 (51.7)
$AUC_{0-\infty}$ (ng·h/mL)	20.1 (62.9)	17.0 (19.2)
$t_{1/2}$ (h)	24.0 (86.3)	26.7 (28.1)

Consequences of possible genetic polymorphism

Based on this high first pass metabolism and its high clearance, asenapine can be classified as a high extraction ratio drug. In addition, asenapine is cleared by multiple mechanisms and enzymes, including several cytochrome P450 enzymes and glucuronidation. No single clearance pathway predominates.

In Study 25546 no significant difference in PK parameters was found for Japanese and Caucasian subjects.

Dose proportionality and time dependency

Dose proportionality

Asenapine PKs are nonlinear within the recommended dose range.

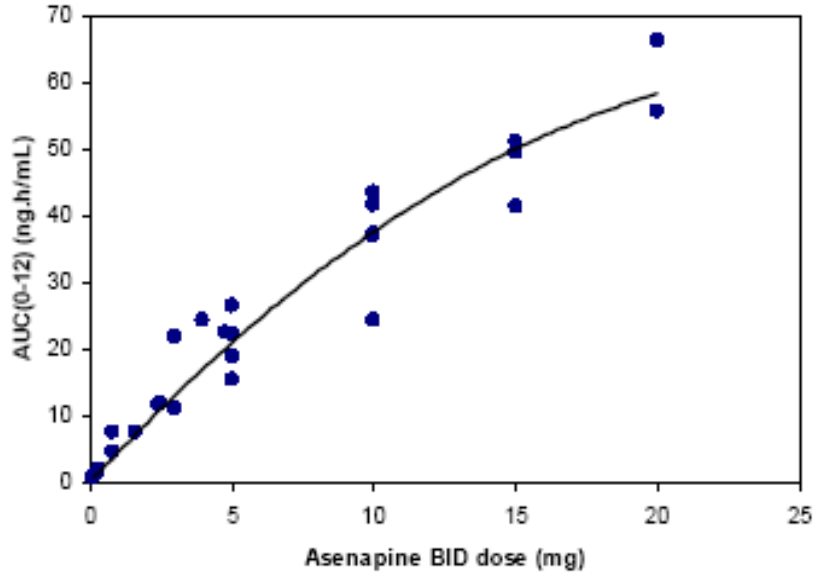
Up to 5 mg bd SL, C_{max} and AUC increase proportional to the dose. Within the range 5–10 mg bd, there is a deviation from dose-proportionality, with C_{max} and AUC increasing a factor 1.7 with a two-fold increase in dose. At above 10 mg bd, this deviation from dose-proportionality is more pronounced.

In Study 25546 Caucasians AUC_{0-12} and C_{max} decreased with increasing dose both after single dose and at steady state.

In a population PK analysis (Report INT00036661), in healthy volunteers and patients with schizophrenia based on data from Phase 1 and Phase 2 trials, the less than dose-proportional increase in exposure was characterized by an effect of dose on relative bioavailability (F). In the model, this was linearly related to log(Dose), resulting in a lower F with increasing dose. The estimate (standard error [SE]) of the slope was 0.379 (0.0405). This report was supported by Report INT0007901 that also sampled Phase 2/3 data from schizophrenia and bipolar patients.

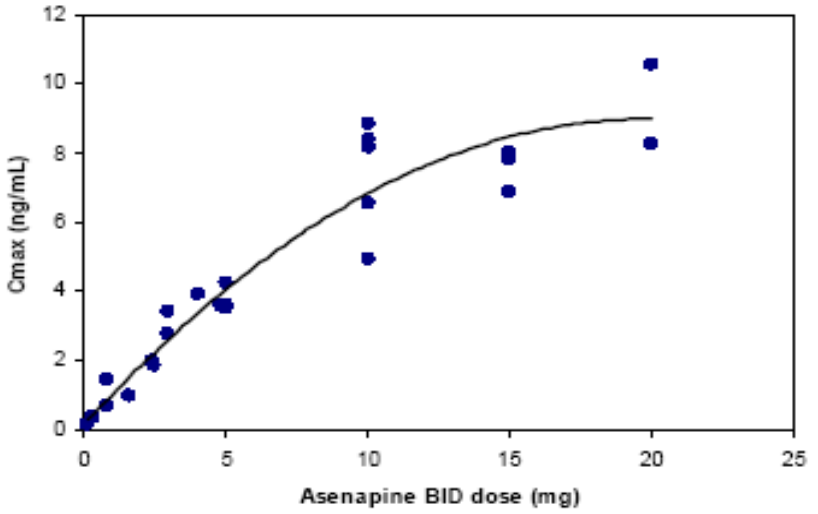
The less than proportional increase of C_{max} and AUC with SL dose may be attributed to limitations in the absorption capacity from the oral mucosa, so that with higher doses a larger portion of the dose may be swallowed as indicated by the metabolite ratios N-desmethylasenapine/asenapine. Since after oral administration N-desmethylasenapine plasma concentrations are considerably higher, the ratio N-desmethylasenapine/asenapine is expected to increase when part of the sublingual dose is swallowed. The relationships between bd dose and AUC_{0-12} (Figure 4) and bd dose and C_{max} (Figure 5) of asenapine across studies in healthy subjects and patients at steady state are shown in Figures 4 and 5.

Figure 4: Relationship between bd dose and AUC_{0-12} of asenapine across studies in healthy subjects and patients at steady state



Note: Markers represent mean AUC0-12 values per trial treatment arm; solid line represents trend line (second order polynomial).

Figure 5: Relationship between bd dose and C_{max} of asenapine across studies in healthy subjects and patients at steady state



Note: Markers represent mean C_{max} values per trial treatment arm; solid line represents trend line (second order polynomial).

Time dependency

In Study 25511, a Phase I, double-blind, placebo controlled, parallel groups, multiple, sublingual dose study with asenapine in healthy male volunteers to assess its tolerability as well as its pharmacodynamic and pharmacokinetic characteristics showed that at 150 µg bd, some parameters show statistically significant differences between treatment days. These differences could in most cases be attributed to differences in the duration of treatment between the treatment blocks and to differences in blood sampling schemes between the treatment blocks. There were no obvious increasing or decreasing trends.

In Study 25514, a Phase I, double blind, placebo controlled, parallel groups, multiple, sublingual titrating dose study of 200 to 300 mg asenapine in healthy male volunteers to assess its tolerability as well as its pharmacodynamic and pharmacokinetic characteristics at doses up to 300 µg, at steady-state there were significant differences from after initial single

dosing. That is, there were time-variant kinetics after 6.5 days, probably due to the short measurable time-course after single dosing resulting in an underestimation of its elimination half-life.

In Study 25542, a multiple dose, double-blinded, randomized, placebo-controlled, parallel group, safety and tolerability study with asenapine in healthy male volunteers, a between-subject comparison of the 5 mg steady-state and single-dose parameters showed that the mean accumulation ratio based on the asenapine C_{max} was 0.95 and based on asenapine AUC_{0-12} it was 1.34. The mean ratio of steady-state AUC_{0-12} over single-dose $AUC_{0-\infty}$ was 0.92, which indicates that pharmacokinetics of asenapine are not time dependent.

In Study 041012, a single-centre randomized, double blind, placebo controlled, titration study to evaluate the tolerability of sublingual asenapine up to 20 mg twice daily in subjects with schizophrenia or schizoaffective disorder at doses up to 20 mg, the evening trough levels were found to be significantly lower than the morning trough levels by, on average, 33% (asenapine) and 12% (desmethylasenapine).

In Study 25542 at doses up to 10 mg, evening pre-dose concentrations of asenapine were on average significantly lower (37%) than in the morning. There were no significant differences in AUC_{0-12} and C_{max} between morning and evening dosing.

Variability

Asenapine PKs show considerable variability, as shown by overall variability estimates of 45 % and 37 % for C_{max} and AUC, respectively.

Pharmacokinetics in the target population

PK studies were only conducted in schizophrenia patients. The efficacy and safety studies included PK results in both disorders. The population PK analysis (Report INT00079701) gave as its population, 888 patients with schizophrenia (78.1%) and 249 patients with Bipolar disorder (21.9%), with the majority of numbers from efficacy studies. That report could show no effect of disease state. PK parameters in patients with schizophrenia are shown in Table 7.

Table 7: Mean asenapine PK parameters at steady state in schizophrenia patients[a]

Study	**041001**	**041009**	**A7501001**	**041012**	**A7501001**	
Parameter Mean (SD)	**0.8mg N = 19**	**5 mg N = 5**	**5 mg N = 28**	**10 mg N = 2**	**10 mg N = 25**	
C_{max} (ng/mL)		3.50 (1.32)	4.23 (1.92)	8.84	6.56 (3.33)	
t_{max} (h)	1.48 (0.39)	1.00	1.79 (0.842)	1.25	2.01 (0.925)	
AUC_{0-12} (ng.h/mL)	0.697 (0.396)	18.963 (6.483)	26.6 (10.2)	37.3	43.4 (23.0)	
$T_{1/2}$ (h)	17.96 (7.23)			38.1	24.1 (9.97)	
Study	**041012**	**041014**	**041014**	**A7501001**	**041012**	**A7501001**
Parameter Mean (SD)	**15 mg N = 12**	**1x15 mg N = 8**	**3x5 mg N = 8**	**15 mg N = 33**	**20 mg N = 3**	**20 mg N = 29**
C_{max} (ng/mL)	7.80 (3.54)	6.38 (2.76)	6.89 (3.08)	8.05 (4.37)	1.03	10.6 (5.11)
t_{max} (h)	1.05	1.00	1.25	1.66 (1.09)	8.28 ± 3.72	1.70 (0.953)
AUC_{0-12} (ng.h/mL)	49.5 (18.9)	41.1 (17.1)	41.3 (18.2)	51.2 (28.7)	55.7 ± 34.9	66.1 (30.7)
$T_{1/2}$ (h)	39.0 (26.1)				31.0 ± 10.6	22.4[2] (5.23)

[a] Study A7501021 patients had psychosis with no further diagnosis breakdown. Study A7501022 had adolescent Subjects who had a documented history of schizophrenia, bipolar disorder, autism, conduct disorder, oppositional defiant disorder, or any condition for which there was chronic use of antipsychotic medication, with no further breakdown of numbers by diagnosis.

The population PK analysis (Report INT00036661) suggested a different absorption pattern between patients and healthy volunteers with a shorter lag time and slower absorption rate in patients.

These differences were most likely due to a less dense sampling scheme in the patient studies. No clinically meaningful differences were found.

Pharmacokinetics in special populations

Children

The application includes a copy of a European Medicines Agency (EMA) waiver in relation to a paediatric investigation plan. The proposed PI carries a warning of inadequate data in relation to patients under the age of 18 years. Study A7501022, a randomised, parallel group, multiple-dose study with asenapine in adolescent subjects had patients who had a documented history of not just schizophrenia or bipolar disorder but also autism, conduct disorder, oppositional defiant disorder, or any condition for which there was chronic use of antipsychotic medication, with no further breakdown of numbers by diagnosis. There were 9 adolescents aged 12 years in the study. Lower asenapine exposure observed in the 10 mg dose group in adolescents in this study was attributed to subjects swallowing a larger portion of the dose based on metabolite ratios.

Asenapine exposure after 5 mg in the adolescent population appears similar to that observed in adults.

Elderly

For elderly patients there were only interim study results from A7501021, a parallel group, multiple dose, 6-week study to evaluate safety, tolerability and pharmacokinetics of asenapine in elderly subjects with psychosis (selection criteria not given). A direct comparison of the PKs with A7501001 was made, showing asenapine 30% higher in elderly patients. But the report referred to the differing sampling schemes and the high variability (40-45 %), in adults in A7501001 making the difference of “limited clinical relevance”.

The population PK analysis (Report INT00036661) had a mean age of 33 years with a range of only 18-57 years and detected no effect of age. Report INT00079701 (mean age 40.3 years, range 17-73 years) showed a small but statistically significant decrease of asenapine clearance with increasing age (Age on CL/F /year was -0.0072 [SE 0.0012, CV 16.8%]).

Gender

Based only on population PK analyses (Reports INT00036661 & 79701) there was no difference in PKs based on gender.

Weight

The population PK analysis (Report INT00036661) had a population weight range of 44.7–134.5 kg. Weight on clearance (CL) was minus 0.0439 [SE 0.0902]), while in the subsequent analysis (INT00079701) weight had 0.15% increase/kg effect on clearance.

Race

In Study 25546 after single dosing and at steady state no significant difference in PK parameters (C_{max}, AUC, $CL_{/f}$ or wn-$CL_{/f}$,) of asenapine desmethyl-asenapine and asenapine-glucuronide was found between Japanese and Caucasian subjects.

The population PK analysis (Report INT00036661) produced an estimated elimination rate in black subjects that was 13.8 % smaller than that of other races. However this was eliminated as an effect in the subsequent modelling (INT00079701).

Impaired renal function

In Study 25532, 48.9 ± 9.0% of the dose of C^{14} was recovered in urine and in Study 25546 the amount of asenapine excreted unchanged into the urine was less than 0.1% of the dose administered, that is, renal impairment is unlikely to affect asenapine.

Study A7501017 did look at the effect of renal impairment on asenapine 5 mg and found no statistically significant differences in asenapine PK parameters. However, these tests were not considered sensitive due to the small sample size and variability in asenapine PKs.

Impaired hepatic function

There is considerable hepatic metabolism. In Study A7501018, discussed under *Distribution*, C_{max} decreased 10 and 43% (unbound C_{max} increased 10% and decreased 30%) with mild and moderate liver disease respectively but increased by 3% (43% unbound) in severe liver disease. While $AUC_{0-\infty}$ was similar to the reference with a12% increase (unbound 39 and 34%) for mild and moderate liver disease it was increased 5.5 fold (unbound 7.7 fold) in severe (Child-Pugh C) liver disease.[9] Desmethyl-asenapine C_{max} was reduced in mild or moderate hepatic impairment (ratio 70.2 and 66.7%) and markedly so in patients with severe hepatic impairment (ratio 32.7%), conversely AUC increased from a long $t_{1/2}$ (ratio: mild 117%, moderate 115%, severe 167%). Subjects with mild or moderate hepatic impairment had similar asenapine-glucuronide exposure to that of healthy subjects. Asenapine-glucuronide AUC was increased (ratio 129%) while C_{max} decreased (ratio 52.8%) in subjects with severe hepatic impairment.

Smoking

In Study 25545, an open label, randomized, two-way crossover, bioequivalence trial in healthy, smoking volunteers to assess the effect of smoking during sublingual asenapine dosing on the absorption of asenapine, smoking and non-smoking results were bioequivalent. For C_{max}, the ratio was 1.02 (90% CIs 0.87-1.20) and for $AUC_{0-\infty}$, the ratio was 1.06 (90% CIs 0.91-1.22).

Evaluator's overall comments on pharmacokinetics in special populations

There are limitations to the results of studies referred to in the proposed PI that should be explained but these are outside the scope of this AusPAR.

Pharmacokinetic interactions with other medicinal products or substances

In vitro pharmacokinetic interactions

There were several *in vitro* studies that suggested the potential for interactions including:

- Studies R&DRR NL0010293 & 0060848 that undertook characterization of the CYP450 enzymes involved in the metabolism of asenapine, using a number of inhibitors.

[9] The **Child-Pugh score** is used to assess the prognosis of chronic liver disease. The score employs five clinical measures of liver disease. Each measure is scored 1-3, with C indicating most severe derangement.

- Studies that looked at the inhibition of CYP450 enzymes by asenapine (Studies R&DRR NL0017588, 0050059, 0013163, 0050307, DM2005-00522-009 and RR 764-04914).
- Study RR 764-04914 looked at the Induction potential of asenapine on CYP450 enzymes.

Asenapine is cleared by multiple mechanisms and enzymes, including several CYP450 enzymes and glucuronidation. No single clearance pathway predominates and therefore no clinically relevant pharmacokinetic drug interactions would be expected.

In vivo pharmacokinetic interactions

The following effects on asenapine were noted:

- A population PK analysis (INT0003666151) in 346 subjects showed no effect of smoking (induction of CYP1A2) on asenapine, while in Study 25545 smoking and non-smoking results were bioequivalent for C_{max} and $AUC_{0-\infty}$.
- In Study 25525 the effect of multi-dose paroxetine on CYP2D6 had little effect on single dose asenapine with an $AUC_{0-\infty}$ ratio of 0.91 (90% CIs 0.85-0.97) and a C_{max} ratio of 0.87 (0.80-0.96) despite paroxetine producing greater CYP2D6 inhibition.
- In Study 25526 (CYP1A2, CYP2C19) of the effect of a single dose of imipramine on the single dose PKs of asenapine and desmethyl-asenapine, produced a significant effect but not clinically so (ratio 1.17 [90% CIs 1.05-1.30]) on the C_{max} of asenapine. Otherwise no interaction effects seen.
- In Study 25527 steady state valproate (glucuronyltransferase inhibition) had no effect on the single dose PKs of asenapine; on desmethyl-asenapine it lowered the AUC but not the C_{max} (ratio 0.65[90% CI 0.55-0.76]); with a greater effect on asenapine glucuronide (C_{max} ratio 0.15 [90% CI 0.13-0.18]; AUC ratio 0.06 [90% CI 0.04-0.10] with many results below the lowest level of quantification [LLQ]).
- In Study 25528 (induction of CYP3A4), investigating the effect of steady state carbamazepine on single dose asenapine, showed that it lowered AUC and C_{max} for asenapine (AUC ratio 0.83 [90% CI 0.76-0.90]; C_{max} ratio 0.84 [90% CI 0.74-0.95]) and desmethyl-asenapine (AUC ratio 0.66 [90% CI 0.61-0.71]; C_{max} ratio 0.70 [90% CI 0.66-0.74]) but only the AUC (ratio 0.84 [90% CI 0.75-0.94]) and not the C_{max} (ratio 0.90 [90% CI 0.82-0.99]) for asenapine N+-glucuronide.
- In Study 25529 (CYP1A2, CYP2D6 and CYP3A4inhibition), investigating the effect of steady state cimetidine on single dose asenapine, showed that it lowered asenapine C_{max} (ratio 0.87 [90% CI 0.77-0.98]) but not AUC (ratio 0.99 [90% CI 0.90-1.10]); it raised desmethyl –asenapine both C_{max} (ratio 1.50 [90% CI 1.32-1.70]) and AUC (ratio 2.22 [90% CI 1.90-2.58]); while it raised asenapine-glucuronide AUC (ratio1.15 [90% CI 0.97-1.36]) but not C_{max} (ratio 1.07 [90% CI 0.95-1.21]).
- In Study 041033 (CYP1A2 inhibition), investigating the effects of multi-dose fluvoxamine on single dose asenapine, showed that it raised asenapine C_{max} (ratio 1.13 [90%CI 0.99-1.30]) and AUC (ratio 1.29 [90%CI 1.15-1.45]); it raised desmethyl –asenapine AUC (ratio 1.97 [90%CI 1.66-2.35]) but not C_{max} (ratio 0.99 [90%CI 0.83-1.18]) and; it lowered asenapine-11-O-sulfate AUC (ratio 0.71 [90%CI 0.52-0.98]) and C_{max} (ratio 0.71 [90%CI 0.30-0.52]).

The following effects of asenapine were noted:

- In Study 25525, multi-dose asenapine prolonged the exposure to single dose paroxetine ($AUC_{0-\infty}$ ratio 1.92 [90% CIs 1.70-2.17], C_{max} ratio 1.82 [1.59-2.09]). In this study the effects of both drugs on the CYP2D6 activity was assessed by the dextrorphan/dextromethorphan ratio and showed asenapine to be a relatively weak inhibitor (2.5 times vs 30 times ratio decrease).
- In Study 25526, investigating the effect of a single dose of asenapine on the single dose PKs of imipramine and its metabolite desipramine, no interaction effects were seen.

Evaluator's overall comments on pharmacokinetic interactions

The dose of fluvoxamine used in study 041033 at 25 mg bd was less than usual in clinical practice (100-300 mg/day) so that an effect on asenapine levels in clinical practice is likely.

The clinical relevance of the other changes to asenapine, especially in the light of the high variability is doubtful. These results are all tabulated in the proposed PI.

Evaluator's overall conclusions on pharmacokinetics

1. Because of the high first pass metabolism after oral ingestion, the sublingual route was chosen. This is a long established route that has been exploited for lipophilic drugs often off label for quicker onset (for example, nifedipine), as well as for avoiding first pass metabolism. It does however introduce more variables into the absorption process.

The sponsors have compared smokers and non-smokers, finding no difference. While the sponsors were concerned about induction of CYP1A2, there is also some possibility of action on salivary secretion.[10] In Study 25537, exploratory analysis showed a significant disintegration time effect, with longer disintegration times resulting in higher exposure.

There were two studies comparing the effect on absorption of different sites in the oral cavity:

Study 25512 showed with 100 µg asenapine, based on C_{max} and AUC, that buccal and sublingual administration were bioequivalent but not supralingual and sublingual.

Bioequivalence was not shown between asenapine single dose 5 mg sublingually supralingually and buccally in Study 041030, based on C_{max} and AUC. Buccal and sublingual administration $AUC_{0-\infty}$ were the only parameters within the range for bioequivalence.

In Study 25540, the results support that a part of the SL dose is swallowed further complicating absorption.

It is thus not surprising that there is considerable inter and intra subject variability.

2. The statement on absolute bioavailability in the proposed PI is misleading as its implied accuracy it is at best an approximation.[11] In Study 041036 after IV administration of asenapine to the first 3 subjects (pilot phase), plasma concentrations were found to be too low to determine the half-life and to calculate the AUC and bioavailability. In Study 25533 after intravenous micro-dosing of 14C-labeled asenapine no reliable 14C-asenapine and 14C-N-desmethylasenapine concentrations were obtained from the 14C-bioanalysis. Therefore no pharmacokinetic analysis could be performed for the intravenously administered 14C-labeled asenapine and thus absolute bioavailability could not be determined. Sublingual bioavailability measurement relative to oral is altered by the extent of swallowing. However, from Study 25540 a comparison of the results for asenapine without charcoal show oral C_{max} is 6.8% of the sublingual C_{max}, while oral $AUC_{0-\infty}$ is 8.8% of the sublingual $AUC_{0-\infty}$.

3. The statement concerning water intake in the proposed PI is supported:

"The intake of water several (2 or 5) minutes after asenapine administration resulted in decreased (19% and 10%, respectively) asenapine exposure. Therefore, ~~eating~~ ~~and~~ drinking should be avoided for 10 minutes after administration."

[10] Macgregor IDM. Smoking, saliva and salivation. J Dentistry 1988; 16: 14-17. This review presents evidence that smoking increases salivary flow rate.

[11] The IV PK results of two uncompleted trials were combined. An overall mean $t_{½}$ from a series of 13 sublingual PK trials was used to calculate $AUC_{0-\infty,IV}$ for these combined iv data. From these same trials, also an overall estimate of $AUC_{0-\infty,SL}$ was obtained to calculate the absolute bioavailability.

In Study 25537 after 10 mg of asenapine SL followed by 150 mL water at 2, 5, 10 and 30 minutes later, bioequivalence was not shown between the time periods, except for 10 versus 30 minutes. That is, C_{max} and AUC were lower after water at 2 and 5 minutes than after water at 30 minutes.

However the evidence for the statement about avoiding eating is not submitted. In Study 041029 the only evidence for a food effect was for dosing 5 mg immediately after consumption of a high-fat meal and then only for the AUC with the associated C_{max} a food effect could not be considered absent; nor could it be considered absent where given a high-fat meal 4 hours after dosing–but it was not shown to occur in those circumstances for either AUC or C_{max}.

4. The data on the elderly arise from an interim analysis lacking detail. It showed C_{max} was ~30% higher in the elderly and AUC was 30-40% higher in the elderly.

5. Likewise the data on adolescents is not good, in that the number of patients suffering from the two proposed indications is unclear, as is the extent to which the other disorders in the study may affect the results, thus reference to the trial under Precautions and Dosage and Administration is of concern, the indication sought does not include adolescents, nor is there adequate evidence submitted.

Pharmacodynamics

Mechanism of action

The exact mechanism of action of asenapine in schizophrenia and bipolar disorder is unknown. The efficacy of asenapine appears to be mediated, at least in part, through a combination of antagonist activity at D_2 and 5-HT_{2A} receptors.

Asenapine's antagonism of α_1 adrenergic receptors may be associated with cardiovascular effects, such as orthostatic hypotension. Antagonism of histamine H_1 receptors may be associated with somnolence in clinical practice.

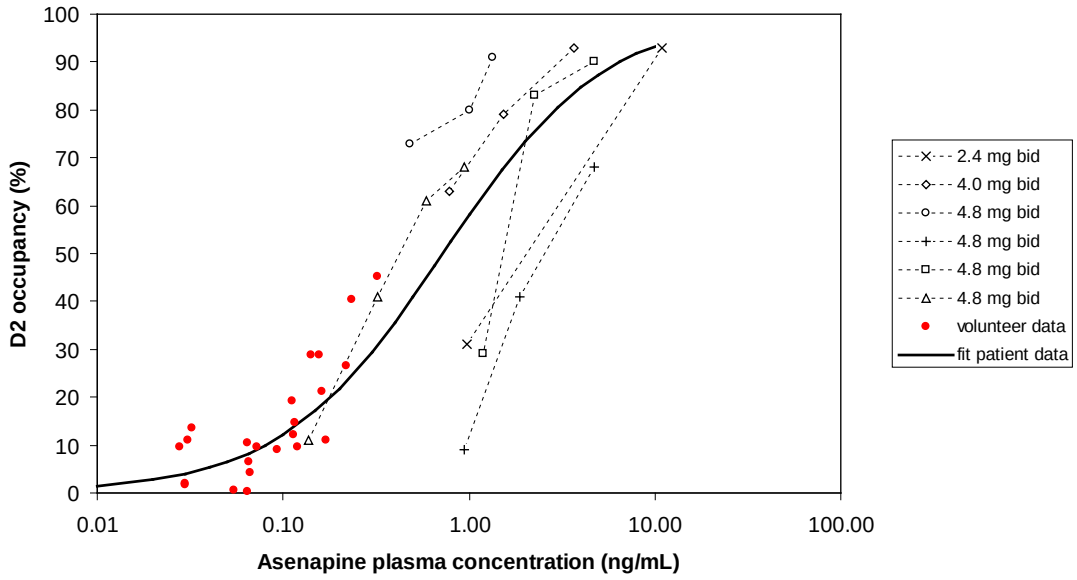
Both efficacy as well as safety aspects (extrapyramidal symptoms) have been shown to be related to different degrees of D_2 occupancy (Kapur et al, 2001).[12]

Primary pharmacology

Binding to the D_2 receptor in brain is plasma-concentration dependent (Figure 6), with the target of 80% occupancy[13] at a concentration of 3.2 ng/mL, which corresponds with the C_{max} value of SL asenapine of 5 mg bd (3.6 ng/mL). Twice daily dosing of asenapine seems required to maintain sufficient D_2 occupancy.

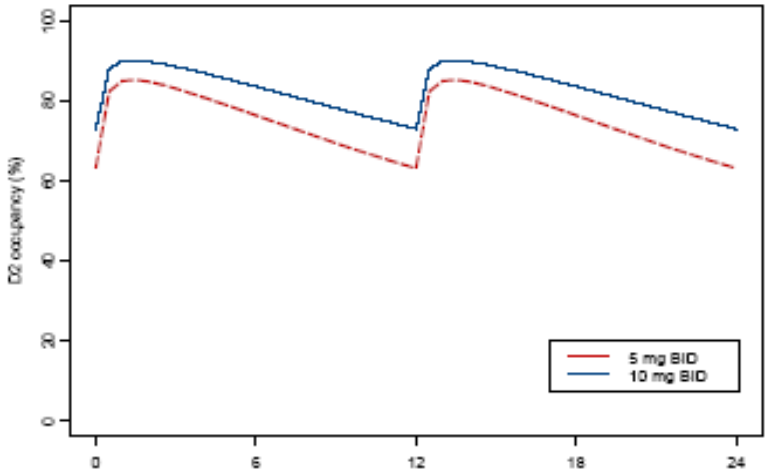
[12] Kapur S, Remington G. D_2 receptors and atypical antipsychotic action. Biol Psychiatry 2001; 50: 873–883.
[13] INT00039258 An initial modelling analysis based on PK, D_2 occupancy and short-term clinical efficacy data of several antipsychotics established a quantitative relationship between D_2 occupancy and effects on total PANSS.(to produce a decrease of ≥ 10 vs placebo).

Figure 6: D_2-occupancy (%) versus asenapine plasma concentrations.



PK/PD analysis showed no time delay between plasma concentrations and occupancy and, combined with the shape of the C/t curve, this suggests bd dosing desirable (Figure 7).

Figure 7: Predicted D_2-occupancy (%) vs time at steady state of asenapine 5 mg bd and 10 mg bd.



In the early dose finding studies:

Study 25511 (see *Time Dependency)* used multi-dose asenapine 150 µg SL. The polysomnographic EEG recordings showed significant day*treatment interactions for parameters of "total time awake" and "sleep efficiency". The psychometric tests showed no significant differences between the treatments.

The asenapine-treated subjects had statistically but not clinically significant higher levels of prolactin on Day 6 than the placebo-treated subjects (p = 0.003).

Asenapine (150 µg) induced on Day 1 (acute; +2.25 hours):

- an enhanced increase of heart rate (and a decrease of high frequency band (HFB) power of heart rate) from supine to sitting position;
- a reduction of low and mid frequency band (LFB and MFB) power of heart rate and a reduced increase of MFB power of the systolic blood pressure (SBP) from sitting to

standing position;

- a reduction in SBP levels during sitting and standing position;
- an increase in blood pressure variability (variation coefficients of SBP and DBP, LFB and MFB power of SBP); discontinuation of measurements due to complaints of dizziness/feeling faint, mostly during the orthostatic challenge task, in five of the eighteen subjects.
- from Day 1 to Day 6 a small increase in heart rate and a decrease in HFB power of heart rate and baroreflex sensitivity.

After multi-dose asenapine, washout effects on Day 9 and Day 16 were:

- heart rate on Day 9 and Day 16 did not return to baseline levels;
- blood pressure on Day 9 appeared moderately increased.

Study 25514 employed bd SL 200 µg asenapine for 2 days, then 300 µg for 4. 5days. Psychometric tests, descriptive statistics and analysis of variates (ANOVA) based on the split-plot design were performed to explore whether the interaction treatment*hour was different for the first three days after dosing. If not significant, the results of the two assessments per day were averaged per subject and an ANOVA based on the split-plot design was performed to explore whether the pattern of differences between treatment means varied from day to day. If not significant, assessments at the first three post-dosing days were averaged per subject and an analysis of covariates (ANCOVA) was performed with factors group and treatment and baseline values as covariates. The differences between the treatment effects of asenapine and placebo, including 95% confidence interval, were estimated.

Prolactin: for log-transformed responses measured on Day 6, an ANCOVA was performed with factors group and treatment and the baseline values as covariates and the treatment effect of asenapine relative to placebo (in %), including 95% confidence interval, was estimated.

Secondary pharmacology

The sponsor's *Pharmacology Summary* states that no secondary PD studies have been performed with asenapine.

Asenapine has 2.5 times the local anaesthetic potency of lignocaine.

Asenapine's antagonism of α_1 adrenergic receptors may be associated with cardiovascular effects, such as orthostatic hypotension. Antagonism of histamine H_1 receptors may be associated with somnolence in clinical practice.

Extrapyramidal symptoms have been shown to be related to different degrees of D_2 occupancy.

In study 25506, one healthy subject collapsed in asystole after 45 minutes of a 0.7 mg IV infusion, the other subject had dizziness.

In Study 25533, involving 5 mg SL and 10 µg IV to healthy subjects, related adverse effects (AEs) of severe intensity were somnolence, akathisia and dizziness. Related AEs of moderate intensity were dizziness, oral hypoaesthesia, fatigue and nasal congestion. The most frequently reported related AEs were somnolence, fatigue, akathisia and dizziness. These AEs started between 20 minutes and 4 hours after asenapine administration and their duration ranged from 40 minutes until 10.5 hours.

In Study A 7501001 involving patients with schizophrenia, ECG analysis showed that asenapine had a positive effect on the QTc interval in this trial. The difference from placebo

in time-matched change from baseline at t_{max} for asenapine was 2.6 milliseconds (ms), 10.5 ms, 6.4 ms and 5.2 ms respectively for the 5 mg, 10 mg, 15 mg and 2 mg bd doses.

In Study 041001 that involved patients with schizophrenia and escalating bd doses of asenapine from 200 µg to 300, 400, 600 and 800 µg. No important drug related safety issues were found to relate to plasma levels.

In Study 041007, doses up to and including 4800 µg bd:

- There were mean decreases in prolactin levels from baseline at most doses for both treatment groups.[14]
- Clinically significant increases in heart rate occurred but there was no apparent dose or level of exposure at which subjects began to have increased heart rate and not all subjects had increases in heart rate.
- There was a marginal mean increase in body weight on all treatment groups.
- The ECG and ECG telemetry monitoring measurements did not reveal any significant cardiac event in asenapine treated subjects. No systematic changes in QTc or heart rate means over dose, block or treatment group were evident.
- There was little mean change on scores at endpoint for any treatment group in the measurement of extrapyramidal symptoms.

Study 041012 employed asenapine up to 20 mg for 4 days. There were no clinically significant arrhythmias in the asenapine group. There were no mean increases in heart rate or QTc. Four of 18 patients with normal baseline values had clinically significant increases in prolactin values (> 2x upper limit of normal [ULN]).

Pharmacodynamic interactions with other medicinal products or substances

No PD drug interaction studies have been performed with asenapine.

Genetic differences in pharmacodynamic response

Genetic PD differences do not appear to have been explored.

Evaluator's overall conclusions on pharmacodynamics

The principle concern is the cardiovascular side effects in particular the case of asystole early in the investigations. The sponsor suggested that in comparison with N-desmethyl asenapine, asenapine produced more fall in arterial BP and rise in heart rate while the former produced negative inotropy.

While efficacy has been related to different degrees of D_2 occupancy, so to have extrapyramidal symptoms (EPS), the claimed decreased potential for EPS appears to be based on the relatively higher doses of asenapine needed to induce catalepsy in rats compared to doses showing activity in tests predictive of antipsychotic activity.

Efficacy in Schizophrenia

Introduction

The following studies were submitted to support the Indication:

Treatment of schizophrenia including prevention of relapse and maintenance of clinical improvement during continuation therapy

In acute treatment (up to 6 weeks):

14 This may be explained by the fact that most subjects were taking "typical" antipsychotics prior to trial entry.

- Study 041023 (pivotal): the active comparator (haloperidol) was more effective than placebo, asenapine 5 mg bd was likewise more effective than placebo but asenapine 10 mg bd was not.
- Study 041004: the active comparator (risperidone) was no more effective than placebo, asenapine 5 mg bd was more effective than placebo.
- Study 041021: the active comparator (olanzapine) was more effective than placebo but asenapine both 5 mg and 10 mg were not different from placebo.
- Study 041022: the active comparator (olanzapine) was no more effective than placebo and neither asenapine 5 mg bd nor 10 mg was more effective than placebo.

In maintenance of clinical improvement:

- Study 041502 (an extension of Study 041004) (selected population - responders), active comparator olanzapine remained no more effective than placebo.
- Study 041512 (after 041021 or 041022; selected population - responders): the active comparator was olanzapine as effective as asenapine, however, patients who had been on placebo previously received asenapine improved more than the other 2 groups.
- Study 041513 (after 041023, therefore pivotal; selected population - responders): the active comparator was haloperidol - almost three times as effective in the primary endpoint as those maintained on asenapine, (patients who had been on placebo previously received asenapine and were between the other 2 groups in the primary endpoint).

In prevention of relapse:

- Study A7501012 (pivotal) had no active comparator; asenapine (mean 17.5 ± 3.31 mg/day) was more effective than placebo in the primary endpoint.

In Persistent Negative Symptoms (PNS) maintenance of clinical improvement (22 weeks initially):

- Study 25543 (predominantly negative symptoms) no placebo, asenapine was not significantly different from the active comparator (olanzapine) in the primary endpoint.
- Study A7501013 (predominantly negative symptoms) no placebo, asenapine was not significantly different from the active comparator (olanzapine) in the primary endpoint.
- Study 25544 (an extension of Study 25543 - predominantly negative symptoms) with primary endpoint extending from start of previous study (selected population - responders), no placebo, active comparator olanzapine (no significant difference).

Studies 25504, 041002, 041500, 04105, 041590 and 041013 used sub-therapeutic doses of asenapine.

Dose response studies

There were 3 dose finding studies:

- Study 25504; Oct 1990 - Feb 1993
- Study 041002; May 1998 - May 2000
- Study 041013; Feb 2000 - June 2001

All used less than the proposed dosage (5-10 mg) and were not significantly different from placebo in their primary end points. The dose of 5 mg bd used in trial 041004 (Aug 2001-

May 2002) was justified on the basis of 4 patients in Study 041007[15] who received 4.8 mg bd for a mean 7 days (range 2.5-16 days). The fixed doses of 5 mg and 10 mg in Study 041021 (May 2005-May 2006) were justified on the basis of Study 041004 and an un identified safety study using up to 20 mg bd.

Main studies related to acute treatment

Only one study (041023) showed more efficacy than placebo both for the active comparator and asenapine but then only for the 5 mg group and not for 10 mg group. A summary of study outcomes is shown in Table 8.

Table 8: Schizophrenia acute study outcomes.

	Primary endpoint showing more efficacy than placebo		Study validated by Active comparator
	Asenapine 5 mg	Asenapine 10 mg	
041004	ü	Not done	X
041021	X	X	ü[b]
041022	X	X	X
041023	ü	X	ü[a]

[a] active comparator haloperidol (a conventional antipsychotic) [b] active comparator olanzapine (an atypical antipsychotic)

Study 041023

The primary objective of this study was to compare the effectiveness of asenapine 5 and 10 mg bd with placebo in the treatment of schizophrenia.

Secondary objectives included:

- To compare the effectiveness of asenapine 5 and 10 mg bd with placebo in the treatment of negative symptoms of schizophrenia.
- Evaluating treatment effects of asenapine compared with placebo with respect to:
  - Other dimensions of schizophrenia (positive, negative, disorganized thought, hostility/excitement, anxiety/depression and general psychopathology)
  - Neurocognition and cognitive functioning
  - Anxiety
  - Suicidal thinking
  - Quality of life and subject functionality
  - Readiness to discharge
  - Safety and tolerability
  - Depression

The null hypothesis for all endpoints was that the results observed in each asenapine treatment group were no different from those in the placebo treatment group. The alternative hypothesis was the result for at least one asenapine treatment group was different from those in the placebo treatment group.

Additionally, the null hypothesis of no difference between the results of the haloperidol and placebo treatment groups was to be tested in order to assess assay sensitivity only.

[15] A double blind, placebo-controlled titration trial primarily to establish the maximum tolerated dose of SL asenapine up to and including 4800 µg bd in patients.

The study was conducted in 49 centres in the USA, India, Russia and Romania from 29 June 2005 to 16 September 2006.

Study Participants

Inclusion criteria

Subjects with schizophrenia were eligible to participate in the trial if they:

- had a current diagnosis of schizophrenia of paranoid, disorganized, catatonic or undifferentiated subtype (the MINI interview was be used);[16]
- had a minimum PANSS total score of 60 at screening and baseline;[17]
- had a score of at least 4 (moderate) in two or more of 5 items in the positive subscale of the PANSS (delusions, conceptual disorganization, hallucinatory behaviour, grandiosity, suspiciousness/persecution) at screening and baseline;
- had a Clinical Global Impressions-Severity (CGI-S) scale score of at least 4 (moderately ill) at baseline;[18]
- had responded positively to an antipsychotic medication other than clozapine;

Exclusion criteria

Potential participants will be excluded from the trial if they had (were):

- a 20% or greater decrease in PANSS total score from screening to baseline;
- a diagnosis of schizophrenia of residual subtype or schizoaffective disorder;
- a concurrent psychiatric disorder other than schizophrenia coded on Axis I; a primary diagnosis other than schizophrenia;
- narrow angle glaucoma;
- a seizure disorder beyond childhood or taking anticonvulsants to prevent seizures;
- received antidepressants (for at least 7 days) or mood stabilizers during the three-month period prior to the Screening visit;
- taken clozapine within the last 12 weeks;
- unable to reduce his or her daily benzodiazepine intake during hospitalization to a maximum of 4 mg per day of lorazepam (or the equivalent dose of another short-acting benzodiazepine).
- an imminent risk of self-harm or harm to others;

[16] The MINI is also called the MMSE: The **mini-mental state examination** (**MMSE**) is a brief 30-point questionnaire test that is used to screen for cognitive impairment. It is used to estimate the severity of cognitive impairment at a given point in time and to follow the course of cognitive changes in an individual over time, thus making it an effective way to document an individual's response to treatment.

[17] **Positive and Negative Syndrome Scale (PANSS):** The PANSS is a 30-Item scale that was designed to assess various symptoms of schizophrenia including delusions, grandiosity, blunted affect, poor attention and poor impulse control. The 30 symptoms are rated on a 7-point scale that ranges from 1 (absent) to 7 (extreme psychopathology). This scale has been shown to be sensitive to medication treatment, provide a balanced representation of positive and negative symptoms and gauge their relationship to one another and to global psychopathology.

[18] **CGI-S = Clinical Global Impression - Severity**. The investigator rates the severity of a subject's condition on a 7-point scale 1=not ill, 2=very mild, 3=mild, 4=moderate, 5=marked, 6=severe and 7=extremely severe.

- been non-compliant in the management of their disease;
- current (past 6 months) substance abuse or dependence

Treatments

Asenapine 5 mg, 10 mg and placebo were prepared as indistinguishable tablets, which disintegrate in the mouth in less than 10 seconds. Haloperidol 4 mg and its matching placebo were prepared as indistinguishable capsules. The medication plan is shown in Table 9.

Table 9: Trial medication plan

Group	Drug	Dosage Form	AM	PM	Duration
1	Asenapine 5 mg BID	Fast-dissolving tablets	5 mg BID SL + PBO PO	5 mg BID SL + PBO PO	6 weeks (42 days)
2	Asenapine 10 mg BID	Fast-dissolving tablets	10 mg BID SL[a] + PBO PO	10 mg BID SL[a] + PBO PO	6 weeks (42 days)
3	Haloperidol	Capsules	4 mg BID PO + PBO SL	4 mg BID PO + PBO SL	6 weeks (42 days)
4	Placebo	Fast-dissolving tablets and capsules	PO SL + PBO PO	PO SL + PBO PO	6 weeks (42 days)

[a] Except on day 1, when 5 mg bd was administered. BID=bd, PBO=placebo

Outcomes/endpoints

The primary efficacy endpoint was defined as the change in the PANSS total score from baseline to endpoint (using the Last Observation Carried Forward [LOCF] methodology to replace missing data points).

There were multiple secondary endpoints:

- PANSS total score at multiple time points.
- Change from Baseline in the PANSS total score at multiple time points.
- PANSS positive, negative and general psychopathology subscale scores at multiple time points.
- Change from baseline in the PANSS positive, negative and general psychopathology subscale scores at multiple time points.
- PANSS Marder positive, negative, disorganized thought, hostility/excitement, anxiety / depression symptom factor scores at multiple time points.[19]
- Change from Baseline in the PANSS Marder positive, negative, disorganized thought, hostility/excitement, anxiety/depression symptom factor scores at multiple time points.
- The number and proportion of PANSS responders[20] at multiple time points.
- Time to onset of effect[21]
- CGI-S score at multiple time points.
- Change from Baseline in the CGI-S at multiple time points.
- CGI-I score at multiple time points.[22]

[19] The PANSS was originally organized into three domains consisting of positive symptoms, negative symptoms and general psychopathology. The appropriateness of these hypothesized 3 psychopathology domains has been examined in several published factor analyses. Lindenmayer et al proposed a five-factor model that better explained the variance of the symptomatology of patients with schizophrenia (Cognitive, Depression, Excitement, Positive and Negative) as an alternative model to the original Positive, Negative, General Psychopathology domains of the PANSS. Marder et al developed a slightly modified version of the five factor model of Lindenmayer, comprised of Negative, Positive, Disorganized Thought, Uncontrolled Hostility/Excitement and Anxiety/Depression.

[20] A subject was considered a PANSS responder at a given visit if the subject experienced a 30% or more decrease from Baseline in PANSS total score at that visit.

[21] Time to onset of effect on the change from PANSS scores is defined at the time point (days) at which a statistical separation from placebo was observed in either of the treatment groups and was sustained at each observation point thereafter.

[22] CGI-I: Clinical Global Impression - Improvement

- Number and proportion of responders of CGI-I at multiple time points.[23]
- CDSS score (sum of Items 1-9) at 4 time points.[24]
- Change from Baseline in the CDSS at 3 time points.
- Change from baseline in each of the cognitive symptom domain scores as measured by the CNS Vital Signs (CNS-VS) Cognitive Battery at endpoint. The domains are: Verbal Memory, Visual Memory, Processing Speed, Social Acuity, Reasoning, Executive Functioning, Working Memory, Sustained Attention, Composite Memory (consisting of the verbal memory and visual memory domains).
- ISST-Modified total score (Items 1-12) at multiple time points.[25]
- Change from baseline in the total score of ISST Modified at 3 time points.
- Days to adequate control[26] over aggression and impulsivity (RDQ),[27]
- Days to ability to carry out basic activities of daily living (RDQ),
- Days to ability to take medicine independently (RDQ),
- Days to delusions and hallucinations which do not significantly interfere with functioning (RDQ),
- Days to Full Agreement (RDQ),
- Days to CGI-S ≤ 4,
- Days to discharge ready status (RDQ),
- QLS total score (Items 1-21) and change from baseline at 2 time points.[28]
- QLS interpersonal relations subscale score (Items 1-8) and change from baseline at 2 time points.
- QLS instrumental role subscale score (Items 9-12) and change from baseline at 2 time points.
- QLS intrapsychic foundations subscale score (Items 13-17, 20, 21) and change from baseline at 2 time points.
- QLS common objects and activities subscale score (Items 18, 19) and change from baseline at 2 time points.
- PETiT total score and its change from baseline at 2 time points.[29]
- PETiT treatment impact on psychosocial functioning and quality of life subscale score (Items 1-24) and its change from baseline at 2 time points.
- PETiT medication, tolerability and treatment subscale score (Items 25-30) and endpoint and its change from baseline at 2 time points.
- Q-LES-Q leisure time activities subscale score (Items 1-6) and its change from baseline at 2 time points.[30]

[23] CGI-I responder was defined as a subject with a CGI-I score of 1 ["very much improved"] or 2 ["much improved"] relative to Baseline.

[24] CDSS: Calgary Depression Scale for Schizophrenia

[25] ISST-Modified: Modified InterSePT Scale for Suicidal Thinking

[26] defined as the number of days from randomization to first time that the subject has a response of "Strongly Agree" or "Agree" on RDQ Item 2 (or Item b in eCRF).

[27] RDQ: Readiness to Discharge Questionnaire

[28] QLS: Quality-of-Life Scale scores

[29] PETiT: Personal Evaluation of Transitions and Treatments scores

- Q-LES-Q social relations subscales subscale score (Items 7-17) and its change from baseline at 2 time points.

Statistical considerations

With a power of 90% and an overall significance level of 0.05 and adjusting for multiple comparisons using the Bonferroni method, it was estimated that the sample size of 101 subjects in each of the treatment groups was be sufficient to detect a 10 point change from baseline in the total PANSS score from placebo, assuming a standard deviation (SD) of 20 points.

Blocks of randomized treatments were centrally generated and were assigned to centres sequentially as needed. At each centre, subject treatments were assigned sequentially from their block. When all of the treatments in a block assigned to the centre were allocated, the next subject received their treatment from the next available block of randomized treatment to be assigned to the centre.

All hypothesis testing was conducted using two-sided tests with alpha = 0.05 level of significance and used the ITT population. Missing values for PANSS total score were replaced using the LOCF.

The parameters tested was the treatment group means for all parametric analyses, treatment group medians for non-parametric analyses and treatment group proportions for binary endpoints.

Change-from-baseline endpoints, including the primary efficacy endpoint, were analysed using ANCOVA[31], time-to-event endpoints were analysed using Kaplan-Meier (KM) survival[32] methods, categorical endpoints were summarized and binary endpoints were analysed using the Cochran-Mantel-Haentzel test.

For the primary endpoint, the Hochberg adjusted p-values for the comparisons of asenapine versus placebo were presented.

All investigative sites with fewer than 8 ITT subjects were to be combined into a single pooled site for analysis purposes.

Results

Participant flow

A total of 513 subjects were screened and 55 withdrew during screening with the two major reasons being failure to meet the selection criteria and withdrawn consent. There were 458 randomised subjects, 455 treated subjects and the ITT population was 448 (placebo 122, asenapine 5 mg 109, asenapine 10 mg 105, haloperidol 4 mg 112). The trial was completed by 70 placebo patients (56.9%), 70 asenapine 5 mg patients (63.1%), 71 asenapine 10 mg patients (67.0%) and 68 haloperidol patients (59.1%).

Rescue Treatment

During the screening period and the inpatient portion of the trial, 6 mg of lorazepam or an equivalent dose of another benzodiazepine could be used on a daily basis for agitation, anxiety, or insomnia. Partial benzodiazepine agonists including zolpidem (2.5-10 mg/day), zaleplon (5-20 mg/day), zopiclone (7.5-15 mg/day) or any equivalent short half-life non-

[30] Q-LES-Q: Leisure time activities and social relations subscale score

[31] with fixed effects for treatment and investigative site (or pooled site) and baseline value as a covariate included in the model.

[32] Differences in the survival distributions between treatment groups) were assessed using two-sided log-rank tests with alpha = 0.05 level of significance.

benzodiazepine hypnotic, if zolpidem, zaleplon or zopiclone were not available in specific countries, could also be used for insomnia or sleep disturbances. It was recommended that, for subjects older than 65 years of age, no more than one-half of the recommended maximum suggested hypnotic dose be used. Medium- and long-acting benzodiazepines were excluded from the trial.

For the outpatient portion of the trial, benzodiazepines (4 mg/day lorazepam or equivalent dose of another benzodiazepine) for agitation, anxiety, or insomnia, or the partial benzodiazepine receptor agonists listed above (for insomnia) could be used up to four days per week.

Drugs used to treat agitation, anxiety, or insomnia or drugs with known sedative effects could not be used within 12 hours prior to efficacy assessments.

Baseline data

Except for gender, the four treatment groups were similar demographically at baseline. In the placebo group, 52.0% were male while in the haloperidol, asenapine 5 mg and asenapine 10 mg groups the percentage of males were 67.6%, 63.2% and 54.8% respectively.

The primary and secondary analyses were based on the ITT population

Outcomes

The primary efficacy endpoint is shown in Table 10. The active comparator (haloperidol) was more effective than placebo, asenapine 5 mg bd was likewise more effective than placebo but asenapine 10 mg bd was not.

Table 10: Primary Efficacy endpoint

PANSS (Mean ± SD)	Asenapine 5 mg (N = 109)	Asenapine 10 mg (N = 105)	Placebo (N = 122)	Haloperidol 4 mg (N = 112)
Baseline	89.2 ± 12.01	89.1 ± 12.88	88.9 ± 11.67	88.6 ± 12.15
Endpoint	73.3 ± 21.39	74.4 ± 20.42	78.4 ± 19.88	73.5 ± 19.33
Endpoint Change (Range)	−15.9 ± 17.69 (−51, 43)	−14.6 ± 19.31 (−62, 31)	−10.4 ± 18.05 (−75, 34)	−15.1 ± 16.29 (−51, 21)
P-value	0.0290	0.0680	NA	0.0342

There was a significant treatment-by-centre interaction ($p < 0.0210$), driven by one site. Dropping this site from the analysis did not greatly affect the primary efficacy results. When data from subjects at this site were excluded, the least squares (LS) mean change from baseline in the PANSS total score was -10.5 for placebo, -17.8 for asenapine 5 mg bd ($p = 0.0020$), -14.3 for asenapine 10 mg bd ($p = 0.079$) and -15.6 for haloperidol ($p = 0.018$). Consequently, the conclusions were unaffected when the site was not included in the analysis.

Major secondary endpoints are shown in Table 11.

Table 11: Major secondary Efficacy endpoints

		Placebo (N = 122)	Asenapine 5 mg (N = 109)	Asenapine 10 mg (N = 105)	Haloperidol 4 mg (N = 112)
PANSS Responders[a] n (%)	Responders	40 (32.8)	60 (55.0)	51 (48.6)	48 (42.9)
	Non-responders	82 (67.2)	49 (45.0)	54 (51.4)	64 (57.1)
	P-value[a]		0.0005	0.0150	0.0927
PANSS positive subscale	Endpoint Change LSM[b] (SE)	-3.7 (0.52)	-5.8 (0.54)	-5.4 (0.55)	-5.8 (0.53)
Possible score 7 - 49	P-value[b]		0.0052	0.0243	0.0035
PANSS negative subscale	Endpoint Change LSM[b] (SE)	-2.4 (0.40)	-3.4 (0.42)	-3.5 (0.43)	-3.1 (0.42)
Possible score 7 - 49	P-value[b]		0.0649	0.0531	0.187
CGI-S,	Endpoint Change LSM[b] (SE)	-0.63 (0.092)	-0.93 (0.098)	-0.86 (0.100) [c]	-0.93 (0.096)
Possible score 1-7	P-value[b]		0.0219	0.0818	0.0220
CGI-I responders, n (%)	Responders	41 (33.6)	52 (47.7)	46 (44.2)[c]	49 (43.8)
	Non-responders	81 (66.4)	57 (52.3)	58 (55.8) [c]	63 (56.3)
	P-value[d]		0.0272	0.1348	0.1016
CDSS[e]	Endpoint Change LSM[b] (SE)	-0.72 (0.241)	-1.61 (0.267)	-1.13 (0.259)	-0.99 (0.264)
Possible score 1-27	P-value[b]		0.0122	0.2397	0.4473
QLS total score	Endpoint Change LSM[b] (SE)	0.88 (1.276)	4.54 (1.343)	3.33 (1.357)	3.22 (1.413)
Possible score 0-126	P-value[b]		0.0437	0.1797	0.2101

[a] A PANSS responder was defined as a subject who at a given visit had at least a 30% reduction from baseline in the PANSS total score at the visit. P-values are for comparison of active treatments vs placebo based on Cochran Mantel-Haentzel test adjusted by pooled investigative site.

b Based on an ANCOVA model with treatment and pooled investigative site as fixed effects and baseline as a covariate. P-values are based on the difference in the LS mean change for active treatment versus placebo.

[c] n = 104.

[d] P-values are for comparison of active treatments vs placebo based on Cochran Mantel-Haentzel test adjusted by pooled investigative site.

[e] n = placebo 116, asenapine5 mg 96, asenapine 10 mg 100, haloperidol 97

No statistically significant differences between any active treatment and placebo were observed in the LS mean changes from baseline in the ISST-Modified total scores

Ancillary analyses

The primary endpoint observed-case analysis confirmed the findings of the LOCF analysis for asenapine 5 mg. The observed-case analysis indicated that asenapine 5 mg and 10 mg but not haloperidol, separated from placebo at Day 42 (placebo [-19.1] vs asenapine 5 mg [-23.9],

p = 0.0171, vs asenapine 10 mg [-23.2], p = 0.0398, vs haloperidol [-21.9], p = 0.1567).

The repeated measures analysis showed that each of the three active treatments resulted in statistically significantly greater overall LS mean decreases from baseline in the PANSS total score (placebo [-10.3] vs asenapine 5 mg [-13.4], p = 0.023, vs asenapine 10 mg [-13.5], p = 0.0188, vs haloperidol [-13.7], p = 0.012).

Study 041004

The primary objective of this study was to compare the effectiveness of asenapine 5 mg bd to risperidone 3 mg bd and placebo bd to treat the symptoms of schizophrenia as measured by the total score on the Positive and Negative Syndrome Scale (PANSS).

Secondary objectives were to evaluate the comparative effects of additional measures of efficacy (the 3 subscales of the PANSS, the Calgary Depression Scale, the Clinical Global Impression Scale and a cognitive assessment battery).

The primary hypothesis to be tested was that there is no difference in efficacy between asenapine and placebo. Secondarily, to validate the trial, the hypothesis to be tested was that there is no difference in efficacy between risperidone and placebo.

Group comparisons were also performed between the asenapine 5 mg and risperidone groups.

The study was conducted at 27 sites in the USA between August 2001 and May 2002.

Study Participants

Inclusion Criteria

· DSM-IV schizophrenia: paranoid, disorganized catatonic or undifferentiated subtypes[33]

· in an acute exacerbation;

· a PANSS Score ≥ 60 at screening and baseline; Baseline PANSS score ≥ 80% of the screening PANSS score;

· a score of ≥ 4 or in ≥ 2 of the 5 items from the positive PANSS scale at screening and baseline;

· a CGI score ≥ 4 at baseline;

· responded to an antipsychotic medication other than clozapine,

· those who had discontinued all antipsychotic medication≥ 3 days prior to baseline and augmenting medications (valproic acid, divalproex, carbamazepine) 5 days prior.

Exclusion Criteria

· a primary psychiatric diagnosis other than schizophrenia;

· schizophrenia of the residual type or schizo-affective disorder

· patients with a history of neurological disease (including seizure disorder or more than one childhood febrile convulsion) or if they were taking anticonvulsants to prevent seizures.

· a score > 2 on any item of the Abnormal Involuntary Movement Scale (AIMS) at screening;

· concomitant psychotropic drugs other than zolpidem zaleplon or chloral hydrate (for sleep induction) for sleep, or benzodiazepines for agitation;

[33] Diagnostic and Statistical Manual of Mental Disorders, 4th Edition

- actively suicidal during the pre-treatment period;
- < 75% compliant in the administration of the washout medication;
- previous exposure to asenapine.

Treatments

Asenapine and risperidone placebos were physically indistinguishable. Study medications were titrated to the fixed dose (asenapine 5 mg bd or risperidone 3 mg or placebo) in 1 mg steps. There was an initial placebo washout of 3 to 7 days and active treatment of 42 days.

Outcomes/endpoints

The primary efficacy variable was the change from baseline in the total PANSS score at the endpoint visit.

There were multiple secondary endpoints. The asenapine 5 mg group was compared with the placebo group with respect to[34]:

- The change from baseline total score of each of the three subscales of the PANSS
- The CGI - Severity of Illness change from baseline scores at all post baseline visits.
- The CGI-Global Improvement raw scores at all post baseline visits.
- The change from baseline total score of the Calgary Depression Scale (CDS); Day 21 and Day 42.
- Cognitive assessments: Verbal fluency, Category naming, Verbal Memory, Letter Number Span Test, Visual Reproductions, Trials A & B (from Halstead Reitan Battery), Digit Symbol – Substitution Test, Finger Tapping Test, Wisconsin Card Sorting, Wide Range Achievement Test.

Statistical considerations

With 60 subjects per group and a significance level of alpha = 5%, the power to detect a treatment difference in the change from baseline in the total PANSS score of 9 to 15 points between groups ranges from 56% for a 9 point difference using an SD of 23.4 (obtained from three risperidone trials) to 96% for a 15 point difference using an SD of 21.65–the maximum observed SD on the PANSS in Study 041002.

Allocation numbers were assigned to subjects in the order of their enrolment in the study at each site.

All statistical tests were two-sided and considered statistically significant if $p \leq 0.05$.The efficacy analysis was performed for both the ITT and per protocol (PP)[35] populations for the primary and secondary parameters.

For all analyses, group differences were tested using an ANOVA with treatment and centre as factors and the comparison between asenapine treatment group and placebo was performed using t-test. The 95% CIs for the difference in the means was calculated using t-test and the model based estimated SE. The treatment by centre interaction was examined.

Comparison of risperidone to placebo was also performed in the same manner.

Likewise exploratory analysis was performed to compare asenapine to risperidone.

Results

Participant flow

A total of 182 patients were randomised and the ITT population comprised 58 patients taking asenapine, 56 patients taking risperidone and 60 patients taking placebo. The trial was

[34] additionally, the risperidone group was compared with the placebo group for many endpoints

[35] The Per-Protocol analyses of the efficacy parameters were only to be performed if the number of subjects differed substantially between the treatment groups (that is, more than 15% within at least one of the treatment groups).

completed by 27 asenapine patients (46%), 25 risperidone patients (42%) and 21 placebo patients (34%).

Baseline data

Except for gender, the four treatment groups were similar demographically at baseline. For asenapine the male/female distribution was 46/13 while for risperidone and placebo it was 36/23 and 49/13 respectively.

Outcomes

Primary Efficacy Endpoint

Asenapine 5 mg was more effective than placebo in reducing the symptoms of schizophrenia in this study, as measured by the change from baseline in total PANSS score (Table 12). In this study, however, risperidone was not significantly different than placebo in the change from baseline in total PANSS score (nor at any of the visits and was only more effective than placebo ($p \leq 0.05$) in the Positive PANSS score from baseline at Weeks 1, 3, 5 and 6).

Table 12: Primary Efficacy Endpoint.

PANSS (Mean ± SE)	Asenapine 5 mg (N = 58)	Risperidone 3 mg (N = 56)	Placebo (N = 60)
Baseline	96.48 ± 2.16	92.18 ± 2.05	92.43 ± 1.93
Visit 6/endpoint	80.62 ± 2.79	81.25 ± 3.02	87.17 ± 2.81
Change	-15.86 ± 2.62	-10.93 ± 2.67	-5.27 ± 2.30
P-value	0.0024	0.1186	NA

Major secondary endpoints are shown in Table 13.

Table 13: Major Secondary Endpoints.

		Asenapine 5 mg (N = 58)	Risperidone 3 mg (N = 56)	Placebo (N = 60)
PNSS (Responders*) n (%)	≥ 30% reduction[a]	22 (38)	22 (39)	15 (25)
PANSS positive subscale Possible score 7 - 49	Endpoint Change mean (SE)	-5.48 (0.84)	-5.13 (0.95)	-2.50 (0.75)
	P-value	0.010	0.0317	
PANSS negative subscale Possible score 7 - 49	Endpoint Change mean (SE)	-3.21 (0.71)	-1.05 (0.75)	-0.55 (0.74)
	P-value	0.0102	0.6134	
PANSS general psychopathology subscale Possible score 16-112	Endpoint Change mean (SE)	-7.17 (1.34)	-4.75 (1.31)	-2.22 (1.13)
	P-value	0.0045	0.1665	
CGI-Severity of Illness Possible score 1-7	Endpoint Change mean (SE)	-0.74 (0.12)	-0.75 (0.13)	-0.28 (0.11)
	P-value	0.0067	0.0041	
CGI-I Global Improvement Possible score 1-7	Endpoint mean (SE)	3.25 (0.15)	3.21 (0.14)	3.73 (0.18)
	P-value	0.0394	0.0236	
CGI – - Quality of Life Possible score 1-7	Endpoint mean (SE)	3.04 (0.19)	3.07 (0.17)	3.71 (0.20)
	P-value	0.0123	0.0151	
CDSS[e] Possible score 1-27	Endpoint Change mean (SE)	-1.70 (0.50)	-1.36 (0.56)	-0.19 (0.51)
	P-value	0.0553	0.1515	

*Responders not defined in this study , [a] from baseline at visit 6/endpoint., p-value not found,

Study 041021

This study was similar to study 041023 except the active comparator was olanzapine 10 mg once daily (od) for 7 days, then 10-20 mg od. The primary efficacy endpoint was defined as the change in the PANSS total score from baseline to endpoint (LOCF). The primary analysis was based on the ITT population. It was conducted in 49 centres in USA, Russia and Ukraine between May 2005 and May 2006. The inclusion/exclusion criteria were similar to study 041023.

All participants had 5 tablets daily regardless of treatment group: placebo, asenapine 5 mg bd, asenapine 10 mg bd, or olanzapine 15 mg od.

Statistical methods were all similar to study 041023.

Results

Participant flow

A total of 491 patients were screened and 417 were randomised. The reasons for withdrawal were failing to meet the selection criteria and consent withdrawal. Of the 417 randomised patients, the ITT population comprised 386 patients with 93 taking placebo, 102 taking asenapine 5 mg, 96 taking asenapine 10 mg and 95 taking olanzapine. The trial was completed by 60 asenapine 5 mg patients (57.7%), 51 asenapine 10 mg patients (50.0%) 58 olanzapine patients (56.9%) and 50 placebo patients (50%).

Baseline data

Except for gender, the four treatment groups were similar demographically at baseline. For asenapine 5 mg the male/female distribution was 77/27, for asenapine 10 mg it was 72/30 while for olanzapine and placebo it was 80/22 and 58/42 respectively.

Outcomes

Asenapine 5 mg and 10 mg bd were not statistically significantly different form placebo in reducing the symptoms of schizophrenia, as measured by the change from baseline in total PANSS score, while olanzapine was significantly more effective ($p \leq 0.05$) t han placebo (that is, the trial was validated) (Table 14).

Table 14: Primary Efficacy Endpoint.

PANSS (Mean ± SD)	Asenapine 5 mg (N = 102)	Asenapine 10 mg (N = 96)	Olanzapine 15 mg (N = 95)	Placebo (N = 93)
Baseline	91.7 ± 15.47	94.4 ± 13.58	93.7 ± 12.93	94.6 ± 12.69
Endpoint	78.1 ± 19.63	81.3 ± 20.13	78.0 ± 18.01	83.8 ± 19.82
End point Change	−13.7 ± 17.24	−13.1 ± 18.49	−15.7 ± 16.15	−10.7 ± 17.00
P-value	0.1278	0.3046	0.0168	NA

Major secondary endpoints are shown in Table 15.

Table 15: Major secondary Efficacy endpoints.

		Placebo (N = 93)	Asenapine 5 mg (N = 102)	Asenapine 10 mg (N = 96)	Olanzapine 15 mg od (N = 95)
PANSS Responders[a] n (%)	Responders	21 (22.6)	39(38.2)	33 (34.4)	39 (41.1)
	Non-responders	72 (77.4)	63(61.8)	3 (65.6)	56 (58.9)
	P-value[a]		0.0199	0.0796	0.0019
PANSS positive subscale Possible score 7 - 49	Endpoint Change LSM[b] (SE)	-3.6 (0.56)	-5.5 (0.54)	-4.9 (0.56)	-5.6 (0.57)
	P-value[b]		0.0119	0.0967	0.0132
PANSS negative subscale Possible score 7 - 49	Endpoint Change LSM[b] (SE)	-2.8 (0.42)	-2.7 (0.41)	-2.9 (0.42)	-3.2 (0.42)
	P-value[b]		0.8439	0.8501	0.4821
PANSS general psychopathology subscale Possible score 16-112	Endpoint Change LSM[b] (SE)	-4.6 (0.86)	-6.6 (0.83)	-5.6 (0.85)	-7.8 (0.86)
	P-value[b]		0.0890	0.3924	0.0071

[a] A PANSS responder was defined as a subject who at a given visit had at least a 30% reduction from baseline in the PANSS total score at the visit. P-values are for comparison of active treatments vs placebo based on Cochran Mantel-Haentzel test adjusted by pooled investigative site.

Ancillary analyses

Statistical analysis of the LS mean changes from baseline in the PANSS total scores using the observed-case method and results of a mixed model analysis using repeated measures were consistent with the findings of the LOCF analysis for the primary endpoint.

Study 041022

This study was similar to study 041021 (and 041023 except the active comparator was olanzapine 10 mg of for 7 days, then 10-20 mg od).

Results

A total of 347 patients were screened and 277 were randomised. The major reasons for withdrawal were failing to meet the selection criteria and consent withdrawal. Of the 277 randomised patients, the ITT population comprised 259 patients with 89 taking placebo, 85 taking asenapine 5 mg/10 mg and 85 taking olanzapine. The trial was completed by 42 asenapine 5 mg/10 mg patients (46.7%), 43 olanzapine patients (46.7%) and 48 placebo patients (51.6%).

Baseline data

Except for gender, the four treatment groups were similar demographically at baseline. For asenapine 5 mg/10 mg the male/female distribution was 67/23 while for olanzapine and placebo it was 72/20 and 74/19 respectively.

Outcomes

Asenapine was not statistically significantly different from placebo, as measured by the change from baseline in total PANSS score, nor was olanzapine statistically different ($p > 0.05$) from placebo in total PANSS score or any trial visit (Table 16). The failure of olanzapine to separate from placebo made the efficacy data from this trial uninterpretable.

Table 16: Summary of total PANSS scores and change from baseline

PANSS (Mean ± SD)	Placebo (N = 89)	Asenapine 5/10 mg (N = 85)	Olanzapine 10-20 mg (N = 85)
Baseline	85.8 ± 11.23	87.0 ± 12.01	86.9 ±11.84
Endpoint	74.3 ± 20.00	76.3 ± 18.80	74.8 ± 18.86
Endpoint Change	−11.5 ± 17.35	−10.8 ± 15.75	−12.1 ± 16.06
Endpoint Change LSM ± SE	-9.9 ± 1.74	-9.4 ± 1.73	-11.2 ± 1.72
P-value		0.8477	0.5795

Studies in Maintenance of Clinical Improvement

Study 041502 (an extension of study 041004)

Study 041004 was not validated by the active control. The primary efficacy variable was the change from Study 041004 baseline in the total PANSS score at the Study 041502 endpoint. Subjects were to continue taking the same trial drug at the same dose and dosing schedule as taken during Study 041004 trial.

The evaluator found that the report was somewhat confused.[36]

[36] Some of the tables and in the summary state that the endpoint visit of the 041004 trial served as the baseline visit for the 041502 trial. However the *Clinical Trial Report* text and the protocol state that for statistical analyses, 041004 baseline, as defined in the statistical plan of 041004, was to be used as the baseline for statistical analysis. The primary efficacy variable was defined as the change from 041004 baseline in the total

All statistical tests on efficacy parameters were to be considered exploratory in nature.

Results

The enrolment rate was low and the number treated even lower. The primary analysis and secondary analyses of efficacy were based on the ITT population (observed case [OC] only analyses): placebo 5/7; asenapine 5 mg 13/15; risperidone 15/17 and only 1 patient (on risperidone) completed.

Outcomes

The primary endpoint outcomes are shown in Table 17. The active comparator olanzapine remained no more effective than placebo.

Table 17: Primary endpoint PANSS total.

PANSS (Mean ± SD)	Asenapine 5 mg (N = 13)	Risperidone 3 mg (N = 15)	Placebo (N = 5)
Baseline[a]	99.2 ± 16.03	93.4 ± 10.29	88.8 ± 7.73
Endpoint 041004	61.5 ± 17.33	68.3 ± 12.53	62.0 ± 11.02
Endpoint	69.1 ± 21.67	76.2 ± 16.76	69.8 ± 22.73
Endpoint Change	-30.1 ± 24.01	-17.2 ± 18.87	-19.0 ± 18.80

Study 041512

Study 041512 was an extension of studies 041021 and 041022. It should be noted that neither study showed efficacy greater than placebo (Table 8). The study was conducted at 75 centres in Russia, Ukraine and the US between April 2005 and June 2007 for a period of 52 weeks.

The objectives were to assess the long-term safety and maintenance of effect of asenapine with olanzapine control.

Secondary efficacy objectives included:

- The assessment of quality of life and patient functionality outcomes of asenapine with olanzapine control.
- Evaluating treatment effects of asenapine with respect to:
    - Overall symptom control
    - Other dimensions of schizophrenia (positive, negative, disorganized thought, hostility/excitement, anxiety/depression and general psychopathology)
    - Neurocognition and cognitive functioning
    - Suicidal thinking
    - Depression.

No hypothesis testing was performed.

Study Participants

Inclusion criteria

- completed the short-term trials, 041021 and 041022 and would benefit from continued treatment according to the investigator's judgment;
- compliance with trial medication in the short-term trials;

Exclusion criteria

[a] PANSS score at 041502 endpoint.

- a CGI-S score of ≥ 6 (severely psychotic).
- any adverse effects (AEs) or other clinically significant finding(s);
- met any of the exclusion criteria regarding medical and psychiatric status (with the exclusion of PANSS criteria) listed in the short-term trial upon entry into this trial;

Treatments

Subjects continued on their medication (asenapine or olanzapine) into the extension trial and were maintained on the same dosage regimen for the first week of the 041512 trial. Placebo-treated subjects were assigned to asenapine 5 mg bd during the first week of the long-term extension. After one week all blinded asenapine-treated subjects were maintained or titrated in either direction from 5–10 mg bd; blinded olanzapine-treated subjects were titrated from 5-20 mg od during the long-term extension.

Outcomes/endpoints

The primary efficacy analysis was the time to loss of effect compared to active control from the acute phase (pooled across all trials) from those patients who have at least a 30% decrease from acute phase baseline in PANSS at the end of the acute phase on either asenapine or olanzapine using Kaplan-Meier estimates and 95% CIs.

Failure to maintain effect was characterized by any of the following:

1. An increase in PANSS score by at least 30% from baseline score at trial (041512) entry
2. A request for dose increase to improve clinical response in a destabilized subject
3. In the opinion of the investigator, the subject's schizophrenic symptomatology had deteriorated clinically to such an extent that one or more of the following was required:
   - Concomitant use of benzodiazepine for 1 week or more,
   - Increase in the dose of antidepressant medication or start of new antidepressant therapy,
   - Addition of open-label antipsychotic medication,
   - Increase in the level of psychiatric care (for example, supervised living, day hospital care),
   - Hospitalization or increase in level of hospitalization (for psychiatric need), if clinically justified.
4. A CGI-S score of ≥ 6
5. Discontinuation from the trial due to lack of efficacy
6. AE/serious adverse effect (SAE) of worsening of schizophrenia

Statistical considerations

The study was not powered for direct comparison; therefore the number of subjects could not be planned. All eligible subjects completing studies 041021 or 041022 and who might benefit from treatment with asenapine or olanzapine could participate. The number of subjects was determined by the number who completed the short-term studies 041021 and 041022 and who continued into this study.

Patients continued in their previously randomised groups with placebo-treated patients assigned to asenapine.

The primary efficacy analysis was based on the time to loss of effect from those patients who had at least a 30% decrease from baseline in PANSS at the end of the acute phase. There

were no statistical hypotheses for the primary or secondary analysis. No statistical tests were performed. The ITT population was used for primary and secondary endpoints.

Results

Participant flow

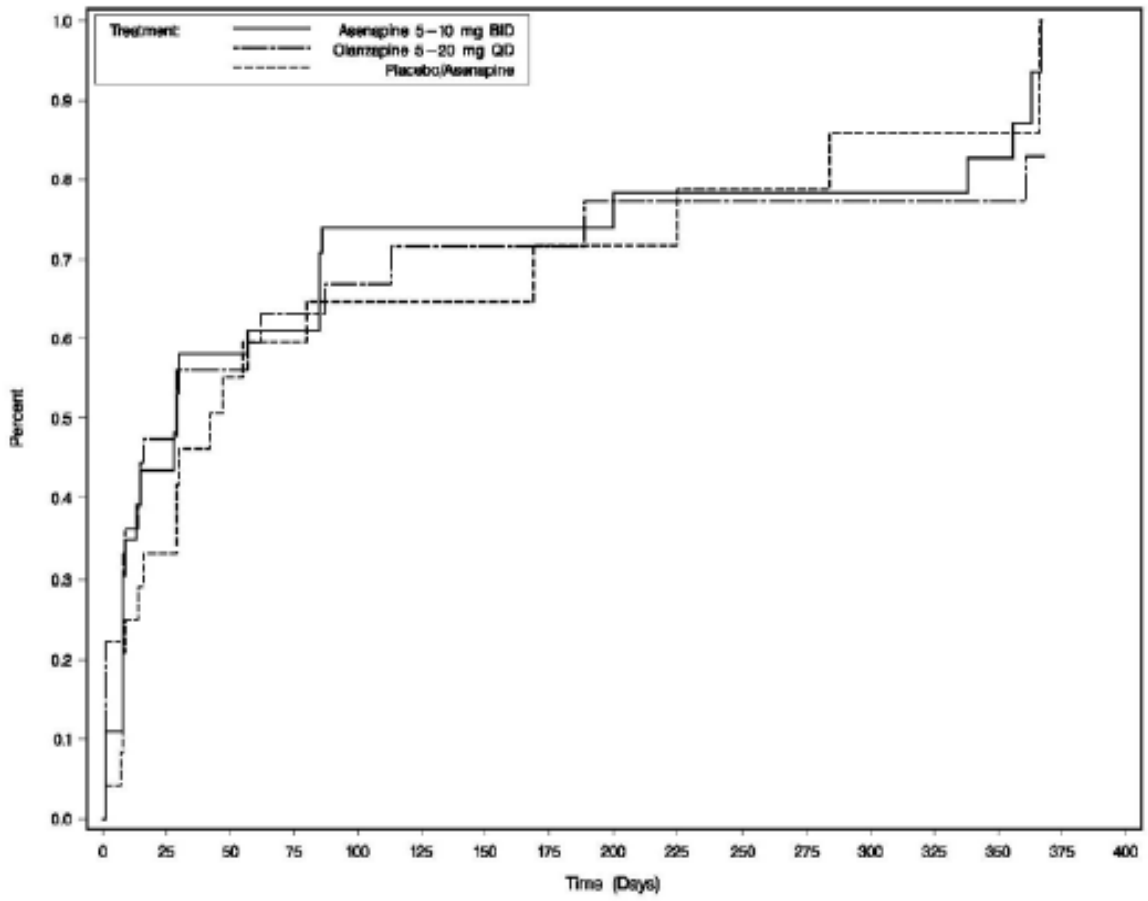
There was an extremely high discontinuation rate. For patients switched from placebo to asenapine, 17/57 (29.8%) completed the study while for asenapine 5/10 mg it was 19/86 (22.1%) and for olanzapine it was 23/62 (37.1%).

Outcomes

Primary Efficacy Endpoint

The Kaplan-Meier estimate of the time to loss of effect is shown in Figure 8. The active comparator olanzapine was as effective as asenapine, however, patients who had been on placebo previously receiving asenapine improved more than the other 2 groups.

Figure 8: Kaplan-Meier estimation of the time to loss of effect, OC (Intent-to-Treat Group).



Study 041513

Study 041513 was an extension of Study 041023. It should be noted that this study was validated and showed efficacy greater than placebo for 5 mg but not 10 mg asenapine and results for both asenapine groups were combined in the study report.

The active comparator was haloperidol 2-8 mg bd; otherwise this study was similar to study 041512 except for participating centres and protocol amendments. It was conducted in 42 centres in the USA, India, Russia and Romania between September 2005 and October 2007.

Results

Participant flow

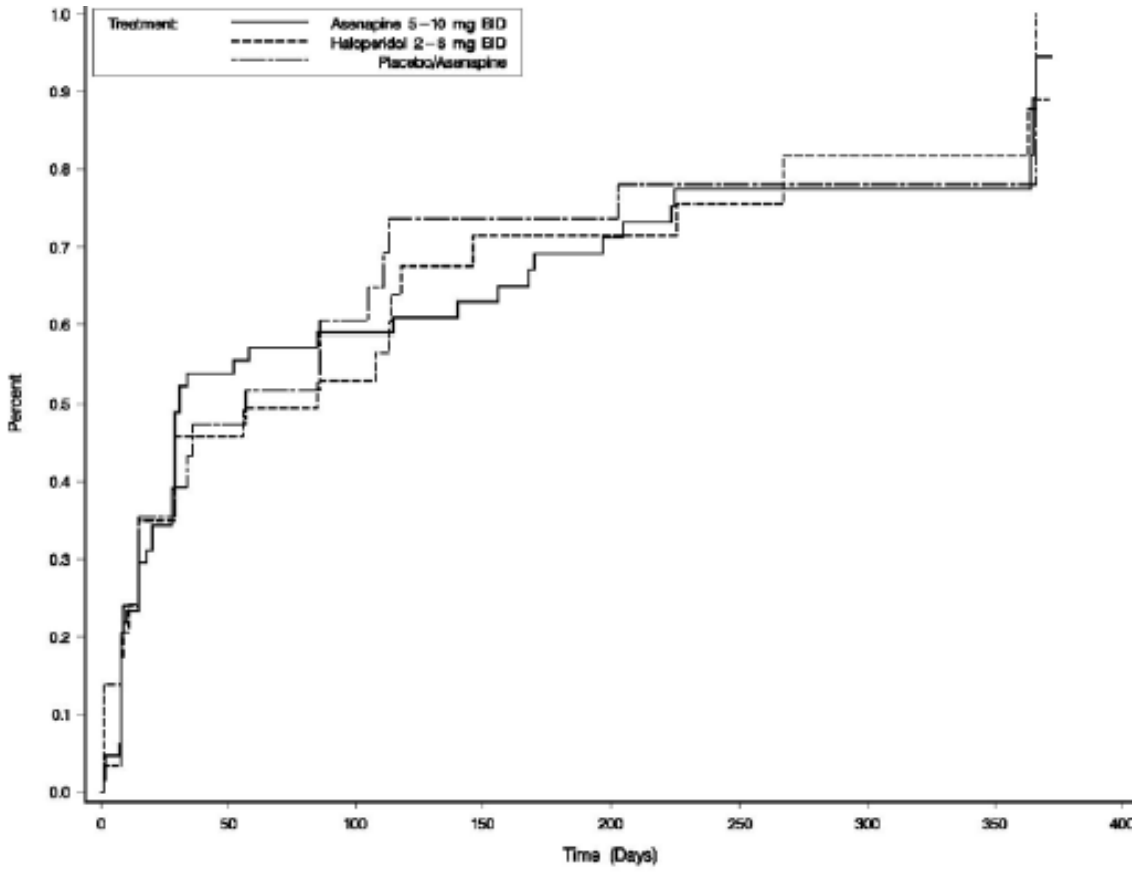
There were 187 randomised subjects and 176 in the ITT population. There were low rates of subjects who completed the trial. For patients switched from placebo to asenapine, there were 20/50 (40%) completers, for asenapine 5/10 mg there were 30/92 (32.6%) while for haloperidol there were 16/43 (37.2%).

Outcomes

Primary Efficacy Endpoint

The Kaplan-Meier estimate of the time to loss of effect is shown in Figure 9. The active comparator haloperidol was almost three times as effective in the primary endpoint as those maintained on asenapine. Patients previously that had been on placebo who received asenapine were between the other 2 groups in the primary endpoint.

Figure 9: Kaplan-Meier estimation of time to loss effect, OC (ITT Group).



The primary efficacy analysis was based on the time to loss of effect from those subjects who had at least a 30% decrease from baseline in PANSS total score in the long-term extension trial using the Kaplan-Meier estimation and 95% CI. The number of responders[37] at extension base line was 65 on asenapine 5-10 mg bd and 29 on haloperidol. By Week 52 there were 22 responders and 4 non-responders on asenapine 5-10 mg bd and 14 responders on haloperidol and there had been by Week 52 a total of 51 events on asenapine 5-10 mg bd (an event is the first visit at which subject failed to maintain effect) and 24 events on haloperidol. By Week 52 the only patients in the study who were responders at baseline and who had not suffered a loss of effect were 5 asenapine and 1 haloperidol patients, all of whose results were censored

[37] Responders mean ≥ 30% reduction in the PANSS Score

at that visit. The evaluator could not interpret this as in the sponsor's *Report* it was stated that "the number of subjects with loss of effect included 55/65 (84.6%) subjects in the asenapine 5-10 mg bd treatment group and 26/29 (89.7%) subjects in the haloperidol 2-8 mg bd treatment group."

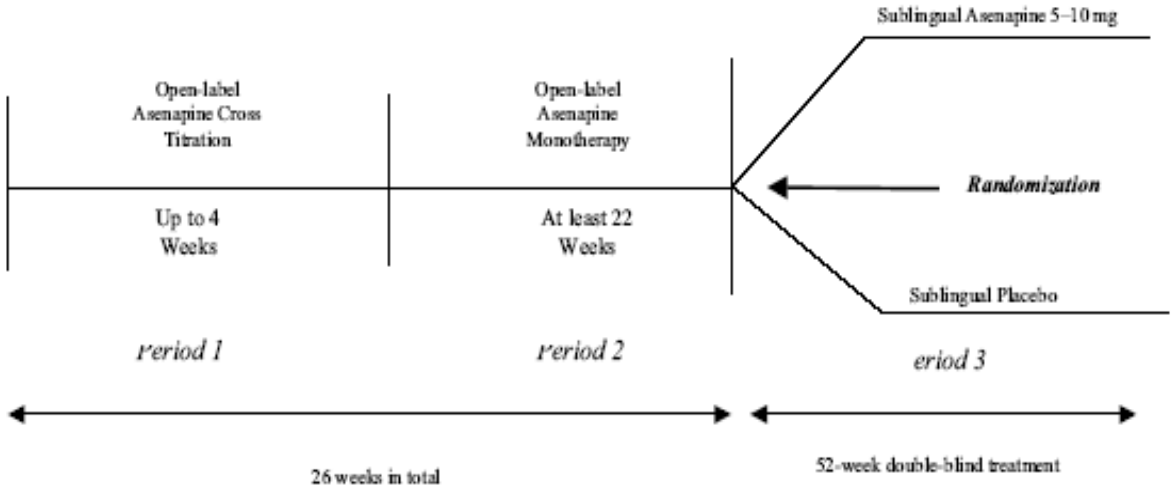
Median survival times for subjects continuing on active treatment from the feeder studies were 31 days (95%CI 28, 140) for subjects treated with asenapine 5-10 mg bd and 85 days (95%CI 15.0, 118.0) for subjects treated with haloperidol 2-8 mg bd.

Study in prevention of relapse

Study A7501012

The study design is shown in Figure 10.

Figure 10: Study design for Study A7501012



The primary objective was to determine the efficacy of asenapine compared with placebo with respect to the time to relapse or an impending relapse in schizophrenia subjects who received treatment with asenapine for 26 weeks.

Secondary objectives included evaluating the effects of treatment with asenapine compared with placebo for up to 26 weeks in schizophrenia subjects previously treated with asenapine for 26 weeks with respect to:

1. The five dimensions of schizophrenia (positive symptoms, negative symptoms, disorganized thought, hostility/excitement, anxiety/depression);
2. Overall clinical impression of severity and improvement;
3. Depressive symptoms;
4. Suicidal thinking;
5. Cognitive function, as assessed with a computerized cognitive battery;
6. Safety and tolerability.

The null hypothesis was that there was no difference in the median time free from relapse or impending relapse between the group treated with asenapine and the group treated with placebo. The alternative hypothesis was that there is a treatment effect and the median time free from relapse or impending relapse was different for each group.

Secondary hypotheses were:

- There was no difference in the median time to early discontinuation for any reason between the group treated with asenapine and the group treated with placebo. The alternative hypothesis was that there is a treatment effect and the median time to early discontinuation is different for each group.
- The null hypothesis for all remaining endpoints tested statistically was that the results observed in the asenapine treatment group were no different from those in the placebo treatment group. The alternative hypothesis was that the results for the asenapine and placebo treatments groups were different.

The trial was conducted in 61 centres in Croatia, India, Latvia, Russia, Ukraine and the US between May 2005 and June 2008.

Study Participants

Inclusion criteria

- a primary diagnosis of schizophrenia (DSM-IV).
- ≥ 1 prior episode of acute schizophrenia in the preceding 3 years;
- a ≥ 1 year history of continuous antipsychotic treatment for schizophrenia;
- patients clinically stable at the time of entry into Period 1 of the study as defined by at least a 4-week period of stable symptoms with no antipsychotic dose increase, no admission arrest or imprisonment and no increase in the level of psychiatric care.

Exclusion criteria

- acute relapse of schizophrenia;
- PANSS total score > 80 at screening;
- CGI-S score > 4 at screening;
- PANSS "unusual thought content," "conceptual disorganization," or "hallucinatory behaviour" ≥ 4 at screening;
- PANSS item score ≥ 4 on items of "hostility" and/or "uncooperativeness" at screening;
- ISST Modified item score of 2 on Item #7 "control over suicidal action," #10 "method: specificity/planning," or #11 "expectancy/anticipation;"
- a psychiatric disorder other than schizophrenia;
- a history of treatment resistance to antipsychotic medication;
- recent administration (within 12 weeks) of clozapine for schizophrenia;
- patients unable to reduce benzodiazepine intake
- An imminent risk of self-harm or imminent risk of harm to others or in the past 2 years;
- A history of non-compliance with antipsychotic medication.
- A positive result on the serum pregnancy test at screening, or the intention to become pregnant or breastfeed during the course of the trial;
- Narrow angle glaucoma;
- A seizure disorder beyond childhood or taking any anticonvulsants to prevent seizures;
- Previously participated in an asenapine clinical trial;

Treatments

This study had 3 phases, which included:

Period 1: Up to 4 weeks of open-label cross-titration from prior medication to SL asenapine 5 or 10 mg bd,

Period 2: At least 22 weeks of open-label monotherapy treatment, during which subjects were maintained on asenapine SL 5 or 10 mg bd,

Period 3: Double-blind treatment phase of up to 26 weeks, during which subjects stabilized on asenapine were randomized in a 1:1 ratio to receive SL asenapine 5 or 10 mg bd or placebo.

An increase in the dose of trial medication was allowed during both the open-label cross-titration and monotherapy phases. During the double-blind treatment phase, the dose of trial medication could only be reduced for poor tolerability, if applicable. The dose of trial medication was not to be increased when undesirable effects subsided.

Open-label treatment with asenapine (Periods 1 + 2) was continued for 26 weeks in total.

When 115 subjects had confirmation of relapse or impending relapse in the database, the trial was terminated.

Outcomes/endpoints

The primary efficacy endpoint was the time, in days, to a relapse or an impending relapse.

Statistical considerations

The modified sample size was estimated based on the assumption that 55% of subjects randomized to receive placebo would relapse within 6 months, compared with an anticipated rate of 35% of subjects randomized to asenapine. A total of 115 relapses needed to be observed for a two-sided log-rank test with a significance level of 0.05 and more than 90% power to detect a constant hazard ratio of 0.54 in the asenapine to placebo relapse rates. The sample size needed to achieve 115 relapses by 6 months was estimated to be 300 randomized subjects (150 per group).

An interim analysis was originally intended to have been performed after 70 relapses had accrued with the intent of stopping the trial if there was evidence that asenapine was effective in preventing relapse compared to placebo. Given the rate of relapse during the trial, it was anticipated that most of the planned subjects would have been exposed to at least 13 weeks of double-blind treatment by the time 70 relapses were accrued. The interim analysis was determined to not be necessary and the trial continued until there were 115 relapses. The final analyses were performed following clinical database closure and the unblinding of all study personnel.

Due to an FDA warning letter received by Site 1117 for studies other than A7501012, the major efficacy and safety tables and figures were produced excluding data from that site.

Patients must have had a continued stable presentation of symptoms during the open-label monotherapy phase of the trial.

Patients were not to be randomized if they met any of the following criteria:

- PANSS total score > 75;
- CGI-S score > 3;
- PANSS item score ≥ 4 on items of "unusual thought content," "conceptual disorganization," or "hallucinatory behaviour;"
- PANSS item score ≥ 4 on items of "hostility" and/or "uncooperativeness;"
- ISST Modified item scores of 2 on Item #7 "control over suicidal action," #10 "method: specificity/planning," or #11 "expectancy/anticipation."

After successfully completing the open-label cross-titration and monotherapy phases and meeting all the randomization criteria, subjects could be randomized. Subjects were randomly assigned to either asenapine or placebo in a 1:1 ratio and assigned randomization code. Randomization was done on Day 1.

All hypothesis testing was conducted using 2-sided tests with alpha = 0.05. The Type I error was to be controlled at 0.05 for the study by use of a Pocock boundary with the study stopped if at the interim analysis the p-value of the log rank test was less than 0.025. If the study was not stopped at the interim analysis, the final analysis was to be tested at $\alpha = 0.025$. No other adjustments were to be made for multiple comparisons since all comparisons, except a single primary comparison, are considered secondary and would be used to support the findings of the primary analysis.

Time to relapse or impending relapse (days) was analysed using Kaplan-Meier (KM) survival methods. The KM survival, its 95% CIs, number at risk, number of events and number of censored observations were presented, by treatment, at each observed time point. Risk relative to placebo was also presented at each observed time point. The differences in the survival distributions between treatment groups was assessed using a 2-sided log-rank test with alpha set at the 0.05 level of significance. Asenapine was to be considered efficacious if the observed p-value on the significance test was≤ 0.05 and the median time to relapse for the asenapine group was greater than the median time to relapse for the placebo group.

Subjects who either completed the trial or discontinued prior to achieving the defined event of interest were censored at their last double-blind dose date.

The secondary efficacy endpoint time, in days, to early discontinuation for any reason was summarized by treatment using KM methods and analysed using a log-rank test.

Results

Participant flow

A total of 445 patients were screened and 386 were randomised. Of the 386 randomised patients, the ITT population comprised 382 patients with 191 taking placebo and 191 taking asenapine. The trial was completed by 135 asenapine patients (69.6%) and 72 placebo patients (37.5%).

Rescue medication

If the subject did not maintain clinical stability, or had demonstrated increased risk of suicide or violence to self or others while on double-blind trial medication but did not meet any of the symptomatic criteria for an impending relapse, the investigator could consider making any of the following interventions for the prevention or treatment of an impending relapse:

- Increase use of lorazepam (or equivalent) by an additional 2 mg per day compared to the highest open-label dose for more than 7 consecutive days,
- Addition of open-label antipsychotic medication,
- Addition or increase in the dose of antidepressant medication or mood stabilizers,
- Increase in the level of psychiatric care (e.g., supervised living, day hospital care),
- Hospitalization or increase in the level of hospitalization,
- Electroconvulsive therapy,

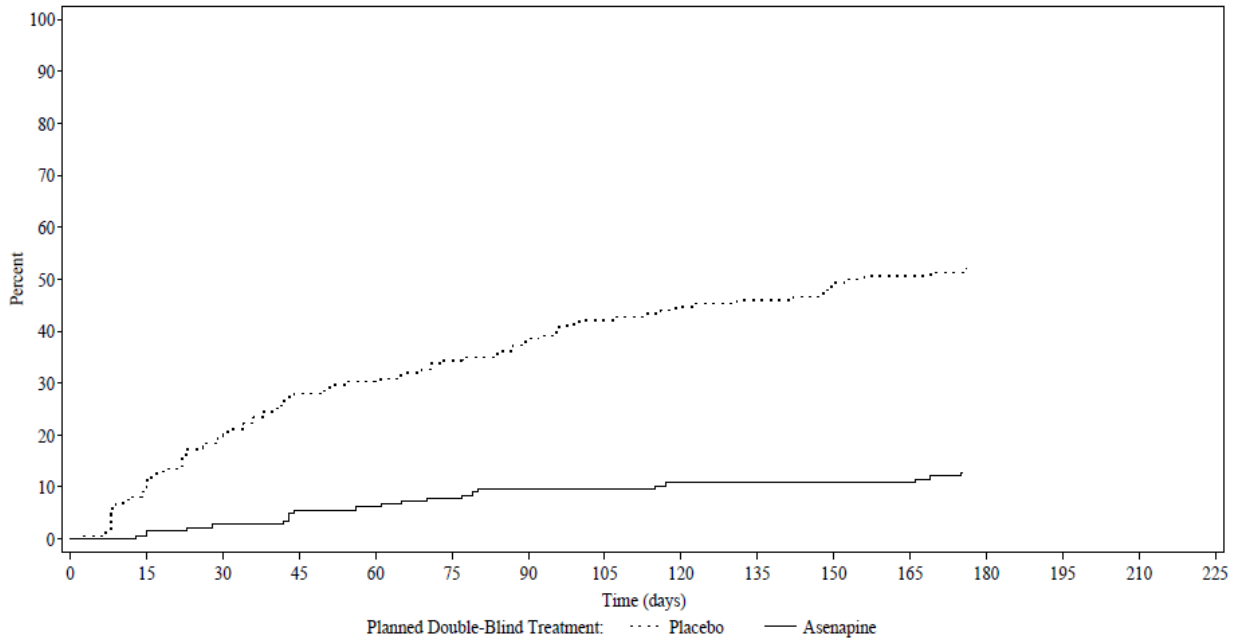
Outcomes

The primary efficacy endpoint was the time, in days, to a relapse or an impending relapse. Number of days to a relapse or impending relapse is the number of days from randomization to declaration, by the investigator, of a relapse or impending relapse. The study Kaplan-Meier

analysis was unable to produce an estimation of Time to Relapse/Impending Relapse for asenapine.

Based on a log-rank test, there was a statistically significant difference in favour of asenapine between the treatment groups with respect to the percentage relapse or impending relapse over time ($p < 0.0001$), that is, the rate of relapse was less in the asenapine group (11.05%) than the placebo group (45.79%) over the double-blind treatment period (Figure 11). The relative risk of experiencing a relapse in the asenapine group compared with the placebo group was 0.26.

Figure 11: Kaplan-Meier Estimation of Percent Relapse/Impending Relapse as Determined by the Investigator Excluding Site 1117 - Intent-to-Treat.

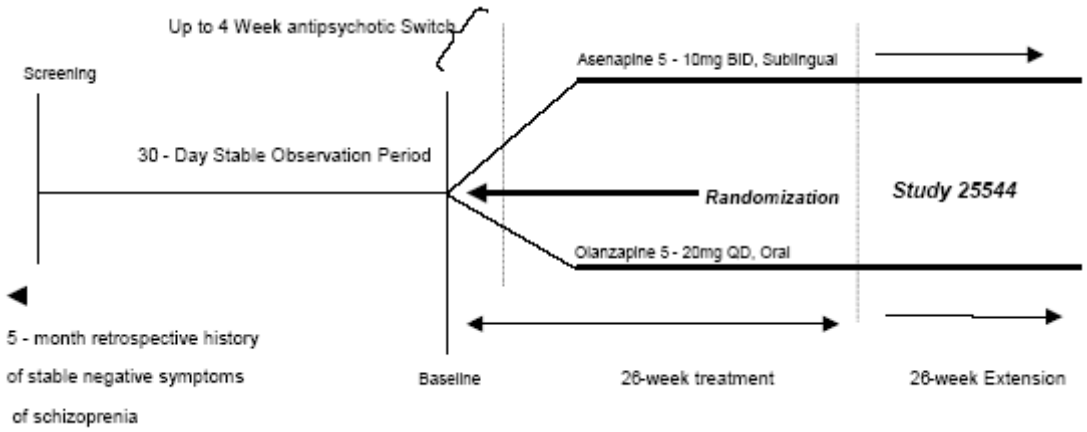


Studies in PNS maintenance of clinical improvement

Study 25543

The study design for Study 25543 is shown in Figure 12. The study was conducting in 102 centres in 15 countries including Australia between March 2005 and July 2006.

Figure 12: Study design for Study 25543



The primary objective was to compare the efficacy of asenapine 5-10 mg bd to that of olanzapine 5-20 mg od in the treatment of predominant, persistent negative symptoms of schizophrenia.

Secondary objectives included:

- Comparing the efficacy of asenapine with olanzapine in psychosocial function in subjects with schizophrenia and predominant, persistent negative symptoms.
- Evaluating treatment effects of asenapine with olanzapine with respect to:
  - Other dimensions of schizophrenia (positive, disorganized thought, hostility/excitement, anxiety/depression and general psychopathology),

- Quality of life and patient functionality,
- Neurocognition.

The primary endpoint was the change from baseline in Negative Symptoms Assessment (NSA) score at the Week 26 visit.

The primary null hypothesis was that there is no difference in the mean change from baseline in NSA total score between the group treated with asenapine and the group treated with olanzapine. The alternative hypothesis is that the two treatment groups have different mean change from baseline in NSA total score.

Study Participants

Inclusion Criteria

- schizophrenia of paranoid, disorganized, catatonic, residual, or undifferentiated subtype;
- PANSS negative subscale score ≥ 20 at screening and baseline, with a score of ≥ 4 on ≥ 3 of the negative Marder factors;
- a PANSS positive (Marder factor) score < the PANSS negative score at screening and baseline; and
- clinical stability for≥ 5 months as assesse d by: no significant changes in schizophrenia symptomatology; no hospitalizations, no increase in psychiatric care, no jailing or imprisonment due to worsening of symptoms of schizophrenia.

Exclusion Criteria

- A psychiatric disorder other than schizophrenia;
- A rating ≥ 4 on ≥ 2 items in the PANSS positive subscale
- A score of 2 on Items 7, 10, or 11 on the ISST (modified) at screening;
- An imminent risk of self-harm or harm to others;
- A score ≥3 on the global Parkinson Item of the ESRS-A;
- Depressive symptoms as defined by a score≥ 9 on the CDSS;
- Antidepressants and/or mood stabilizers during the previous 5 months
- Olanzapine in the previous 5 months with an inadequate response of negative symptoms;
- Clozapine in the previous 5 months for treatment resistant schizophrenia;
- Require high doses of benzodiazepines;
- Narrow angle glaucoma;
- A seizure disorder beyond childhood or taking any anticonvulsants to prevent seizures;
- Been medically non-compliant in the management of their disease.
- Have been previously treated in an asenapine trial;

Treatments

During the stable observation period, subjects took their background antipsychotic medication as they had been taking during the retrospective observation period. These medications were taken as scheduled until at least Day 1. Thereafter, these medications were weaned as the study medications were started. Investigators were encouraged to wean background medications by Day 14 but could take an additional 14 days if needed.

Background antipsychotic medication must have been completely discontinued by Day 28. The dosing schedule is shown at Table 18.

Table 18: Dosing schedule for trial medication.

Group	N	Drug	Dosage Form	Starting Dose	Dose Range	Duration
1	222	Asenapine	Fast dissolving tablets	5 mg SL BID × 1 week	5-10 mg SL BID	26 weeks
2	222	Olanzapine	Film-coated Tablets	10 mg PO QD × 1 week	5-20 mg PO QD	26 weeks

Outcomes/endpoints

The primary endpoint was the change from baseline in the NSA total score at 6 months.

Secondary efficacy endpoints were the scores on the QLS; PANSS, the Marder factor scores (positive, negative, disorganized thought, hostility/excitement, anxiety/depression) and subscale scores (positive symptoms, negative symptoms and general psychopathology) of the PANSS; the Calgary Depression Scale for Schizophrenia, the CGI-S; and CGI-I; the subscales in the Central Nervous System (CNS) Vital Signs Neurocognitive Test Battery; the Personal Evaluations of Transitions and Treatments (PETiT) (total and subscale scores); the Level of Function (LOF) scale; and the Quality of Life Enjoyment and Satisfaction Scale (Q-LES-Q) (Leisure Time Activities and Social Relations). Efficacy scales were to be analysed at all assessed time points.

Statistical considerations

Using data from a previous asenapine study where the results of PANSS negative subscale was mapped to the NSA; it was anticipated that asenapine would be 2 points better on the NSA than olanzapine. The SD of the change from baseline on the NSA in this population was expected to be 7.5 points. Using these assumptions 222 subjects per group gave 80% power to detect 2-point superiority over olanzapine.

The study employed an adaptive design where an interim analysis was to reassess the assumptions of effect size and variance. The adaptive design used the methods of Cui, Hung and Wang (5) to control type I error and include provisions to correct the sample size if needed.

The interim analysis was to be conducted after 120 subjects either have Week 26 NSA and QLS data or have dropped out early. Subjects that dropped from the study would be included in the interim analysis and the missing Week 26 data imputed using the LOCF method.

The primary efficacy analysis, analysis of covariance (ANCOVA) on the change from baseline in NSA total score at Day 182, in the first statistical plan was changed to mixed model for repeated measures (MMRM) ANCOVA on the change from baseline at each visit. The tests for the validity of the assumptions underlying ANCOVA for the primary efficacy analysis in the first plan were removed. The analysis of the primary efficacy endpoint, NSA change from baseline, conducted by the MMRM had effects for treatment, investigative site, visit, treatment by visit interaction and covariates for baseline NSA total score and duration of predominant negative symptoms. Centre-by-treatment interaction effect was to be investigated as secondary analyses. Type III sums of squares was used to test both main effects and interactions. Small centres were pooled to form pseudo-centres.

The hypothesis test comparing the asenapine to olanzapine on the change in NSA scores was performed using a 2-tailed 0.05 significance level. The interim analysis plan was to detail how $\alpha = 0.05$ is distributed between the interim analysis and the final analysis.

Results

Participant flow

A total of 576 patients were screened and 481 were randomised. The major reasons for withdrawal were failing to meet the selection criteria and consent withdrawal. Of the 481 randomised patients, the ITT population comprised 433 patients with 216 taking asenapine 5 mg/10 mg bd and 217 taking olanzapine. The trial was completed by 156 asenapine patients (64.7%) and 193 olanzapine patients (80.4%).

Benzodiazepines (< 4 mg/day lorazepam or equivalent dose of benzodiazepine) could be used for agitation/anxiety. For sleep, partial benzodiazepine agonists including zolpidem 2.5-10 mg/day, zaleplon 5-20 mg/day, zopiclone 7.5-15 mg/day, could be used on a daily basis for insomnia/sleep disturbance. Any equivalent short half-life non-benzodiazepine hypnotic could be substituted if zolpidem, zaleplon, or zopiclone were not available in specific countries (i.e. chloral hydrate). It was recommended for subjects older than 65 years of age that no more than half of recommended maximum suggested hypnotic dose be used. These drugs were not be used 12 hours prior to assessments.

Outcomes

The results for the primary efficacy outcome are shown in Table 19.

Table 19: Primary Efficacy Endpoint.

Total NSA	Asenapine bd 5-10 mg (N=216)*	Olanzapine OD 5-20 mg (N=217)*
Baseline mean± SD	60.3 ± 9.04	60.3 ± 8.62
Endpoint mean± SD	49.3 ± 12.57	48.6 ± 12.03
Endpoint Change mean± SD	−11.0 ± 11.41	−11.7 ± 10.60
Day 182[a] LSM ± SE	-12.2 ± 0.81	-12.5 ± 0.76
p-value	0.7869	
Overall [a] LSM ± SE	-7.8 ± 0.45	-7.9 ± 0.44
Endpoint[b] LSM ± SE	-10.7 ± 0.65	-11.6 ± 0.65
p-value	0.3314	

[a] repeated measures ITT
[b] inferential analysis ITT
* excludes repeat subjects and subjects from 3 sites where data irregularities were observed

Using the Mixed Model for Repeated Measures (MMRM) asenapine was not significantly different from olanzapine on the change from baseline in NSA total score Secondary analyses, showed some small differences with PANSS sub scores and CDSS total score (Table 20).[38]

[38] The primary efficacy analysis on change from baseline to Day 182 in NSA total score using LOCF, which rests upon the assumption of missing completely at random (MCAR), was replaced with mixed model for repeated measures (MMRM). July 2007

Table 20: Major Secondary Efficacy endpoints.

	Change from baseline	Asenapine bd 5-10 mg (N=216)*	Olanzapine OD 5-20 mg (N=217)*
NSA global score	Day 182 LSM[a] (SE)	-1.1 ± 0.08	-1 ± 0.07
	p-value	0.2433	
QLS	Day 182 LSM[a] (SE)	11.7 ± 1.14	11.8 ± 1.05
	p-value	0.9298	
PANSS total score	Endpoint LSM[a] (SE)	-10.9 ± 0.86	-12.8 ± 0.85
	p-value	0.0983	
PANSS negative subscale	Day 182 LSM[a] (SE)	-7.1 ± 0.38	-6.6 ± 0.35
	p-value	0.2962	
PANSS Marder negative symptoms factor score	Day 182 LSM[a] (SE)	-8 ± 0.4	-7.4 ± 0.37
	p-value	0.2695	
CGI-I Responders[b] n (%) Day 182	Responders	51 (45.9)	84 (54.9)
	Non-responders	60 (54.1)	69 (45.1)
	P-value[b]	0.1883	
CGI-S	Day 182 LSM[a] (SE)	-0.8 ± 0.07	-0.9 ± 0.07
	p-value	0.452	
CDSS total score	Endpoint, LSM[a] (SE)	−0.2 ± 0.15	−0.8 ± 0.15
	p-value	0.0055	

* excludes repeat subjects and subjects from 3 sites where data irregularities were observed

[a] Based on a mixed model with defined covariance structure, treatment and pooled investigative site as fixed effects, baseline and duration of neg. symptoms as covariates.

[b] A CGI-I responder was defined as at least much improved i.e. CGI-I ≤ 2. P-values are for comparison of asenapine vs olanzapine based on Cochran Mantel-Haentzel test adjusted by duration of negative symptoms.

Ancillary analyses

The primary endpoint analysis results caused by missing data was checked against potential bias by ANCOVA with effects for treatment and investigative site and covariates for baseline NSA score and duration of predominant negative symptoms. Both LOCF imputation and OC analyses were supportive.

Study A7501013

The design of Study A7501013 was similar to 25543. The study was conducted in 97 centres in 6 countries from November 2004 to December 2008.

The primary objective was to compare asenapine with olanzapine in the treatment of predominant Persistent Negative Symptoms (PNS) of schizophrenia.

Secondary objectives were to compare the effectiveness of asenapine and olanzapine with respect to body weight and psychosocial function in subjects with schizophrenia and predominant PNS.

Additional objectives included evaluating treatment effects of asenapine compared to olanzapine with respect to:

- Other dimensions of schizophrenia (positive, disorganized thought,
- hostility/excitement, anxiety/depression and general psychopathology),
- Neurocognition and cognitive functioning,
- Quality of life.

The primary null hypothesis was that there is no difference in the average change in NSA Total score between the group treated with asenapine and the group treated with olanzapine.

The alternative hypothesis is that there is a treatment effect and the average changes in the NSA Total score are different for each group.

The null hypothesis for all remaining endpoints tested statistically is that the results observed in the asenapine treatment group are no different from those in the olanzapine treatment group. The alternative hypothesis is that the results for the asenapine and olanzapine treatment groups are different.

Inclusion and exclusion criteria were similar to Study 25543.

Treatments

Asenapine: Initial 7 days 5 mg bd, then adjusted as necessary (prn) to a maximum of 10 mg bd.

Olanzapine: Initial 7 days 10 mg od, then adjusted prn to a maximum of 20 mg od.

Duration: 30-day stable observation period, an active treatment period consisting of up to a 4-week antipsychotic switch period followed by a 22-week monotherapy treatment period.

Outcomes/endpoints

The primary efficacy endpoint was the change from baseline in the NSA Total score.

Secondary efficacy endpoints were multiple and included the change from baseline in body weight; the scores on the QLS; PANSS, the Marder factor scores and subscale scores of the PANSS; the Calgary Depression Scale for Schizophrenia, the CGI-S; and CGI-I; Cognitive Functioning Scale (CogFu); the Personal Evaluations of Transitions and Treatments (PETiT) (total and subscale scores); the Level of Function (LOF) scale; and the Quality of Life Enjoyment and Satisfaction Scale (Q-LES-Q) (Leisure Time Activities and Social Relations). Efficacy scales were to be analysed at all assessed time points.

Statistical considerations

Using data from a previous asenapine study where the results of PANSS negative subscale was mapped to the NSA, it was anticipated that asenapine would be 2 points better on the NSA than olanzapine. The standard deviation of the change from baseline on the NSA in this population was expected to be 7.5 points. Using these assumptions a total of 222 subjects per group would be necessary to have 80% power to detect 2-point superiority over olanzapine.

After successfully completing the stable observation period and meeting all randomization criteria, subjects could be randomized.

With some exceptions all hypothesis testing was conducted using two-sided tests with alpha = 0.05 level of significance. Some secondary endpoints were tested at the 2.5% nominal significance level using Bonferroni adjustment to account for multiplicity of the key

secondary comparisons. The primary analysis was conducted on the ITT population and the MMRM model was used to assess treatment differences. Two separate analyses using ANCOVA on the change from baseline in NSA Total score at each visit were performed - LOCF and the observed case (OC) methods. In both analyses, the ANCOVA model includes terms for treatment, centre, baseline NSA Total score and duration of predominant negative symptoms as covariates.

Results

Participant flow

A total of 803 patients were screened and 468 were randomised. The major reasons for withdrawal were failing to meet the selection criteria and consent withdrawal. Of the 468 randomised patients, the ITT population comprised 452 patients with 234 taking asenapine and 218 taking olanzapine. The trial was completed by 121 asenapine patients (49.6%) and 143 olanzapine patients (63.8%).

Outcomes

The results for the primary efficacy are shown in Table 21. Asenapine was not significantly different from the active comparator (olanzapine) in the primary endpoint.

Table 21: Summary of primary efficacy endpoint - NSA Total Score.

NSA (ITT) Mean ± SD	Asenapine 5-10 mg (N=234)	Olanzapine 5-20 mg (N=218)
Baseline	60.1 ± 10.17	61.1 ± 10.79
Day 182	52.7 ±12.96	53.2 ± 12.97
Change to Day182*	-7.4 ± 11.01	-8.0 ± 10.55
Change to Day182* LOCF LSM ± SE	-8.4 ± 0.78	-8.5 ± 0.78
p-value Day182	0.8950	
Change to Day182 OC LSM ± SE**	-9.7 ± 0.95[a]	-9.2 ± 0.89[b]
p-value	0.7177	

[a] n= 81. [b] n = 102 OC=observed cases.

*Based on an ANCOVA model with treatment and pooled site as fixed effects and baseline and 2-level duration of predominant negative symptoms as covariates. The p-value is based on the difference in LS means for asenapine vs olanzapine.

**Based on a repeated measures ANCOVA model with treatment, pooled site, visit and treatment by visit interaction as fixed effects and baseline and 2-level duration of predominant negative symptoms as covariates, with an unstructured covariance structure. The p-value is based on the difference in LS means for asenapine vs olanzapine.

The results for some secondary endpoints are shown in Table 22.

Table 22: Secondary efficacy endpoints.

	Change from baseline	Asenapine bd 5-10 mg (N=234)	Olanzapine OD 5-20 mg (N=218)
QLS Total Score[a] OC	Day 182 LSM (SE)	11.1 (1.54) n = 80	7.1 (1.41) n = 101
	p-value	0.0565	
Weight (kg) [a] OC	Day 182 LSM (SE)	-0.0 (0.43) n = 80	2.6 (0.40) n = 102
	p-value	<.0001	
CGI-I Responders[b] n (%) LOCF Day 182	Responders	57 (24.4)	59 (27.2)
	Non-responders	177 (75.6)	158 (72.8)
	P-value	0.5653 n = 234	n = 217
PANSS total score[a] OC	Endpoint LSM (SE)	-11.6 (1.14) n = 81	-13.8 (1.07) n = 101
	p-value	0.1727	
PANSS Marder[a] negative symptoms score	Day 182 LSM (SE)	-7.0 (0.48) n = 81	-6.7 (0.45) n = 101
	p-value	0.6644	
CDS Total Score[c]	Day 182 LSM (SE)	-0.4 (0.17) n = 227	-0.6 (0.17) n = 213
	p-value	0.3787	

OC=observed cases

[a] Based on a repeated measures ANCOVA model with treatment, pooled site, visit and treatment by visit interaction as fixed effects and baseline and 2-level duration of predominant negative symptoms as covariates, with an unstructured covariance structure. The p-value is based on the difference in LS means for asenapine vs olanzapine.

[b] A subject is a CGI-I responder at a given visit if they have a response of very much improved or much improved at that visit. The p-value for the comparison of asenapine vs olanzapine is based on the Cochran-Mantel-Haenszel chi-squared test, stratified by 2-level duration of predominant negative symptoms.

[c] Based on an ANCOVA model with treatment and pooled site as fixed effects and baseline and 2-level duration of predominant negative symptoms as covariates. The p-value is based on the difference in LS means for asenapine vs olanzapine.

Ancillary analyses

For the primary analysis, the treatment by centre interaction was tested at a 10% significance level. Two separate analyses using ANCOVA on the change from baseline in NSA total score at each visit was performed using LOCF and OC. In both analyses, the ANCOVA model included terms for treatment, centre, baseline NSA total score and duration of predominant negative symptoms as covariates.

Study 25544

The primary objective of Study 25544 was to compare the long-term efficacy of asenapine 5-10 mg bd to that of olanzapine 5-20 mg od in the treatment of predominant persistent negative symptoms of schizophrenia. The study was conducted in 42 centres in the USA, India, Russia and Romania between 6 June 2006 and13 December 2007.

Multiple secondary objectives included the assessment of Quality of Life and patient functionality outcomes and evaluating treatment effects with respect to:

- Overall symptom control
- Other dimensions of schizophrenia (positive, disorganized thought, hostility/excitement, anxiety/depression and general psychopathology)

- Neurocognition

The primary null hypothesis was there is no difference in the mean change from baseline in NSA total score between the group treated with asenapine and the group treated with olanzapine at Day 365. The alternative hypothesis is that the two treatment groups have different mean change from baseline in NSA total score at Day 365. Similar hypotheses were applied to the secondary endpoints.

Study Participants

Participants in the study:

- had completed the 25543 trial and benefited from continued treatment ,
- had demonstrated an acceptable degree of compliance with trial medication in the 25543 trial ,
- continued to meet all demographic and procedural inclusion criteria of the 25543 study upon entry into this extension.

Treatments

Patients continued on the double-blind dose of asenapine 5-10 mg bd or olanzapine 5-20 mg od, received at the end of the Study 25543 (Day 182).

Outcomes/endpoints

The primary efficacy endpoint was the change in total score in the Negative Assessment (NSA) from 25543 baseline at Day 365.

Secondary efficacy endpoints included the Quality of Life Scale (QLS) (total and subscale scores), PANSS Marder factor scores (positive, negative, disorganized thought, hostility/excitement, anxiety/depression), PANSS subscales scores (positive, negative, general psychopathology), the Calgary Depression Scale for Schizophrenia (CDSS), the Clinical Global Impression Scale (severity) (CGI-S) and (improvement) (CGI-I), the subscales in the Central Nervous System (CNS) Vital Signs Neurocognitive Test Battery, the PETiT (total and subscale scores), the Level of Function (LOF) Scale and the Quality of Life Enjoyment and Satisfaction Scale (Q-LES-Q) (Leisure Time Activities and Social Relations subscales).

Statistical considerations

The study was not powered for direct statistical comparison. The number of subjects was to be determined by the number who complete the 25543 study and who continued on.

Patients continued on the randomised double-blind treatment they received in Study 25543 with the assignment of new identification numbers.

The primary efficacy analysis (ITT population), an assessment of the treatment effect after 1 year of therapy, compared asenapine with olanzapine using a mixed model for repeated measurements (MMRM) analysis of covariance. The model included change from baseline in NSA score at each visit as the dependent variable and terms for treatment, centre, visit, treatment by visit interaction and covariates for baseline NSA total score and duration of predominant negative symptoms.

Statistical testing used a 2-sided $\alpha = 0.05$ significance level. However, the treatment by centre interaction was tested at a 10% significance level. If $p > 0.10$ then the term for treatment by centre interaction was dropped from the model;

The duration of the effect, observed at the 6-month time point, was evaluated at each visit from 6 months to 12 months. Statistical testing, along with dropout patterns, reason for dropout and point estimates of group responses, was to be used to describe the maintenance of relative effect observed at 6 months. This analysis set contained all subjects enrolled into this study. The analysis plan could be amended prior to the breaking of the blind if the dropout rate was high.

To assess the robustness of the primary efficacy analysis results, two separate ANCOVA on the change from baseline in total NSA score at each visit were performed (LOCF and OC), including terms for treatment, centre, treatment by centre interaction and baseline NSA total score and duration of predominant negative symptoms as covariates.

Results

Participant flow

The ITT population comprised 122 patients taking asenapine 5 mg/10 mg bd and 157 taking olanzapine. The trial was completed by 113 asenapine patients (84.3%) and 153 olanzapine patients (89.0%).

Outcomes

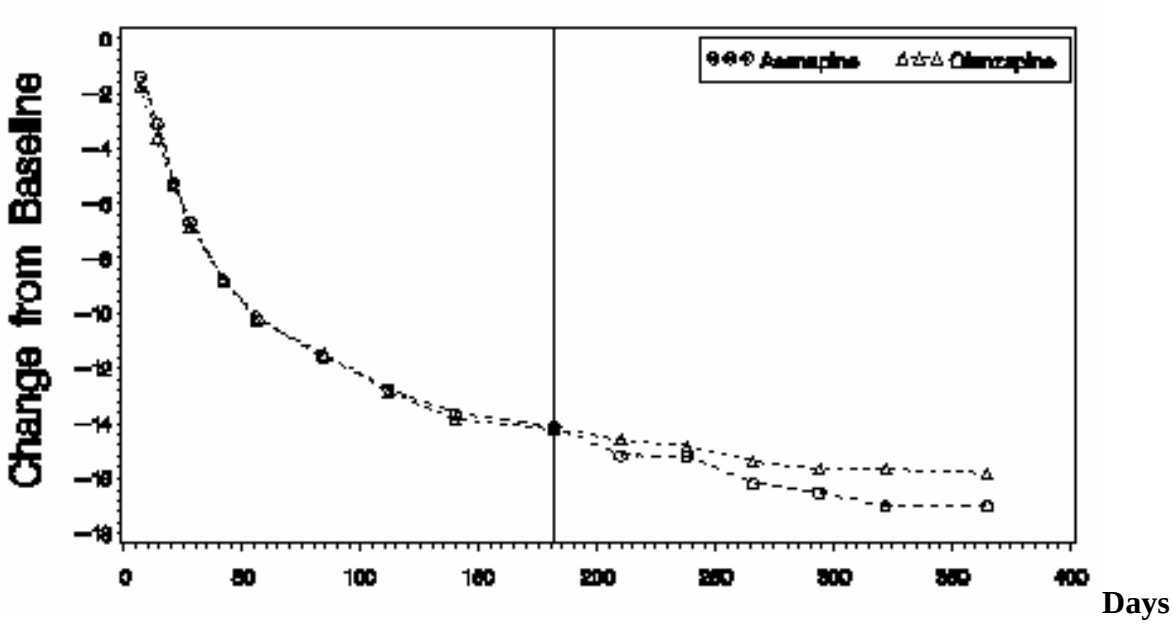
The primary efficacy endpoint results are shown in Table 23. There was no significant difference between asenapine and the active comparator olanzapine. It is also illustrated in Figure 13 where separation in favour of asenapine can be seen after about 180 days of treatment.

Table 23: Repeated measurements analysis of change from 25543 baseline in total NSA scores at Day 365, excluding sites 111 and 157 (ITT group in 25544).

Visit		Asenapine (N=122)	Olanzapine (N=157)
Overall	LS Mean Change (SE) *	-11.2 (0.62)	-10.8 (0.55)
	p-value *	0.5791	
Day 182	LS Mean Change (SE) *	-13.8(0.87)	-13.6 (0.76)
	p-value *	0.8361	
Day 365	LS Mean Change (SE) *	-16.9 (0.98)	-15.4 (0.85)
	p-value *	0.2344	

* Based on a mixed model with defined covariance structure. treatment and pooled investigative site as fixed effects, baseline and duration of neg. symptoms as covariates.
P-values are based on the difference in the LS means for Asenapine vs Olanzapine

Figure 13: NSA Total Score: change from 25543 baseline (by visit; MMRM during one year period).



Analysis performed across trials (pooled analyses and meta-analysis)

Study INT 00039918 was an exposure response analysis of total PANSS based on Phase 2 and Phase 3 trials for asenapine. It was designed to substantiate the efficacious dose range of asenapine in the treatment of schizophrenia and assess the impact of such factors as exposure, patient population and drop-out on the outcome of clinical studies with asenapine. The observed outcomes of the study arms were well predicted for all placebo arms and all 5 and 10 mg arms in the Phase 3 trials, although the outcomes of three of the treatment arms in Phase 2 and the flex-dose arm in Phase 3 were not within the 90% prediction interval

Evaluator's overall conclusions on clinical efficacy in Schizophrenia

In relation to acute treatment of schizophrenia the sponsor submitted two validated Phase 3 studies:

1. Study 041021 failed to show efficacy greater than placebo for either asenapine 5 mg bd (102 patients) or 10 mg bd (96 patients);
2. Study 041023 showed efficacy greater than placebo for asenapine 5 mg bd (109 patients) but not for asenapine 10 mg bd (105 patients).

In a further study 041004 where the active comparator did not demonstrate statistically significant efficacy, efficacy of asenapine greater than placebo was shown (but only 5 mg bd was tested on 58 patients). The final study for acute treatment of schizophrenia was Study 041022. This was a failed study in which none of the treatments (asenapine 5 or 10 mg bd or olanzapine) demonstrated statistically significant efficacy.

Thus the balance of these studies does not favour 5 mg bd being more efficacious than placebo in acute treatment of schizophrenia. Asenapine 10 mg bd was not shown to be more efficacious than placebo in acute treatment of schizophrenia.

In relation to the prevention of relapse the sponsor submitted study A7501012 which showed efficacy greater than placebo in the rate of relapse for asenapine 5-10 mg bd. The number of patients taking asenapine 5 mg and asenapine 10 mg was not given, only that the total taking 5 mg or 10 mg was 189. This demonstration of efficacy in prevention of relapse is limited to those patients who were able to be successfully stabilised on asenapine open-label therapy. Given that efficacy of asenapine in acute treatment of schizophrenia has not been adequately

demonstrated it is difficult to see how asenapine could be used for prevention of relapse in the selected population in which its efficacy has been demonstrated.

The sponsor also submitted this study as evidence for the maintenance of clinical improvement based on a secondary objective PANSS total score. The LSMs for this at Week 26 OC showed no significant difference ($p = 0.4426$) between those continued on asenapine (110) and those given placebo (55) after an initial$\geq$ 22 weeks of asenapine. However if the patients that relapsed are included, that is, LSMs at the endpoint for the PANSS total score showed significant difference ($p < 0.0001$) between the 189 on placebo and the 189 on asenapine.

In the extension studies;

- Study 041502 was an extension of 041004 that could not be validated and only assessed asenapine 5 mg bd.
- Study 041512 was an extension of studies 041021 and 041022 neither of which showed efficacy for asenapine greater than placebo and the latter was not validated by having an active comparator that was statistically significantly superior to placebo.
- Study 041513 was an extension to 52 weeks of Study 041023 without placebo control (patients previously on placebo received asenapine). Study 041023 was validated by its active control and showed efficacy greater than placebo for asenapine 5 mg bd but not 10 mg bd. The data from both doses of asenapine were not separated in the study report. There was no hypothesis testing and only summary statistics were presented for efficacy endpoints. The primary endpoint was the time to failure to maintain effect for those patients who had at least a 30% decrease from baseline in PANSS at the end of the acute phase. In the extension period the PANSS total score OC at the end point for those continually on asenapine rose (that is, deteriorated) by 1.9 from 62.4 (88 patients), while that for haloperidol decreased by -4.1 from 64.4 (41 patients). The baseline score at the start of 04123 was 86.1 for asenapine and 87.0 for haloperidol. There were 51 patients (of 65, 78%) on asenapine 5-10 mg bd and 24 patients (of 29, 83%) on haloperidol who had an initial episode of loss of effect during this extension trial. Median survival times for subjects continuing on active treatment from the feeder studies were 31 days for subjects treated with asenapine 5-10 mg bd and 85 days for subjects treated with haloperidol 2-8 mg bd. These results strongly suggest that asenapine is less effective than haloperidol in maintenance treatment of schizophrenia however there was no statistical comparison between the active treatments.

The numbers completing the longer term use studies were small:

- Study 041512- overall completion on asenapine was 15/296 (5.1%) and on olanzapine 20/194 (10.3%),
- Study 041513 Overall completed; asenapine 30/217 (13.8%); haloperidol 16/115 (13.9%), and
- Study 041502 Overall completion on asenapine was 0/59; risperidone 1/59 (1.7%); placebo 0/62.

If the assessment of the maintenance of clinical improvement is taken to include those patients who underwent relapse (that is, OC at endpoint) then asenapine 5-10 mg showed efficacy greater than placebo in study A7501012. However if the effect of these patients is eliminated (that is, OC at 26 weeks) then asenapine has not been demonstrated to be more effective than placebo in maintenance treatment of schizophrenia.

The study designs met the requirements of the TGA-adopted EU guideline.[39] The fixed doses of 5 mg and 10 mg in Study 041021 were justified on the basis of Study 041004 and an unidentified safety study using up to 20 mg bd. However there were some matters of concern in that multiple centres were involved with each centre assessing relatively few patients and some of the endpoints definitions were subjective. Studies 041512 and 041513 defined failure to maintain effect to include any of:

- A dose increase to improve clinical response in a destabilized subject.
- The patient's schizophrenic symptomatology has deteriorated.
- Discontinuation due to lack of efficacy.
- AE/SAE of worsening of schizophrenia.

While Study A 7501012 defined a relapse or impending relapse to include:

In the opinion of the investigator, the subject's symptoms of schizophrenia had deteriorated to such an extent or the risk of violence to self or others or suicide had increased so that 1 or more of the following measures was necessary or had occurred:

• Required at least an additional 2 mg or greater lorazepam (or equivalent) per day as compared to the highest open-label dose of the monotherapy phase;

• Addition of open-label antipsychotic medication or mood stabilizers;

• Addition or increase in the dose of antidepressant medication;

• Increase in the level of psychiatric care (for example, supervised living, day hospital care);

• Hospitalization or increase in the level of hospitalization;

• An arrest or imprisonment for objectionable behaviour;

• Electroconvulsive therapy;

• Other.

Efficacy in Bipolar Disorder

Introduction

The proposed Indication is:

Treatment of acute mania or mixed episodes associated with bipolar I disorder and maintenance of clinical improvement during the manic episode as monotherapy or in combination with lithium or sodium valproate.

There were 6 studies in patients with acute mania or mixed episodes associated with Bipolar 1 disorder. Two studies were short term, randomised, double-blind, placebo and active-(olanzapine) controlled studies of nearly identical design (studies A7501004 and A7501005). Subjects completing either of those studies could participate in Study A7501006 which permitted continuing treatment for a further 9 weeks. Study A7501008 enrolled subjects with either acute mania or a mixed bipolar 1 episode who had not completely responded to continuing treatment with either valproate or lithium. The final 2 studies assessed use up to 52 weeks and enrolled subjects who had completed either Study A7501006 or A7501008. Study A7501006 was placebo and active (olanzapine) controlled while Study A7501009 was placebo controlled.

The most pertinent points from these studies are summarised below:

Monotherapy - Acute Treatment

[39] EMEA, Committee for Proprietary Medical Products (CPMP), 26 February 1998. Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Schizophrenia, CPMP/EWP/559/95.

- Study A7501004 both asenapine 5 mg bd and active comparator (olanzapine) more effective than placebo.
- Study A7501005 both asenapine 5-10 mg bd and active comparator (olanzapine) more effective than placebo.

The TGA-adopted EU guideline recommends studies of the acute manic episode be 3 arm (including placebo) studies to 3 weeks then out to 12 weeks with the active comparator.[40]

Monotherapy - Maintenance of Clinical Improvement

- Study A7501006 no placebo active comparator olanzapine the evaluator has concerns about the statistics of the non-inferiority analysis
- Study A7501007 an extension of study A7501006.

  The relevant guideline recommends studies of the maintenance of effect of 3-6 months are needed

In Combination- Acute Treatment

- Study A7501008: no active comparator, asenapine 5-10 mg was more effective than placebo in the primary endpoint.

In Combination - Maintenance of Clinical Improvement

- Study 7501009 (after 7501008): no statistical analysis.

Dose response study

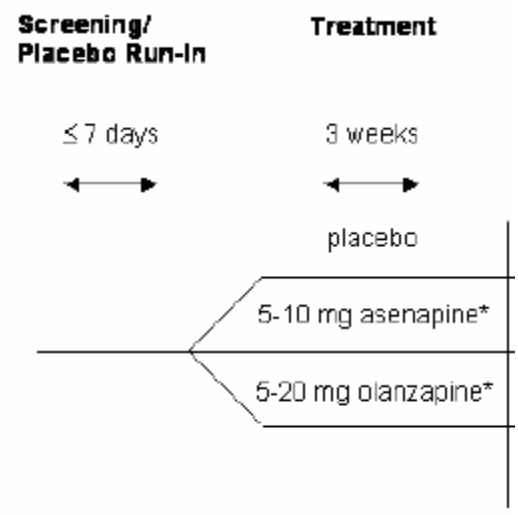
No dose ranging studies were performed for bipolar disorder. Starting dose was chosen on the basis of results for schizophrenia.

Main (pivotal) studies related to Monotherapy - Acute Treatment

Study A7501005

The trial design for Study A7501005 is shown in Figure 14. The study was conducted at 55 centres, 29 in the US, 2 in Bulgaria, 6 in India, 3 in Korea, 1 in Malaysia, 2 in the Philippines, 2 in Romania, 4 in the Russian Federation, 2 in Turkey and 4 in Ukraine between 14 December 2004 and 8 April 2006.

Figure 14: Study A7501005 design



[40] EMEA, Committee for Proprietary Medicinal Products (CPMP), 26 April 2001. Note for guidance on clinical investigation of medicinal products in the treatment and prevention of bipolar disorder (CPMP/EWP/567/98).

The primary objective was to demonstrate the efficacy of asenapine compared with placebo in treatment of patients with manic or mixed episodes associated with bipolar I disorder.

Secondary objectives included treatment effects of asenapine vs placebo with respect to:

- Clinical Global Impressions Scale for use in Bipolar Disorder (CGI-BP),
- Montgomery-Asberg Depression Rating Scale (MADRS),[41]
- PANSS,
- Readiness to Discharge Questionnaire (RDQ),
- Short Form-36, (SF-36v2),[42]
- Treatment Satisfaction Questionnaire for Medication (TSQM),
- Cognitive symptoms, as assessed with a computerized cognitive battery.

[41] MADRS = Montgomery-Åsberg Depression Rating Scale. The MADRS is a validated depression rating scale with 10 items that cover the core depressive symptoms (apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, suicidal thoughts). Each item is scored from 0 (item is not present or is normal) to 6 (severe or continuous presence of the symptom). The total MADRS score can range from 0 to 60, with higher scores representing more severe depression.

[42] SF-36 = Medical Outcomes Short-Form 36. The SF-36v2 is version 2 of a validated, patient-based, measure of health-related quality of life. It is a 36-item questionnaire measuring 8 domains (physical functioning, role-physical, role-emotional, social functioning, bodily pain, mental health, vitality and general health). Responses to questions within each dimension are summed and linearly transformed to scale scores that range from 0 (worst health) to 100 (optimal health) (Ware, 1993). In addition, 2 component scale scores, Standardized Physical Component Summary Scale and the Standardized Mental Component Scale, are computed based on weighted combinations of the 8 domain scores.

Study Participants

Inclusion criteria

- Bipolar I disorder, current episode manic or mixed at screening that must have begun ≤ 3 months prior;
- A YMRS score ≥ 20 at screening and at baseline;[43]
- At least one previous moderate-to-severe mood episode with or without psychotic features (manic or mixed);

Exclusion criteria

- A primary diagnosis other than bipolar I disorder;
- A diagnosis of schizophrenia, schizoaffective disorder, or other psychotic disorders;
- Narrow angle glaucoma;
- A seizure disorder beyond childhood or were taking anticonvulsants to prevent seizures;
- An imminent risk of self-harm (ISST-modified score of 2 on Item 7, 10, or 11 at screening) or of harm to others;
- A history of rapid cycling[44];
- unable to reduce daily benzodiazepine intake;
- A lithium level greater than 0.6 mEq/L, a valproate level greater than 50 µg/mL, or a carbamazepine level greater than 4 µg /mL prior to baseline, or have taken lithium, valproate, or carbamazepine within 3 days of baseline;
- Patients who had received clozapine for the treatment of bipolar disorder within 12 weeks or a monoamine oxidase inhibitor within 2 weeks prior to baseline.

Treatments

After an up to 7 day single-blind placebo run in period during which patients received single-blind placebo (placebo/olanzapine), the active treatment period was initiated on Day 1 with placebo, asenapine 10 mg bd, or olanzapine 15 mg od. Thereafter, treatment continued with flexible dosing (asenapine 5-10 mg bd, olanzapine 5-20 mg od or placebo), based on efficacy and tolerability.

Lorazepam for the treatment of agitation was allowed at a maximum dose of 4 mg/day during the screening phase and for the first 7 days following the baseline assessment. The use of benzodiazepines after Day 7 was not permitted.

[43] YMRS = Young Mania Rating Scale. The YMRS is a validated measure of the severity of mania, based on the subject's subjective report of their condition over the previous 7 days or since the last visit (whichever was shorter) and the clinician's behavioural observations during the interview, with emphasis on the latter. It consists of 11 items: 7 items (elevated mood, increased motor activity, sexual interest, sleep, language-thought disorder, appearance and insight) are scored on a scale of 0 to 4; 4 items (irritability, speech rate and amount, content and disruptive-aggressive behaviours) are scored on a scale of 0 to 8. Possible scores range from 0 to 60. A higher score indicates more severe mania. A clinically significant difference was 4 as defined by the non-inferiority margin in study A7501006.

[44] Rapid cycling was defined as four or more (including current episode) mood episodes during the previous 12 months that met both the duration and symptom criteria for a major depressive, manic, mixed, or hypomanic episode. Each previous episode was to be demarcated by either a period of full remission or by a switch to an episode of the opposite polarity. Manic, hypomanic and mixed episodes were counted as being on the same pole (e.g., a manic episode immediately followed by a mixed episode counted as only 1 episode).

Outcomes/endpoints

The primary efficacy endpoint was the change from baseline to Day 21 on the YMRS total score (LOCF).

Secondary efficacy variables for asenapine vs placebo included:

- CGI-BP: (at multiple time points.);
- PANSS (at multiple time points.);
- MADRS: (at multiple time points.
- RDQ: (at multiple time points.);
- ISST (modified version): (Day 1);
- CogState cognitive battery: (at multiple time points.).

Statistical considerations

A sample size of 480 subjects randomized as 2:2:1 (192 asenapine: 192 olanzapine: 96 placebo) would have 95% power to detect a 5-point difference in means on the YMRS using a two group t test with a 0.05 two-sided significance level and assuming a common standard deviation of 11 points.

Subjects were randomly assigned to receive asenapine, olanzapine, or placebo treatment (in a ratio of 2:2:1) after completing all screening and baseline assessments and meeting all inclusion and exclusion criteria.

The primary efficacy endpoint, change from baseline to Day 21 on the YMRS total score, was analysed by a fixed-effects ANCOVA (LOCF IT), with the baseline score as a covariate and allowed for variability due to centre and treatment. For the primary endpoint only, centre by treatment interaction was investigated as a secondary analysis. Type III sums of squares were used to test both main effects and interactions. Comparisons between treatment groups were made using the difference in the model-based LSMs. The p-value for the difference in the model-based LSMs for the treatment group comparisons was presented. Small centres were pooled for analysis.

Hypothesis testing for YMRS responder and remitter analyses used Pearson's chi-squared test. Hypothesis testing for CGI-BP severity of mania used ANCOVA with baseline CGI-BP severity of mania in the model.

Hypothesis testing for MADRS and CGI-BP severity of depression used ANCOVA with baseline total MADRS score and CGI-BP severity of depression in the model, respectively.

Results

Participant flow

A total of 654 patients were screened and 489 were randomised. Of the 489 randomised patients, the ITT population comprised 480 patients with 103 taking placebo, 189 taking asenapine and 188 taking olanzapine. The trial was completed by 64 placebo patients (61.5%), 122 asenapine patients (62.9%) and 152 olanzapine patients (79.6%).

Outcomes

Both asenapine 5-10 mg bd and the active comparator (olanzapine) were more effective than placebo (Table 24).

Table 24: YMRS Total Score and Inferential Analysis of Change from Baseline LOCF ITT.

Visit		Placebo (N = 103)	Asenapine (N = 189)	Olanzapine (N = 188)
Baseline	Mean[a] (SD)	29.0 (6.14)	28.3 (5.53)	28.6 (5.88)
Day 21	Mean (SD)	23.5 (12.57)	17.7 (11.29)	16.1 (9.43)
	Mean Change (SD)	-5.5 (10.63)	-10.5 (11.13)	-12.5 (9.71)
Baseline	LS mean[b] (SE)	29.6 (0.52)	28.7 (0.39)	29.1 (0.39)
	95% CI[b]	(28.5, 30.6)	(27.9, 29.4)	(28.4, 29.9)
Day 21	LSM Change from Baseline [c] (SE)	-5.5 (1.01)	-10.8 (0.75)	-12.6 (0.76)
	p-value[c]		<.0001	<.0001

YMRS total score range= 0-60; higher scores indicate greater severity of symptoms.
[a] Baseline mean is the mean for those subjects completing the visit with a non-missing change score. Baseline is the last non-missing assessment on or prior to Day 1 (randomization).
[b] Based on an ANOVA model with fixed effects for treatment and pooled investigative site.
[c] Based on an ANCOVA model with treatment and pooled investigative site as fixed effects and baseline as a covariate. P-values are based on the difference in the LS means for active treatment versus placebo.

Table 25 provides a summary of YMRS responders. Both active treatments showed significant results.

Table 25: Summary of YMRS Responders, LOCF – ITT.

		Placebo (N = 103)	Asenapine (N = 189)	Olanzapine (N = 188)
Day 2	Responders, n (%)	2 (2.0)	11 (6.0)	13 (7.1)
	p-value[a]		0.1467	0.0941
Day 4,	Responders, n (%)	6 (5.8)	22 (11.6)	26 (13.8)
	p-value[a]		0.1448	0.0487
Day 7	Responders, n (%)	10 (9.7)	38 (20.1)	42 (22.3)
	p-value[a]		0.0216	0.0066
Day14	Responders, n (%)	17 (16.5)	63 (33.3)	66 (35.1)
	p-value[a]		0.0024	0.0007
Day 21	Responders, n (%)	26 (25.2)	80 (42.3)	94 (50.0)
	p-value[a]		0.0049	<0.0001

[a] P-values are for comparison of placebo vs asenapine and placebo vs olanzapine based on Fisher's Exact test.
The denominator for percentages is the number of subjects in each treatment group with a non-missing responder status at that visit.
A subject is a YMRS responder at a given visit if they have a 50% decrease from baseline in YMRS total score at that visit.
Baseline is the last non-missing assessment on or prior to Day 1 (randomization).

Table 26 shows the change from baseline in CGI-BP severity of mania. Both active treatments showed significant results.

Table 26: Summary Day 21 change from baseline in CGI-BP severity of mania, LOCF – ITT

	Placebo (N = 103)	Asenapine (N = 189)	Olanzapine (N = 188)
Day 21, n	103	189	188
Baseline mean (SD)[a]	4.7 (0.79)	4.7 (0.86)	4.6 (0.75)
Day 21 mean (SD)	4.0 (1.54)	3.5 (1.41)	3.2 (1.16)
Mean change from baseline (SD)	-0.7 (1.34)	-1.2 (1.52)	-1.4 (1.20)
LS mean change from baseline[b] (SE)	-0.7 (0.13)	-1.2 (0.10)	-1.4 (0.10)
p-value[b]		0.0017	<.0001

Baseline is the last non-missing assessment on or prior to Day 1 (randomization). CGI-BP range = 1 (normal) to 7 (very severely ill).
[a] Baseline mean is the mean for those subjects completing the visit with a non-missing change score.
[b] Based on an ANCOVA model with treatment and pooled investigative site as fixed effects and baseline as a covariate. P-values are based on the difference in the LS means for asenapine and olanzapine treatments vs placebo.

Ancillary analyses

For the primary efficacy endpoint, the robustness of the results against potential bias caused by missing data was checked by:

• An observed case (OC) analysis.

• A mixed-model analysis using repeated measures.

Study A7501004

This study was the same as Study A7501005, conducted at the same time but conducted in different centres. It was instead conducted at 61 centres, including 32 in the US, 2 in Bulgaria, 6 in India, 2 Korea, 3 Malaysia, 3 Philippines, 2 Romania, 4 Russia and 7 in the Ukraine. All 61 centres randomized subjects.

Results

Participant flow

A total of 611 patients were screened and 488 were randomised. Of the 488 randomised patients, the ITT population comprised 480 patients with 94 taking placebo, 183 taking asenapine and 203 taking olanzapine. The trial was completed by 57 placebo patients (56.2%), 124 asenapine patients (67.0%) and 161 olanzapine patients (78.5%).

Outcomes

Both asenapine 5-10 mg bd and the active comparator (olanzapine) were more effective than placebo (Table 27).

Table 27: YMRS Total Score and Inferential Analysis of Change from Baseline LOCF ITT.

Visit		Placebo (N = 94)	Asenapine (N = 183)	Olanzapine (N = 203)
Baseline	Mean[a] (SD)	28.3 (6.32)	29.4 (6.72)	29.7 (6.64)
Day 21	Mean (SD)	20.4 (12.70)	7.7 (11.91)	14.9 (10.47)
	Mean Change (SD)	-7.9 (11.46)	-11.7 (11.34)	-14.8 (10.37)
Baseline	LS mean[b] (SE)	28.1 (0.59)	29.3 (0.42)	29.7 (0.40)
	95% CI[b]	(26.9, 29.2)	(28.5, 30.2)	(28.9, 30.5)
Day 21	LSM Change from Baseline [cb] (SE)	-7.8 (1.11)	-11.5 (0.80)	-14.6 (0.76)
	p-value[c]		0.0065	<0.0001

YMRS total score range= 0-60; higher scores indicate greater severity of symptoms.
Baseline is the last non-missing assessment on or prior to Day 1 (randomization).
[a] Baseline mean is the mean for those subjects completing the visit with a non-missing change score.
[b] Based on an ANOVA model with fixed effects for treatment and pooled investigative site.
[c] Based on an ANCOVA model with treatment and pooled investigative site as fixed effects and baseline as a covariate. P-values are based on the difference in the LS means for active treatment versus placebo.

Table 28 shows YMRS responders. Only olanzapine was significant.

Table 28: Summary of YMRS Responders, LOCF – ITT.

		Placebo (N = 94)	Asenapine (N = 183)	Olanzapine (N = 203)
Day 2	Responders, n (%)	3 (3.2)	9 (5.1)	19 (9.5)
	p-value[a]		0.5518	0.0606
Day 4,	Responders, n (%)	7 (7.4)	25 (3.7)	35 (17.2)
	p-value[a]		0.1646	0.0306
Day 7	Responders, n (%)	17 (18.1)	46 (25.1)	56 (27.6)
	p-value[a]		0.2262	0.0835
Day14	Responders, n (%)	26 (27.7)	66 (36.1)	92 (45.3)
	p-value[a]		0.1791	0.0049
Day 21	Responders, n (%)	32 (34.0)	78 (42.6)	111 (54.7)
	p-value[a]		0.1951	0.0011

[a] P-values are for comparison of placebo vs asenapine and placebo vs olanzapine based on Fisher's Exact test.
The denominator for percentages is the number of subjects in each treatment group with a non-missing responder status at that visit.
A subject is a YMRS responder at a given visit if they have a 50% decrease from baseline in YMRS total score at that visit.
Baseline is the last non-missing assessment on or prior to Day 1 (randomization).

Table 29 shows the change from baseline in CGI-BP severity of mania. Both active treatments showed significant results.

Table 29: Change from baseline to Day 21 in CGI-BP severity of mania, LOCF – ITT

	Placebo (N = 94)	Asenapine (N = 183)	Olanzapine (N = 203)
Day 21, n	94	183	203
Baseline mean (SD)[a]	4.5 (0.79)	4.6 (0.79)	4.6 (0.77)
Day 21 mean (SD)	3.6 (1.39)	3.3 (1.45)	3.0 (1.24)
Mean change from baseline (SD)	-0.8 (1.33)	-1.3 (1.43)	-1.5 (1.28)
LS mean change from baseline[b] (SE)	-0.8 (0.13)	-1.2 (0.10)	-1.5 (0.09)
p-value[b]		0.0116	<0.0001

[a] Baseline mean is the mean for those subjects completing the visit with a non-missing change score.
[b] Based on an ANCOVA model with treatment and pooled investigative site as fixed effects and baseline as a covariate. P-values are based on the difference in the LS means for asenapine and olanzapine treatments versus placebo.

Ancillary analyses

Statistical analysis of the LS mean changes from baseline in the YMRS total scores using the OC method and results of a mixed model analysis using repeated measures were consistent with the findings of the LOCF analysis.

The primary analysis was tested for a pooled-site by treatment interaction. A significant treatment by centre interaction was observed (p = 0.0136).

Post-hoc analyses under two different assumptions about site-to-site variability were performed.

The first assumption was that the site-to-site variation was atypical and that the treatment by centre interaction was driven by outliers. Five sites had large but not atypical responses (improvements over placebo more than 25 points). When two of these sites (4103 and 4125) were excluded from the analysis the treatment by centre interaction was no longer significant (p = 0.3411); however, asenapine was no longer significantly different from placebo (-10.64 asenapine vs -8.70 placebo, p = 0.1412).

The second assumption was based on a table of mean change and SD in YMRS scores by site. The responses for sites 4103 and 4125 were large but not unusual. Two analyses were performed under the assumption that the site-to-site variation was typical for this type of study: 1) the pre-specified secondary analysis using the model that included an interaction term and 2) a post-hoc analysis using a random effects model. The post hoc analysis using the random effects model was performed because of the large number of sites and the large between-site variability.

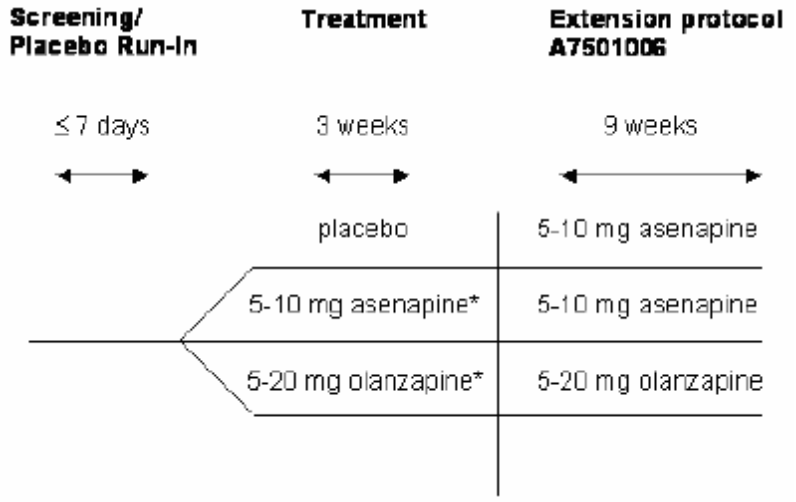
The LS means using the pre-specified model with the interaction term provided an unweighted mean in which each site contributed equally. This analysis showed that asenapine was statistically superior to placebo. The LS mean change from baseline was minus 11.39 for the asenapine group versus -8.59 for the placebo group (p = 0.0473). That is, a difference of 2.80 which is less than the non- inferiority limit of 4 set in Study A7501006 and is thus considered not clinically significant.

Studies related to Monotherapy - Maintenance of Clinical Improvement

Study A7501006

The trial design for Study A7501006 is shown in Figure 15. The trial was conducted in up to 123 investigation sites in 11 countries between 7 January 2005 and 28 June 2006.

Figure 15: Study A7501006 trial design



The primary objective of this trial was to demonstrate non-inferiority of the maintenance of effectiveness of asenapine, compared with olanzapine, in treatment of acute mania in subjects with manic or mixed episodes associated with bipolar I disorder for up to 12 weeks.

Secondary objectives included evaluating treatment effects of asenapine compared with olanzapine with respect to:

- overall clinician impression of severity and improvement,
- depression,
- psychotic symptoms,
- readiness to discharge,
- quality of life,
- treatment satisfaction,
- cognitive symptoms.

Study Participants

- Had a primary diagnosis of bipolar I disorder .
- Had completed studies A7501004 or A7501005 without major protocol violations and compliant with medication.

Treatments

Patients previously on asenapine or olanzapine continued on that treatment. Those previously on placebo on Day 1, received 5 mg asenapine bd; on Days 2 to 63, the daily dose could be adjusted within a dose range of 5 - 10 mg bd, based on efficacy, safety and tolerability.

Outcomes/endpoints

The primary efficacy endpoint was the change from baseline YMRS (of the feeder study) to Week 12.

Secondary endpoints included:

For mania: time to failure to maintain response; percent YMRS responders and remitters; change from baseline in severity of mania on CGI-BP; and change from previous state of mania on CGI-BP. For depressive symptoms: change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score; change from baseline in CGI-BP severity of depression; CGI-BP change from baseline state of depression; and modified

InterSePT Scale for Suicidal Thinking (ISST) total score.

For overall bipolar state: change from baseline in CGI-BP severity of overall bipolar state; change from previous state in CGI-BP overall bipolar state; time to discharge ready status from the Readiness to Discharge Questionnaire (RDQ); and time to full agreement from the RDQ.

For psychotic symptoms: change from baseline in each of the Positive and Negative Syndrome Scale (PANSS) Marder factor symptom scores and the PANSS total score.

Also analyses of cognitive symptom endpoints (change from baseline in each domain score of the cognitive symptoms battery) and outcome research endpoints (Short Form-36, version 2.0 [SF-36v2] and Treatment Satisfaction Questionnaire for Medication [TSQM]) were conducted.

Statistical considerations

There was no sample size determination.

Subjects participating in this study (A7501006) retained the same subject identification and randomization numbers assigned to each subject in the feeder trial.

Evaluator comment

There is some inconsistency in the labelling of days but of much more concern is the analysis procedure.

Baseline assessments were defined to be the most recent non-missing assessment prior to first dose of randomized therapy in the feeder trial unless otherwise specified.

The *Clinical Trial report* states:

The validity of combining data from the feeder studies was assessed for the primary efficacy endpoint by examination of the residual values from an analysis of covariance (ANCOVA) model with fixed effects for treatment and trial and baseline as a covariate included in the model.

The primary analysis was conducted using a one-sided test with alpha = 0.025 level of significance. All other hypothesis testing was conducted using two-sided tests with alpha = 0.05 level of significance. No adjustments for multiple comparisons were necessary since only two treatment groups (asenapine and olanzapine) were included in the efficacy analyses. Comparisons between asenapine and olanzapine treatment groups for all efficacy endpoints, other than that for the YMRS, were considered secondary and were used to support the findings of the primary analysis.

And under *Primary Efficacy Variables*:

The primary efficacy endpoint was the change from baseline in YMRS score at the Week 9 visit (Day 84 [12 weeks] since beginning randomized therapy) in the PP population. The non-inferiority limit was set at four points on the YMRS scale. An ANCOVA with fixed effects for treatment and investigative site (or pooled site) and baseline YMRS scores as a covariate was used to test the hypothesis of non-inferiority using a one-sided $\alpha = 0.025$ significance level. The primary treatment comparison between asenapine and olanzapine was based on the difference in the model based least square means (LSMEANs). Missing values for YMRS total score were not replaced. Centre-by-treatment interaction was investigated as secondary analyses. Type III sums of squares were used to test both main effects and interactions. Small centres were pooled to form pseudo-centres and the decisions regarding pooling were documented in the SAP prior to unblinding the data.

The robustness of the results against potential bias caused by missing data were checked by repeating the analysis using the ITT population by imputing missing values using the last observation carried forward (LOCF) method and by using a mixed model repeated measures analysis.

These statements are acceptable but:

Study A7501006 was to demonstrate non-inferiority of asenapine, compared to olanzapine. The primary endpoint was change from baseline at Week 9 in YMRS score PP population (non-inferiority margin 4 YMRS points).

An improvement in YMRS is a fall in the total score.

Non inferiority is shown if the improvement of the test (asenapine) has a difference from comparator (olanzapine) that with its one sided CI falls within 4 improvement points less than no difference (or the olanzapine score).

In their analysis results the sponsors state that before undertaking analysis the YMRS score only was improved[45] by 4 points, the rationale for comparing an improved YMRS score with the actual olanzapine score in an effort to show non-inferiority could not be found.

For non-inferiority tests [46]

$H_0 : T - S \leq -\delta$ vs $H_A : T - S > -\delta$ (T = test; S = standard)

The null hypothesis for the primary (non-inferiority) analysis is that the change from baseline (of the feeder study) in the YMRS is > 4 points greater for olanzapine (S) than asenapine (T). The alternative hypothesis is that the change from baseline in the YMRS is ≤ 4 points greater for olanzapine than asenapine.

$H_0 : S - T > 4$ i.e. $T-S > -4$ or $-\delta$

$H_A : S - T \leq 4$ i.e. $T - S \leq -4$ or $-\delta$

Instead of testing hypotheses, one can equivalently use the CI approach. It should be noted that when the CI approach is used to assess equivalence, the type I & II errors are reversed to those of conventional significance testing, because the null and alternative hypotheses are reversed…

The TGA-adopted EU guideline notes that:[47]

In order to demonstrate non-inferiority, the recommended approach is to pre-specify a margin of non-inferiority in the protocol. After study completion, a two-sided 95%

[45] Study A7501006 report states that "based on an ANCOVA model with treatment and pooled investigative site as fixed effects and baseline as a covariate. P-value and 97.5% CI are based on the difference in the LS means, calculated as asenapine-olanzapine. The YMRS Total Score was **reduced** by 4 points prior to calculating change from baseline for the asenapine group only. The analysis is based on the difference in the adjusted change from baseline score in the asenapine group versus the unadjusted score in the olanzapine group." *A reduction in YMRS score is an improvement.*
The statistical plan likewise states "Non-inferiority will be declared if the lower limit of the 97.5% confidence interval on the difference in the LS Means is ≤ 0. The difference tested will be Asenapine - Olanzapine." The YMRS total score used in the analysis for the asenapine group will be adjusted for each subject to account for the non-inferiority margin of 4 points on the YMRS scale (i.e., YMRS total score – 4) *the score is improved*; the score used in the analysis for the olanzapine group will be the unadjusted, raw YMRS total score.

[46] Hwang, Morikawa. Design Issues in Non-inferiority/Equivalence Trials Drug Information J 1999; 33: 1205-18.

[47] EMEA, Committee for Medicinal Products for Human Use (CHMP), 27 July 2005. Guideline on the Choice of the Non-Inferiority Margin, CPMP/EWP/2158/99.

confidence interval (or one-sided 97.5% interval) for the true difference between the two agents will be constructed. This interval should lie entirely on the positive side of the non-inferiority margin.

In addition, the TGA-adopted EU guideline states that:[48]

Statistical analysis is generally based on the use of confidence intervals.…..…

For non-inferiority trials a one-sided interval should be used. The confidence interval approach has a one-sided hypothesis test counterpart for testing the null hypothesis that the treatment difference (investigational product minus control) is equal to the lower equivalence margin versus the alternative that the treatment difference is greater than the lower equivalence margin.

This study did not demonstrate a difference between asenapine and olanzapine in maintenance of acute effectiveness in subjects who had acute manic or mixed Bipolar 1 episodes. The margin for no clinically significant difference has been indicated and it is not clear how or why the individual YMRS scores for subjects given asenapine were adjusted to account for the non-inferiority margin but not those of subjects given olanzapine.

Results

Participant flow

Of the 504 randomised patients, the subjects comprised 94 patients switched from placebo to asenapine, 181 taking asenapine and 229 taking olanzapine. The trial was completed by 50 switch patients (53.2%), 112 asenapine patients (61.9%) and 146 olanzapine patients (63.8%).

Outcomes

The results for the primary outcome are shown in Table 30.

Table 30: Day 84 Change from baseline YMRS total score, OC – PP and LOCF-ITT Day 84.

YMRS total score	**Asenapine N = 175**	**Olanzapine N = 222**
OC – Per-protocol n =	86	128
Baseline mean (SD)a	29.6 (6.13)	28.8 (5.39)
Day 84 mean (SD)	5.2 (6.00)	4.9 (5.34)
Mean change from baseline (SD)	-24.4 (8.72)	-23.9 (7.92)
LS mean Change (SE)**	*-27.3 (0.64)*	-23.7 (0.55)
97.5% CI**	*-Inf, -2.06*	_
p-value**	*<.0001*	
LOCF –ITT n =	175	222
Baseline Mean* (SD)	29.0 (6.05)	28.8 (5.89)
Day 84Mean (SD)	8.9 (9.21)	7.5 (7.70)
Mean Change (SD)	-20.1 (10.67)	-21.3 (9.57)
LS mean Change (SE)**	*-24.6 (0.65)*	-21.8 (0.61)
97.5% CI**	*-Inf, -1.19*	-

[48] EMEA, ICH Topic E9, Statistical Principles for Clinical Trials, 18 March 1998. Note for Guidance on Statistical Principles for Clinical Trials, CPMP/ICH/363/96.

p-value**	*0.0004*	

Baseline is the last non-missing assessment on or prior to Day 1 (randomization).
[a] Baseline mean is the mean for those subjects completing the visit with a non-missing change score.
*Based on an ANOVA model with fixed effects for treatment and pooled investigative site.
Based on an ANCOVA model with treatment and pooled investigative site as fixed effects and baseline as a covariate. P-value and 97.5% CI are based on the difference in the LS means, calculated as asenapine-olanzapine. ***The YMRS Total Score was reduced by 4 points prior to calculating change from baseline for the asenapine group only.* The analysis is based on the difference in the adjusted change from baseline score in the asenapine group versus the unadjusted score in the olanzapine group. Higher scores indicate greater severity of symptoms.

No summary of the change from Day 21 to Day 84 (the period of maintenance of change) was found. For entry into this study patients only had to complete the initial study without major protocol violation (no selection by response or investigator opinion). Overall responders at Day 84 were 77/379 (20.3%) for asenapine and 118/395 (29.9%) for olanzapine.

Ancillary analyses

The primary analysis was tested for a pooled-site by treatment interaction. A significant treatment by centre interaction was observed (p = 0.0006). This interaction complicated the interpretation of the results, so post-hoc analyses were performed.

The first post-hoc analysis was an examination of whether the site variation in response was atypical. The mean change in YMRS total scores for individual sites ranged from +8 to -48. This variation among sites was reduced prior to analysis since small centres were pooled for statistical analysis. The range in responses over pooled centres as used in the primary analysis model was well within expectations for a 12 week study (from –10.0 to –42.3).

The second set of post-hoc analyses was to examine the estimated LS means and the significance of the comparison between asenapine and olanzapine across 3 alternative models of site effects.

Study A7501007

Study A7501007 was an extension of study A7501006. To enter this study patients had to:

- have completed Trial A7501006 without a major protocol violation;
- been compliant in the management of their disease;
- and to have been willing to refrain from the use of psychotropic medications during the treatment period, except for those specified in the protocol.

Of 308 patients who completed Study A7501006 only 218 entered this extension study and continued on the same treatment, (32 on placebo/asenapine, 79 on asenapine and 107 on olanzapine).

Objectives

There were no primary efficacy endpoints; all efficacy endpoints were considered secondary for this study. Secondary analyses supportive of efficacy in mania used the ITT population.

Hypotheses were tested only for YMRS responders and remitters (using Fisher's Exact test) and Time to response failure (using the log-rank test). All other variables were presented

Outcomes

180 patients (76 asenapine, 104 olanzapine) entered the ITT population. 133 patients completed the trial (13 placebo/asenapine, 52 asenapine and 68 olanzapine). Overall 25/175 (14.3%) on asenapine and 39/222 (17.6%) had ≥ 52 weeks treatment. Mean (SD) duration treatment was asenapine (312.8days); olanzapine 300.3days (98.10). A summary of the YMRS total score is shown at Table 31.

Table 31: Summary of YMRS Total Score, OC and LOCF – ITT.

	Asenapine (N = 79)	**Olanzapine (N = 107)**
OC Week 52, n	45	63
Baseline Mean (SD)	30.3 (7.32)	29.6 (5.66)
Mean (SD)	1.7 (3.41)	1.3 (2.78)
Mean Change (SD)	-28.6 (8.10)	-28.2 (6.79)
LOCF Week 52, n	76	104
Baseline Mean (SD)	29.5 (6.64)	29.3 (5.77)
Mean (SD)	3.8 (7.21)	3.2 (5.96)
Mean Change (SD)	-25.7 (10.41)	-26.1 (8.48)

A summary of responders and remitters is shown at Table 32.

Table 32: Summary of YMRS responders and remitters, OC – ITT.

	Asenapine (N = 79)	Olanzapine (N = 107)
OC Week 52, n	45	63
Responders, n (%)	44 (97.8)	62 (98.4)
p-value[a]		1.0000
Remitters, n (%)	44 (97.8)	62 (98.4)
p-value[a]		1.0000

The denominator for percentages is the number of subjects in each treatment group with a non-missing status at that visit.
A subject is a YMRS responder at a given visit if they have a 50% decrease from baseline in YMRS total score at that visit.
A subject is a YMRS remitter at a given visit if they have a YMRS total score of 12 or lower at that visit.
Baseline is the last non-missing assessment on or prior to first dose of double-blind study medication.
Study endpoint is the last non-missing post-baseline assessment on or prior to last double-blind dose date + 3days.
[a] p-values are for comparison of asenapine vs olanzapine based on Fisher's Exact test.

Days to response failure was only calculated for subjects who achieved responder status.

The Kaplan-Meier Estimation of percent response failure uses for the number at risk, not the number of responders at previous visit (overall asenapine 63, olanzapine 93) but the ITT population (asenapine 76, olanzapine 104) some of whom, having not responded, would not be at risk of response failure.

Interpretation of the p-value from this table for comparison of asenapine vs olanzapine based on a log-rank test is thus uncertain. The sponsor interprets it as

Time to response failure among those who responded was statistically significantly longer in the asenapine group than in the olanzapine group (p = 0.0127).

The evaluator did not accept this interpretation.

Studies related to Use in Combination- Acute Treatment and Maintenance

Study A7501008

The design for Study A7501008 is shown at Figure 16. The trial was conducted in 14 centres (2 in Australia) in 8 countries between 30 May 2005 and 28 February 2007.

Figure 16: Study A7501008 design

Objectives

The primary objective was to demonstrate clinical and statistical superiority of asenapine

compared to placebo in subjects who have not completely responded to continuing treatment with lithium or valproate to treat acute manic or mixed episodes associated with bipolar I disorder.

Secondary objectives included evaluating the adjunctive treatment effects of asenapine compared to placebo with respect to:

• Overall clinical impression of severity of and improvement in, mania, depression and overall bipolar state,

• Depression,

• Psychotic symptoms,

• Anxiety,

• Readiness to discharge,

• Quality of life,

• Cognitive function,

• Suicidal thinking.

The null hypothesis for all endpoints was that the results observed in the asenapine treatment group are no different from those in the placebo treatment group. The alternative hypothesis is the results for the asenapine and placebo treatments groups are different. The parameter tested by this hypothesis is the treatment group means for all parametric analyses, treatment group medians for non-parametric analyses and treatment group proportions for binary endpoints.

Participants

Inclusion criteria

To have been eligible for this trial, subjects must have:

- Bipolar I disorder, current episode manic, or mixed that began < 3 months prior to screening;
- a YMRS score ≥ 20 at screening and at baseline;
- a history of ≥ 1 previous moderate-to-severe mood episode with or without psychotic features in the previous 5 years (manic or mixed);
- patients continuously treated with lithium or valproate for at least 2 weeks prior to screening, with a therapeutic trough blood level of lithium (0.6-1.2 mmol/L) or valproate (50-125 µg/mL) at screening; and

Exclusion criteria

- a primary diagnosis other than bipolar I disorder;
- schizophrenia, schizoaffective disorder, or other psychotic disorders;
- borderline personality disorder, antisocial personality disorder, or mental retardation
- an imminent risk of self-harm (an ISST-mod score of 2 on Item 7, 10, or 11 at screening), or harm to others;
- narrow angle glaucoma;
- a seizure disorder beyond childhood or were taking anticonvulsants to prevent seizures;
- during the previous 12 months had ≥ 9 a Major Depressive, Manic, Mixed, or Hypomanic Episode, demarcated by either full remission or by a switch to the opposite polarity;

- hospitalized for ≥ 3 weeks for the manic or mixed episode;
- unable to reduce his or her daily lorazepam equivalent intake;
- patients who had received clozapine within 12 weeks or a monoamine oxidase inhibitor within 2 weeks of baseline.

Treatments

On Day 1, subjects received asenapine 5 mg bd or placebo bd. On Days 2 to 84, double-blinded asenapine (or placebo) was dosed flexibly based on efficacy, safety and tolerability. All subjects continued open treatment with lithium or valproate for the duration of the trial; switching from one mood stabilizer to the other was prohibited. During randomized therapy, mood stabilizer dose adjustments were made based on targeted trough serum levels (lithium [0.6-1.2 mEq/L] or valproate [50-125 µg/mL]) obtained at the discretion of the investigator. An exception to this scenario was that dose reductions were permitted in the event of AEs due to the mood stabilizer.

Outcomes/endpoints

The primary endpoint was the change from baseline to Week 3 in the YMRS LOCF score, (ITT) data set:

There were multiple secondary efficacy endpoints

- Change from baseline in YMRS total score,
- YMRS responder rates,
- YMRS remitter rates,
- Change from baseline in CGI-BP Severity of Mania,
- Change from baseline in the MADRS total score,
- Change from baseline in CGI-BP Severity of Depression,
- CGI-BP Change from Baseline State of Depression,
- Change from baseline in the total score on the InterSePT Scale for Suicide Thinking (ISST) (Modified version),
- Change from baseline in CGI-BP Severity of Overall Bipolar Illness,
- CGI-BP Change from Baseline State of Overall Bipolar Illness,
- Days to Full Agreement, to each of RDQ Items 1 – 5,
- Days to discharge ready status,
- Change from baseline in PANSS Marder factor positive symptom score,
- Change from baseline in PANSS Marder factor negative symptom score
- Change from baseline in PANSS Marder factor disorganized thought symptom score,
- Change from baseline in PANSS Marder factor hostility/excitement symptom score,
- Change from baseline in PANSS Marder factor anxiety/depression symptom score, Change from baseline in PANSS Total score,
- Change from baseline in each of HAM-A Total and subscales (Psychic and Somatic) scores,
- Change from baseline in each of the Central Nervous System Vital Signs (CNSVS) Neurocognitive Test Battery domain scores.

Statistical considerations

A sample size of 320 subjects (160 asenapine: 160 placebo) had 90% power to detect a difference in means of at least 4 points on the YMRS change score assuming a common standard deviation of 11 points using a 2 group t-test with a 0.05 two-sided significance level.

Eligible subjects were randomly assigned in a 1:1 ratio, to one of the two double-blinded treatments: flexible-dose asenapine or placebo.

All hypothesis testing was conducted using two-sided tests with $\alpha = 0.05$ level of significance. The primary analysis compared asenapine with placebo using a fixed effects ANCOVA with baseline YMRS scores and site as covariates. Sensitivity to dropout was explored using LOCF analysis, observed case (OC) analysis and mixed modelling. The primary model used the baseline score as a covariate and allowed for variability due to centre and treatment. Centre-by-treatment interaction was investigated in a secondary analysis. Type III sums of squares were used to test both main effects and interactions.

Small centres were pooled to form single aggregated centres and the decisions regarding pooling were documented in the statistical analysis plan (SAP) prior to unblinding the data.

The robustness of the results against potential bias caused by missing data was checked by 2 methods: 1) an observed case (OC) analysis and 2) a mixed model analysis using repeated measures.

Results

Participant flow

Of 438 patients screened 326 were randomised. Of the 438 randomised patients, the ITT population comprised 430 patients with 163 taking placebo and 155 taking asenapine. The trial was completed by 55 placebo patients (32.9%) and 61 asenapine patients (38.4%).

Outcomes

The primary efficacy endpoint results are shown in Table 33. Asenapine 5-10 mg was more effective than placebo in the primary endpoint.

Table 33: Summary of change from baseline to Day 21 in YMRS total score, LOCF – ITT.

YMRS total score	Placebo N = 163	Asenapine N = 155
Baseline mean (SD)[a]	28.2 (5.76)	28.0 (5.65)
Day 21 mean (SD)	20.5 (10.38)	18.2 (10.28)
Mean change from baseline (SD)	-7.7 (9.61)	-9.7 (10.06)
LS mean change from baseline[b] (SE)	-7.9 (0.76)	-10.3 (0.79)
p-value[b]		0.0257

Baseline is the last non-missing assessment on or prior to first dose of double-blind study medication.
[a] Baseline mean is the mean for those subjects completing the visit with a non-missing change score.
[b] Based on an ANCOVA model with treatment and pooled investigative site as fixed effects and baseline as a covariate. P-values are based on the difference in the LS means for asenapine versus placebo.

In the ITT populations, by Day 84 39/155 (25.2%) randomised to asenapine and 33/163 (20.2%) randomised to placebo were responders.

Ancillary analyses

Analysis of the LS mean OC changes from baseline in the YMRS total scores showed no statistically significant difference between the asenapine and placebo groups ($p = 0.2279$). Nor, with an additional MMRM analysis using an unstructured variance model, was there a statistically significant difference ($p = 0.0991$) in the change from baseline to Day 21 in YMRS total score, between the asenapine and placebo groups. A treatment by centre interaction was not seen.

Studies related to Use in Combination - Maintenance of Clinical Improvement

Study A7501009

Study A7501009 was a continuation of Study 7501008. To enter this study patients had to:

- have completed Trial A7501008 without a major protocol violation;
- been compliant in the management of their disease;
- and able to completely avoid the use of psychotropic medications, with the exception of antidepressants as specified in the protocol;

Of 116 patients who completed Study A7501008 only 77 entered this extension study and continued on the same treatment (41 on asenapine and 36 on placebo). Of these, 71 patients (38 asenapine, 33 placebo) entered the ITT population. Only 34 patients completed the trial (19 asenapine, 15 placebo). Overall 7/163 (4.3%) on placebo and 9/155 (5.8%) on asenapine had ≥ 365days treatment.

All subjects could receive benzodiazepine and/or antidepressant rescue medication as needed.

Objectives

The primary objective was to characterize the long-term safety and tolerability of asenapine in bipolar I disorder patients who had not completely responded to continuing treatment with lithium or valproate for the treatment of an acute manic or mixed episodes upon enrolment into the 12 week lead in study, A7501008.

Also described as a primary objective was to characterize the long-term maintenance of effect of asenapine on YMRS and MADRS scores, after the initial 12 weeks of treatment (in the A7501008 lead-in trial) with adjunctive therapy. At the end of the study no statistical analyses were performed.

Outcomes

The summary YMRS total score is shown at Table 34.

Table 34: Summary of YMRS Total Score, OC ITT.

	Placebo N = 33	**Asenapine N = 38**
Week 52, n	13	13
Baseline Mean* (SD)	29.2 (7.69)	27.7 (6.21)
Mean (SD)	2.7 (3.95)	5.7 (7.91)
Mean Change (SD)	-26.5 (7.51)	-22.0 (11.04)

Baseline is the last non-missing assessment on or prior to first dose of double-blind study medication.
Study Endpoint is the last non-missing post-baseline assessment on or prior to last double-blind dose date + 3 days.
*Baseline mean is the mean for those subjects completing the visit with a non-missing change score

This OC greater fall from a higher initial score with placebo contrasts with the LOCF results (Table 35).

Table 35: Summary of change from baseline to Week 52 in YMRS and MADRS total scores, LOCF - ITT

	Placebo (N = 33)	Asenapine (N = 38)
Y-MRS total score		
Baseline mean (SD)[a]	28.0 (6.12)	27.6 (6.30)
Week 52 mean (SD)	8.4 (9.77)	10.3 (10.97)
Mean change from baseline (SD)	-19.7 (11.81)	-17.2 (13.65)
MADRS total score		
Baseline mean (SD)[a]	9.6 (8.86)	10.1 (7.59)
Week 52 mean (SD)	5.8 (8.09)	6.8 (9.31)
Mean change from baseline (SD)	-3.9 (7.71)	-3.3 (9.75)

Baseline is the last non-missing assessment on or prior to first dose of double-blind study medication.
[a] Baseline mean is the mean for those subjects completing the visit with a non-missing change score.

Analysis performed across trials (pooled analyses and meta-analysis)

Study INT 00039919 was an exposure-response analysis relating asenapine exposure to YMRS total score in bipolar disorder. Data included two Phase 3 placebo-controlled studies A7501004 and A7501005 in patients with an acute or mixed episode associated with bipolar 1 disorder. Doses started at 10 mg bd on Day 1 but then adjusted prn to 5-10 mg bd for up to 3 weeks. Models were developed to characterize the ER relationship between asenapine exposure and the YMRS response. Covariate effects, other than the Race effect on the terminal elimination rate constant in the PK model, were not considered. The ER model was formulated in two steps:

1. The placebo sub-model was chosen considering the homogeneity of the residual variance and the structure of the population mean prediction. A power model in TIME was considered adequate to describe the placebo patients' profiles.

2. Drug effect sub-models (4) which related asenapine plasma concentrations to YMRS responses were evaluated. Ultimately, a log-linear drug submodel was selected as the most adequate model; it had the lowest estimate of residual variability.

Thus an exposure-response relationship was established between asenapine PK and the YMRS response. A delay in onset of effect was observed relative to PK accumulation of approximately 3-4 days. While both 5 and 10 mg bd were predicted to produce a response that was significantly different from placebo, 10 mg bd was likely to result in a larger response than 5 mg bd. The predictive check confirmed that effect site exposure provided the best fit to the data. Dropout models were not formulated for these data.

Evaluator's overall conclusions on clinical efficacy in bipolar disorder

Acute treatment of mania or mixed episodes in monotherapy

Two studies were submitted: one (A7501005) that was validated by olanzapine, showed a clinically significant difference in YMRS total score at 3 weeks (5.3) between asenapine and placebo; however the other study (A7501004) at 3.7 did not quite reach the clinically significant difference of 4 as defined by the non-inferiority margin in study A7501006. Further, a significant treatment by centre interaction was observed ($p = 0.0136$). When the relevant centres were excluded from analysis there was either no difference from placebo or no clinically significant difference in efficacy. On the data provided olanzapine appears marginally better than asenapine however there were no statistical comparisons between active treatments.

Maintenance of clinical improvement in monotherapy

In their statistical analysis of the primary endpoint for Study A7501006, the YMRS score was adjusted for each subject to account for the non-inferiority margin of 4 points on the YMRS scale; the score used in the analysis for the olanzapine groups was the unadjusted, raw YMRS total score. The sponsor should be required to justify why this adjustment was performed.

Justification of the choice of non-inferiority margin was also requested as it appears quite wide and larger than the mean difference from placebo seen in the acute treatment studies. This would have the effect of reducing the ability of the study to detect differences between asenapine and olanzapine.

The treatment by centre interaction present in Study A751004 persisted in this study due to the same study sites. The significance of this interaction is unclear.

Study A7501007 had no statistical analysis of the principal parameter used in other studies YMRS total score. This was primarily a safety study however long-term efficacy of asenapine compared with olanzapine was assessed as a secondary objective. Mean changes from baseline to trial endpoint in YMRS total score were -25.8 for asenapine vs -26.1 for olanzapine. Responder and remitter rates were also similar for the two actives. This study had a very high withdrawal rate with few subjects completing the full 52 weeks of exposure. The sponsor has claimed that in this study, time to response failure among those who responded to treatment was statistically significantly longer in the asenapine group than in the olanzapine group ($p = 0.0127$). This was not accepted by the evaluator because in determining the time to response failure, the source table uses as the number at risk, not the number of responders but the ITT population some of whom, having not responded, would not be at risk of response failure.

Acute treatment of mania or mixed episodes in combination with lithium or sodium valproate

Study A7501008 was submitted to support this claim. There was no active comparator to validate the study. While statistically superior to placebo, the efficacy results were smaller than seen with asenapine monotherapy (at 3 weeks difference LSMs = 2.4 and 12 weeks difference LSMs = 3.4). This may reflect a more resistant population as these subjects had not adequately responded to monotherapy lithium or valproate. Confirmatory analyses did not consistently demonstrate statistical significance from placebo but all trended towards asenapine as being more effective than placebo when in combination with either lithium or valproate. Remitter rates and CGI-BP were statistically significantly in favour of asenapine.

Maintenance of clinical improvement in combination with lithium or sodium valproate

Among the study participants in Study A7501009, the difference between those receiving asenapine and those on placebo favoured asenapine at Week 12 by 0.9 and by Week 52 patients who had asenapine added to their lithium or valproate did worse than those without it by 2.0.

This study was small and had substantial differences with reasons for discontinuation between the placebo and asenapine groups. Discontinuation due to withdrawal of consent, loss to follow-up and lack of efficacy were more frequent in the placebo group while discontinuation due to adverse events was more frequent in the asenapine group. Only 13 subjects in each group completed the 52 weeks and among that small sample there was an apparent trend towards those taking placebo doing better, however given the high withdrawal rates and small numbers of subjects this result is irrelevant to a determination of longer term efficacy

The numbers completing the studies plus extension were small:

Study A7501007 - overall completed; asenapine 52/379 (13.7%); olanzapine 68/395 (17.2%); placebo/asenapine 13/202 (6.4%),

Study A7501009 - overall completed; asenapine 19/158 (12.0%); placebo 15/167 (9.0%).

Safety

Introduction

Safety data from 60 completed studies using sublingual asenapine were included in an analysis of safety. Serious adverse event data was also available from 4 incomplete studies. Safety data from the oral asenapine studies were not integrated into the safety analysis. A total of 4565 subjects received asenapine sublingual formulation in the completed studies including 3457 patients in Phase 2 and 3 studies. Within the proposed dose range 1301 subjects have received asenapine for at least 6 months and 779 have received asenapine for at least 12 months.

Under clinical safety all results from therapeutic levels of exposure (safety population) have been accepted.

Some studies used sub-therapeutic doses while others included patients with disorders other than schizophrenia. They included pharmacology studies 041001 and 041007 which used sub-therapeutic doses and studies 041009,041012, 041014 and A7501022 that included patients other than schizophrenics and the 6 week schizophrenia studies 041002 and 041013 which used sub-therapeutic doses and long term “schizophrenia” studies 25517 and 25520 that included patients other than those with schizophrenia.

There were a number of safety related cross-study reports:

- Study INT00102764: Exploratory Exposure Response Analyses of Extrapyramidal Symptoms (EPS) Based on Phase 2 and Phase 3 Trials for Asenapine
- Study INT00100345: Evaluation of QT Prolongation in Asenapine Phase 3 Studies
- Study 754-0046: Exposure-Response Analysis to Assess the Effect of Asenapine, Quetiapine (Seroquel) or Placebo Administration on the QTc Interval in Patients with Schizophrenia (A7501001)
- Study INT00036960: Exposure-Response Analysis to Assess the Effect of Asenapine Administration on the QTc Interval in Patients with Schizophrenia (Phase 3 ACTAMESA Study)
- Study INT00100345: Evaluation of QT Prolongation in Asenapine Phase 3 Studies

Patient exposure

A summary of trial groupings used for the safety data is shown as Table 36 and the numbers of patients involved are shown at Table 37. The summary of duration of exposure is presented at Table 38.

Table 36: Summary of Trial Groupings used for Safety Data Summarization.

Trial Type / Description	Cohort	Trials Included
Phase 2/3 Trials – Sublingual Formulation		
Short-term Schizophrenia (6-weeks)	A1	041002, 041013, 041004, 041021, 041022, 041023
Long-term Schizophrenia (> 6 weeks)	B1	041512, 041513, 25517, 25520, 25543, 25544, A7501012
3-Week Bipolar Mania	C1	A7501004, A7501005
Long-term Bipolar Mania (>3 weeks)	D1	A7501006, A7501007, A7501008, A7501009
Combined Indications (Schizophrenia and Bipolar Mania)	E1	041002, 041004, 041013, 041021, 041022, 041023, 041512, 041513, 25517, 25520, 25543, 25544, A7501004, A7501005, A7501006, A7501007, A7501008, A7501009, A7501012, 041500, 041505, 041502, 041590
Clinical Pharmacology Trials – Sublingual Formulation		
Healthy Volunteers	F1	25509, 25510, 25511, 25512, 25514, 25516, 25521, 25522, 25525, 25526, 25527, 25528, 25529, 25532, 25533, 25537, 25540, 25542, 25545, 25546, A7501015, A7501016, A7501017, A7501018, 041026, 041028, 041029, 041030, 041033
Patients	G1	041001, 041007, 041009, 041012, 041014, A7501001, A7501024, A7501022

Table 37: Number of Subjects in Completed Phase 2/3 Trials Included in the Summary of Clinical Safety.

Trial Description/ Number	PBO	Asenapine						Risp	Olan	Halo
		<5 mg BID	5 mg[a] BID	10 mg[a] BID	5-10 mg[b] BID	5-10 mg BID total[c]	All			
3-week Bipolar Mania (cohort C1)										
A7501004	98				185	185	185		205	
A7501005	105				194	194	194		189	
Total	**203**				379	**379**	379		**394**	
Long-term Bipolar Mania (>3 weeks – 1 year) (cohort D1)										
A7501006 (ext of A7501004, A7501005) / A7501007 (ext of A7501006)					181 *94*[f]	181 ***94***[f]	181 *94*[f]		229	
A7501008 and A7501009 (ext)	**166**				158	**158**	158			
Total	166				433	433	433		229	
All bipolar mania trials										
Total	**369**	0	0	0	631	**631**	631	0	**394**	0
OVERALL TOTAL	**1064**	**298**	274	208	2677	**3159**	3457	**120**	**1139**	**115**

[a] fixed doses
[b] flexible doses
[c] asenapine doses of 5-10 mg bd fixed and flexible
[d] asenapine doses were 0.2, 0.4 and 0.8 mg bd
[e] asenapine doses were 1.6, 2.4 mg bd
[f] placebo subjects that continued into the long-term extension and then received asenapine are counted in the placebo column for the acute phase and in the asenapine column for the long-term extension. For example, 94 subjects received placebo in A7501004 or A7501005 and received 9 weeks of asenapine in A7501006, 181 subjects continued asenapine treatment from the randomized 3-week bipolar trials into the extension trial and received asenapine for 12 weeks total
[g] Subjects were randomized to either asenapine or placebo after a 26-week open-label period during which they all received asenapine. Subjects randomized to placebo were counted in both the placebo group and the asenapine group.
Risp=risperidone 3 mg bd, Olan=olanzapine 10-20 mg OD for schizophrenia trials, 5-20 mg OD for bipolar mania trials, Halo=haloperidol 4 mg bd
bold numbers represent unique subjects.

Table 38: Summary of duration of exposure to asenapine (all subjects).

	Schizophrenia trials (N=2826)	Bipolar mania trials (N=631)
	n (%)	n (%)
1 day or less	32 (1.1)	18 (2.9)
2 days to ≤1 week	156 (5.5)	81 (12.8)
>1 week to ≤4 weeks	506 (17.9)	214 (33.9)
>4 to ≤12 weeks	618 (21.9)	148 (23.5)
>12 to ≤26 weeks	431 (15.3)	50 (7.9)
>26 to ≤52 weeks	629 (22.3)	79 (12.5)
More than 52 weeks	454 (16.1)	41 (6.5)

Adverse events

An overview of adverse events is provided as Table 39. Individual AEs associated with asenapine in the combined Phase 2/3 trials (Cohort E1) are shown at Table 40.

Table 39: Overview of adverse events (combined Phase 2/3 trials, cohort E1).

Adverse Event Category n (%)	Placebo (N=1064)	Asenapine			Risp 3 mg BID (N=120)	Halo 2-8 mg BID (N=115)	Olan 5-20 mg QD (N=1139)
		<5 mg BID (N=298)	5-10 mg[a] BID (N=3159)	All (N=3457)			
Any adverse event	708 (66.5)	246 (82.6)	2484 (78.6)	2730 (79.0)	105 (87.5)	96 (83.5)	893 (78.4)
Related AEs	397 (37.3)	134 (45.0)	1792 (56.7)	1926 (55.7)	64 (53.3)	75 (65.2)	657 (57.7)
Severe AEs	90 (8.5)	59 (19.8)	420 (13.3)	479 (13.9)	21 (17.5)	10 (8.7)	142 (12.5)
SAEs	107 (10.1)	50 (16.8)	491 (15.5)	541 (15.6)	21 (17.5)	13 (11.3)	136 (11.9)
Deaths	1 (0.1)	2 (0.7)	17 (0.5)	19 (0.5)	0	1 (0.9)	5 (0.4
Discontinuations from any AE/SAE[b]	144 (13.5)	57 (19.1)	549 (17.4)	606 (17.5)	28 (23.3)	16 (13.9)	148 (13.0)
D/C'd from SAEs	62 (5.8)	16 (5.4)	235 (7.4)	251 (7.3)	12 (10.0)	6 (5.2)	62 (5.4)

[a] fixed and flexible doses [b] data obtained from action taken on adverse event case report form

Table 40: Incidence of AEs potentially associated with asenapine (occurred at ≥ 2% and were ≥ 2 x the incidence of placebo in the short-term trials) for the combined Phase 2/3 trials (cohort E1).

Adverse Event n (%)	Placebo (N=1064)	Asenapine			Risp 3 mg BID (N=120)	Halo 2-8 mg BID (N=115)	Olan 5-20 mg QD (N=1139)
		<5 mg BID (N=298)	5-10 mg[a] BID (N=3159)	All (N=3457)			
Sedation	43 (4.0)	6 (2.0)	252 (8.0)	258 (7.5)	8 (6.7)	6 (5.2)	146 (12.8)
Somnolence	26 (2.4)	16 (5.4)	363 (11.5)	379(11.0)	5 (4.2)	3 (2.6)	118 (10.4)
Akathisia	30 (2.8)	2 (0.7)	228 (7.2)	230 (6.7)	6 (5.0)	19 (16.5)	52 (4.6)
Hypoaesthesia oral	7 (0.7)	6 (2.0)	108 (3.4)	114 (3.3)	0	0	3 (0.3)
Weight increased	11 (1.0)	1 (0.3)	266 (8.4)	267 (7.7)	6 (5.0)	3 (2.6)	222 (19.5)
Dystonia	5 (0.5)	1 (0.3)	56 (1.8)	57 (1.6)	1 (0.8)	11 (9.6)	8 (0.7)
Increased appetite	6 (0.6)	5 (1.7)	60 (1.9)	65 (1.9)	0	0	48 (4.2)
Parkinsonism	14 (1.3)	0	120 (3.8)	120 (3.5)	0	19 (16.5)	18 (1.6)

[a] fixed and flexible doses

Individual adverse events with asenapine for the 6-week bipolar studies (Cohort A1) are shown in Table 41.

Table 41: Summary of treatment related AEs with incidence ≥ 2% in any asenapine treatment group and ≥ twice the incidence for placebo (6 week non- bipolar studies - Cohort A1).

Preferred term	Placebo (N=1064)	Asenapine			Risperidone 3 mg bd (120)	Olanzapine 10-20 mg OD (194)	Haloperidol 4 mg bd (115)
		5 mg bd Fixed (274)	10 mg bd fixed (208)	5-10 mg bd flexible (90)			
Increased appetite	3[0.6]	7[2.6]	0	2[2.2]	0	4[2.1]	0
Akathisia	10[2.0]	9[3.3]	21[**10.1**]	2[2.2]	4[3.3]	6[3.1]	15[**13.1**]
Dystonia	2[0.4]	6[2.2]	4[1.9]	4[**4.4**]	1[0.8]	0	10[**8.7**]
Parkinsonism	7[1.4]	8[**2.9**]	5[2.4]	1[1.1]	0	1[0.5]	16[**13.9**]
Somnolence	9[1.8]	22[**8.0**]	11[5.3]	3[3.3]	3[2.5]	10[5.2]	1[0.9]
Oral hypoaesthesia	3[0.6]	15[5.5]	13[**6.3**]	1[1.1]	0	0	0
Fatigue	8[1.6]	9[**3.3**]	3[1.4]	2[2.2]	8[**6.7**]	6[3.1]	0
Weight increase	1[0.2]	5[1.8]	3[1.4]	5[**5.6**]	2[1.7]	10[**5.2**]	1[0.9]

A subject with multiple occurrences of a given event is counted only once in that SOC/HLGT/preferred term category.
Treatment−related (S)AEs are those with relationship to drug marked as Possible, Probable or Definite.

In comparing the incidence of akathisia between fixed doses and including sub-therapeutic doses (0.7%), the sponsor noted a dose related trend to increase with increased dose. It cannot be ignored, however this trend in treatment related akathisia does not follow into flexible dosing where the incidence is similar to placebo and both are greater than the effect of sub-therapeutic doses.

A summary of adverse events with asenapine in short term bipolar studies (Cohort C1) is shown in Table 42.

Table 42: Summary of treatment related AEs with incidence ≥ 2% in asenapine treatment group and ≥ twice the incidence for placebo (short term 3 week bipolar mania studies - Cohort C1).

Preferred term	Placebo (N = 203)	Asenapine 5-10 mg bd flexible (379)	Olanzapine 10-20 mg OD (394)
Increased appetite	2[1.0]	15[4.0]	21[5.3]
Anxiety	2[1.0]	8[2.1]	4[1.0]
Dystonia	2[1.0]	9[2.4]	4[1.0]
Tremor	2[1.0]	9[2.4]	4[1.0]
Dizziness	6[3.0]	39[10.3]	26[6.6]
Dysgeusia	1[0.5]	9[2.4]	0
Sedation	8[3.9]	50[13.2]	61[15.5]
Somnolence	3[1.5]	37[9.8]	34[8.6]
Dyspepsia	1[0.5]	9[2.4]	8[2.0]
Vomiting	3[1.5]	12[3.2]	2[0.5]
Hypoaesthesia oral	1[0.5]	17[4.5]	2[0.5]
Dry mouth	2[1.0]	13[3.4]	34[8.6]

Weight increased	1[0.5]	17[4.5]	32[8.1]

.Treatment−related (S)AEs are those with relationship to drug marked as Possible, Probable or Definite.
A subject with multiple occurrences of a given event is counted only once in that SOC/HLGT/preferred term category.

The time to onset of oral hypoaesthesia is short and it is persistent. This is hardly surprising given the known local anaesthetic effect, the much lower incidence and duration in flexible dosing is difficult to explain.

Serious adverse events and deaths

The most common AE leading to death was suicide (12 total, 8 asenapine 5-10 mg bd [0.2%], 4 olanzapine [0.4%]). There were 3 drug overdoses that led to death, 2 in the asenapine 5-10 mg group and 1 in the olanzapine group. Deaths considered possibly related by investigators were 2 suicides and 1 suicide attempt on asenapine and 1 neonatal death with drug exposure during pregnancy. A higher attempted and completed suicide rate is expected in both disorders compared to the overall population. Serious adverse events (SAEs) in combined Phase 2/3 trials (Cohort E1) by MedDRA System Organs Class (SOC) and High Level Group Term (HLGT) are shown at Table 43 and by Preferred Term (PT) in Table 44.[49]

Table 43: SAEs with incidence ≥1% in asenapine 5-10 mg (combined Phase 2/3 trials, cohort E1)

Adverse Event (SOC/HLGT) n (%)	Placebo (N=1064)	Asenapine			Risp 3 mg BID (N=120)	Halo 2-8 mg BID (N=115)	Olan 5-20 mg QD (N=1139)
		<5 mg BID (N=298)	5-10 mg[a] BID (N=3159)	All (N=3457)			
Any SAE	107 (10.1)	50 (16.8)	491 (15.5)	541 (15.6)	21 (17.5)	13 (11.3)	136 (11.9)
Psychiatric Disorders	91 (8.6)	42(14.1)	406 (12.9)	448 (13.0)	15 (12.5)	12 (10.4)	109 (9.6)
Schizophrenia and other psychotic disorders	54 (5.1)	41(13.8)	284 (9.0)	325 (9.4)	12 (10.0)	12 (10.4)	64 (5.6)
Suicidal and self-injurious behaviours	4 (0.4)	3 (1.0)	47 (1.5)	50 (1.4)	2 (1.7)	1 (0.9)	21 (1.8)
Manic and bipolar disorders and disturbances	26 (2.4)	0	45 (1.4)	45 (1.3)	0	0	20 (1.8)
Depressed mood disorders and disturbances	7 (0.7)	0	43 (1.4)	43 (1.2)	3 (2.5)	0	13 (1.1)
Injury, poisoning and procedural complications	2 (0.2)	1 (0.3)	33 (1.0)	34 (1.0)	1 (0.8)	0	11 (1.0)

[a] fixed and flexible doses

[49] MedDRA = Medical Dictionary for Regulatory Activities.

Table 44: SAEs with an incidence of n ≥ 3 (combined Phase 2/3 trials, cohort E1).

Adverse Event (Preferred Term) n (%)	Placebo (N=1064)	Asenapine			Risp 3 mg BID (N=120)	Halo 2-8 mg BID (N=115)	Olan 5-20 mg QD (N=1139)
		<5 mg BID (N=298)	5-10 mg[a] BID (N=3159)	All (N=3457)			
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 (087)
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 (0.10	0	0	0
Overdose	0	0	4 (0.1)	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] fixed and flexible doses. n=3 or greater in all asenapine group. NMS= Neuroleptic malignant syndrome

SAEs considered related to the study drug in clinical pharmacology trials with healthy volunteers were severe gastro-oesophageal reflux, severe sinus bradycardia and mild atrial fibrillation.

Laboratory findings

Asenapine had no adverse effect on haematology parameters. There were some transient elevations in transaminase levels but no clinically relevant trends identified in blood chemistry tests (non-metabolic) of subjects exposed to asenapine. Liver function assessment of patients in combined Phase 2/3 trials, (cohort E1) showed that for aspartate transaminase (AST) >3x ULN increases, there were 10(1.1%) on placebo, 37(1.3%) on asenapine 5-10 mg bd, 2 (1.7%) on risperidone, 19(1.8%) on olanzapine and none on haloperidol and for alanine transaminase (ALT) >3x ULN increases, there were 15(1.6%) on placebo, 97(3.3%) on asenapine 5-10 mg, 5(4.3%) on risperidone, 79(7.4%) on olanzapine and 1(0.9%) on haloperidol.

There were no treatment-related trends observed in the metabolic chemistry (glucose and lipid) parameters based on mean and median changes from baseline except for fasting insulin where a mean increase of 11.8 pmol/L was seen in the asenapine group and the olanzapine group had a mean increase of 23.8 pmol/L.

The median changes from baseline in prolactin levels for asenapine were minus 0.3 µg/L and 4.2 µg/L for olanzapine.

Safety in special populations

Hepatic impairment

Subjects with mild, moderate and severe hepatic impairment (n=8 per group) received a single dose of 5 mg SL asenapine. Two subjects had serious, non-fatal AEs (severe syncope and severe hepatic cirrhosis); both were not considered to be related ; both subjects recovered. The most frequent AEs were somnolence, dizziness, dysgeusia and oral hypoaesthesia. There was no clear pattern in the incidence of AEs across treatment groups. Changes in clinical laboratory values in subjects with hepatic impairment were consistent with their diagnosis. Other laboratory deviations were sporadic and not considered clinically significant.

Renal impairment

A single dose of 5 mg SL asenapine was given to subjects with mild, moderate and severe renal impairment (n=8 per group) compared to age/gender matched controls. There were no deaths, SAEs, or withdrawals because of AEs. All AEs were mild or moderate in intensity.

Elderly

At the time of this submission, an open-label trial in elderly patients with psychosis was ongoing (it includes 33 patients in interim PK analysis, dosage up to 10 mg bd). There were too few subjects for a subgroup analysis based on age.

Paediatric

Safety in paediatric/adolescent subjects has not been established. There were 2 asenapine subjects (0.1%) less than 18 years of age in the combined Phase 2/3 trials (16 and 17 years of age). In clinical pharmacology study A7501022 in 40 adolescents, there were no deaths or SAEs. All AEs were mild or moderate in intensity. The most frequent AEs were somnolence, dysgeusia, sedation, oral paraesthesia, glossodynia and oral hypoaesthesia. Dizziness occurred in 1 subject in each treatment group at doses of 3 mg and greater.

Race

There were no clinically relevant effects of race on the overall distribution of AEs.

Gender

There were no effects of gender on the overall distribution of adverse events.

Pregnancy

Of the 7 pregnant female subjects exposed to asenapine, 4 subjects decided to terminate the pregnancy early, 1 had a pre-term neonatal death (female infant died within 5 minutes of birth due to asphyxia) and 2 had healthy full term infants. In none of the cases were there reports of congenital abnormalities.

Safety related to drug-drug interactions and other interactions

After co-administration of paroxetine during steady state asenapine dosing, commonly reported AEs were somnolence, headache, diarrhoea, hypoaesthesia oral, insomnia, dizziness and nausea. Four subjects discontinued due to headache, ECG changes, hypertension and

elevated ALT. There were no clinically relevant differences in the incidence, nature or intensity of AEs that had started during the multiple dose treatment with asenapine.

The incidence, nature or intensity of AEs after treatment with a single dose of asenapine added to a regimen of steady state paroxetine did not show clinically relevant differences compared to single dosing of asenapine alone, except for a doubling of bradycardia cases (8 vs 4 occurrences). No evidence of a safety signal for bradycardia has been identified in Phase 2/3 trials. A treatment related SAE of atrial fibrillation led to discontinuation in one subject.

In a trial involving co-administration of fluvoxamine with asenapine, 3 SAEs occurred all during the combined treatment: gastroesophageal reflux disease (related to the combination), sinus pauses (related to asenapine) and pulmonary embolism (unlikely related).

During combination treatment of asenapine with fluvoxamine several AEs were reported more frequently: dizziness, headache and gastroesophageal reflux disease.

The effects of interacting drugs on asenapine pharmacokinetics can be considered relatively small compared to the overall variability in pharmacokinetics, except for co-administration of asenapine with therapeutic doses of fluvoxamine, which can be expected to result in relevant increases in asenapine plasma concentrations.

Discontinuation due to adverse events

In the 6-week non- bipolar studies the discontinuations due to AEs for asenapine (8.0%) were comparable to placebo (9.5%). The discontinuations due to lack of efficacy for asenapine (9.4%) were lower than placebo (21.7%). In 3-week bipolar mania studies the discontinuations due to AEs for asenapine (5.3%) were greater than olanzapine (1.0%). The discontinuations due to lack of efficacy for asenapine (7.9%) were higher than olanzapine (5.8%). In the overall studies discontinuations due to AEs for asenapine (6.3%) were lower than risperidone (7.5%) but higher than for haloperidol (5.2%) and olanzapine (4.8%) and discontinuations due to lack of efficacy for asenapine (9.7%) were lower than for placebo (15.9%).

Evaluator's overall conclusions on clinical safety

Patient exposure to asenapine 5-10 mg bd was 1301 subjects for at least 6 months and 779 for at least 12 months was, meeting the guideline requirements for patient long term exposure.[50]

In 3-week bipolar mania studies the discontinuations due to AEs for asenapine (5.3%) were greater than olanzapine (1.0%). The discontinuations due to lack of efficacy for asenapine (7.9%) were higher than olanzapine (5.8%).

The AEs and SAEs were generally comparable with comparators.

Asenapine increased prolactin levels more often than placebo but less than most other comparators. The incidence of prolactin levels > 2 x ULN was 56 (6%) for placebo, 832 (28.9%) for asenapine 5-10 mg, 83 (71.6%) for risperidone, 414 (39%) for olanzapine and 41 (38.7%) for haloperidol. The incidence of prolactin levels > 4 x ULN was 12 (1.3%) for placebo, 563 (19.6%) for asenapine 5-10 mg, 32 (27.6%) for risperidone, 325 (30.6%) for olanzapine and 12 (11.3%) for haloperidol.

[50] pp. 121-125 of Rules Governing Medicinal Products in the European Union 1998 (3C) – 3CC5A, November 1994. The Extent of Population Exposure to Assess Clinical Safety for Medicines Intended for Long-Term Treatment of Non-Life-Threatening Conditions.

Extrapyramidal symptoms had a higher incidence of AEs for asenapine than olanzapine and risperidone in the trials but they were lower than with haloperidol. For example in the case of Parkinsonism: asenapine 5-10 mg 222 (7%), risperidone 2 (1.7%), olanzapine 52 (4.6%) and haloperidol 27 (23.5%). Weight increase by≥ 7% had the highest inciden ce for olanzapine at 344 (31.7%) while for asenapine 5-10 mg it was 374 (12.6%), for risperidone it was 13 (14.6%) and for haloperidol it was 9(8.4%). When assessed across the studies by the incidence of suicide attempts, suicidality was higher than placebo in all medication groups though the numbers were small: placebo 2 (0.2%), asenapine 5-10 mg 16 (0.5%), risperidone 1 (0.8%), haloperidol 1 (0.9%) and olanzapine 8 (0.7%).

Prolonged QT_c had an incidence of 3 (0.3%) for placebo, 24 (0.8%) on asenapine 5-10 mg, 8 (0.1%) on olanzapine and none for risperidone or haloperidol. Pyrexia had an incidence of 8 (0.8%) with placebo, 35 (1.1%) on asenapine 5-10 mg, 5 (4.2%) on risperidone, 3 (2.6%) on haloperidol and 19 (1.7%) on olanzapine. There were 3 cases reported as neuroleptic malignant syndrome (1 of mild intensity, 2 severe) in subjects treated with asenapine, all related to study medication. There were no cases of NMS in either of the comparator groups. Some AEs of interest did not occur frequently enough in the studies for realistic comparison to be made (for example, rhabdomyolysis, seizures).

Some of the AEs occurring post-treatment (placebo incidence > 2 x the incidence in the continuing asenapine treatment) included insomnia (13.5%), weight decreased (8.3%), hallucination (6.8%), agitation (5.7%), delusion (5.7%), irritability (3.6%), schizophrenia, paranoid type (3.6%) and auditory hallucination (3.6%).

Asenapine has not been systematically studied in animals or humans for its abuse potential or its ability to induce tolerance or physical dependence.

No specific information is available on the treatment of overdose with asenapine.

Clinical Summary and Conclusions

Clinical aspects

Pharmacokinetics

PK studies were only conducted in schizophrenia patients, not in patients with bipolar disorders, given the high inter and intra patient variability this is unlikely to be of concern.

Because of the high first pass metabolism after oral ingestion, the sublingual route was chosen. Data comparing oral and sublingual bioavailability were not found. A comparison of the results for asenapine without charcoal show oral C_{max} is 6.8% of the sublingual C_{max}, while oral $AUC_{0-\infty}$ is 8.8% of the sublingual $AUC_{0-\infty}$.

The sublingual route is long established; it does however introduce more variables into the absorption process.

- The sponsors have compared smokers and non-smokers, finding no difference. The minimal effect of smoking was supported by a population PK study. While the sponsors were concerned about induction of CYP1A2, there is also some possibility of action on salivary secretion. Exploratory analysis showed a significant disintegration time effect, with longer disintegration times resulting in higher exposure.
- There were 2 studies investigating the effect on absorption of different sites in the oral cavity. Study 25512 showed with 100 µg asenapine, based on C_{max} and AUC, that buccal and sublingual administration were bioequivalent but not supralingual and sublingual. In Study 041030 single dose 5 mg asenapine sublingually, supralingually and buccally, bioequivalence was not shown based on C_{max} and AUC. The Buccal and sublingual administration $AUC_{0-\infty}$ were the only parameters within the range for

bioequivalence.

- A part of the SL dose is swallowed was supported by the results of Study 25540,
- There may be entero-hepatic circulation after absorption.

It is thus not surprising that there is considerable inter and intra subject variability.

Absolute bioavailability trials were attempted but not completed because of inadequate doses producing measurement problems or higher doses producing unacceptable AEs.

An overall mean $t_{½}$ from a series of 13 sublingual PK trials was used to calculate $AUC_{0-\infty,IV}$ for these combined IV data. From these same trials, also an overall estimate of $AUC_{0-\infty,SL}$ was obtained to calculate the absolute bioavailability. For a 5 mg dose this was calculated at 34.8%.

There were 3 formulations used in the studies and only 2 PK studies used the commercial formulation.

In the reports for these two studies the mean concentration time curves were not presented separately from the comparator.

With 150 mL water at 2, 5, 10 and 30 minutes after 10 mg of asenapine SL, bioequivalence was not shown between the time periods, except for 10 vs 30minutes. That is, C_{max} and AUC were lower after water at 2 and 5 minutes than after water at 30 minutes.

The only evidence for a food effect was for 5 mg dosing immediately after consumption of a high-fat meal and then only for the AUC. With the associated C_{max} a food effect could not be considered absent, nor could it be considered absent where given a high-fat meal 4 hours after dosing but it was not shown to occur in those circumstances for either AUC or C_{max}.

There are limited data for both the elderly and adolescents. An interim analysis of elderly patients showed C_{max} was ~30% higher and AUC was 30-40% higher than that in the general PK population. There is currently a clinical trial ongoing for elderly patients.

Likewise the data on adolescents is limited, in that the number of patients suffering from the 2 proposed indications is unclear, as is the extent to which the other disorders in the study may affect the results, thus reference to the trial under Precautions and Dosage and Administration is of concern, the indication sought does not include adolescents, nor is there adequate evidence submitted to justify use in that population.

In relation to enantiomers, since N-desmethyl-asenapine shows a much lower binding affinity for therapeutically relevant receptors than asenapine and the level of exposure to N-desmethyl-asenapine is lower, the difference in AUC between the N-desmethyl-(R,R)-asenapine and the N-desmethyl-(S,S)-asenapine is considered to be of no clinical relevance.

In mild liver impairment there is an increase of C_{max} by 10% and for moderate disease a reduction of 43% but increased by 3% in severe. While $AUC_{0-\infty}$ was similar to reference (12% increase) for mild and moderate liver disease it was increased 5.5 fold in severe (Child-Pugh C) liver disease.

In relation to renal impairment the statistical tests were not considered sensitive due to the small sample size and variability in asenapine PKs

In relation to race, the population PK analysis quoted in the PI related principally to Black vs Caucasian. Of greater relevance to Australia is the study 25546 that looked at healthy Japanese and Caucasian subjects and found after single dosing and at steady state no significant difference in PK parameters (C_{max}, AUC, $CL_{/f}$ or wn-$CL_{/f}$,) of asenapine desmethyl-asenapine and asenapine-glucuronide.

The dose of fluvoxamine used in Study 041033 was less than usual in clinical practice so that an effect on asenapine levels in clinical practice is likely.

Pharmacodynamics

The principle concern is the cardiovascular side effects in particular the case of asystole early in the investigations. The sponsor suggested that in comparison with N-desmethyl asenapine, asenapine produced more fall in arterial BP and rise in HR while the former produced negative inotropy. QT prolongation is a major issue with atypical antipsychotics. The numbers are low but prolonged QT_c had an incidence of 3 (0.3%) for placebo, 24 (0.8%) on asenapine 5-10 mg, 8 (0.1%) on olanzapine and none for risperidone or haloperidol, thus it should be a matter for ongoing review.

Asenapine increased prolactin levels more often than placebo but less than most other comparators. The incidence of prolactin levels > 2 x ULN was 56 (6%) for placebo, 832 (28.9%), for asenapine 5-10 mg 83 (71.6%) for risperidone, 414 (39%) for olanzapine and 41 (38.7%) for haloperidol. The incidence of prolactin levels > 4 x ULN was 12 (1.3%) for placebo, 563 (19.6%) for asenapine 5-10 mg, 32 (27.6%) for risperidone, 325 (30.6%) for olanzapine and 12 (11.3%) for haloperidol.

While efficacy has been related to different degrees of D_2 occupancy, so to have extrapyramidal symptoms (EPS), the claimed decreased potential for EPS appears to be based on the relatively higher doses of asenapine needed to induce catalepsy in rats compared to doses showing activity in tests predictive of antipsychotic activity.

In many of the study reports the matching placebo for asenapine was formulated with 1% magnesium chloride so that it would also have a bitter taste but there is no discussion of the local anaesthetic properties of asenapine despite oral hypoaesthesia being among the common AEs.

Clinical efficacy

Schizophrenia

In relation to acute treatment of schizophrenia, the sponsor submitted 2 validated Phase 3 studies:

1. Study 041021 failed to show efficacy greater than placebo for either asenapine 5 mg bd (102 patients) or 10 mg bd (96 patients).
2. Study 041023 showed efficacy greater than placebo for asenapine 5 mg bd (109 patients) but not for asenapine 10 mg bd (105 patients).

In a further study (041004) the active comparator did not demonstrate statistically significant efficacy, efficacy of asenapine greater than placebo was shown (but only 5 mg bd was tested on 58 patients). The final study for acute treatment of schizophrenia (Study 041022) was a failed study in which none of the treatments (asenapine 5 or 10 mg bd or olanzapine) demonstrated statistically significant efficacy.

Thus the balance of these studies does not favour 5 mg bd being more efficacious than placebo in acute treatment of schizophrenia. In particular, asenapine 10 mg bd was not shown to be more efficacious than placebo in acute treatment of schizophrenia.

In relation to the prevention of relapse the sponsor submitted Study A7501012 which showed efficacy greater than placebo in the rate of relapse for asenapine 5-10 mg bd. This demonstration of efficacy in prevention of relapse is limited to those patients who were able to be successfully stabilised on asenapine open-label therapy. Given that efficacy of asenapine in acute treatment of schizophrenia has not been adequately demonstrated it is

difficult to see how asenapine could be used for prevention of relapse in the selected population in which its efficacy has not been demonstrated.

The sponsor also submitted this study as evidence for the maintenance of clinical improvement based on a secondary objective PANSS total score. There was no significant difference at Week 26 between those continued on asenapine (110) and those given placebo (55) after an initial ≥ 22 weeks of asenapine. However if the patients that relapsed were included, there was a significant difference at endpoint between the 189 on placebo and the 189 on asenapine.

In the extension studies;

- Study 041502 was an extension of 041004 that could not be validated and only assessed asenapine 5 mg bd.
- Study 041512 was an extension of studies 041021 and 041022 neither of which showed efficacy for asenapine greater than placebo and the latter was not validated by having an active comparator that was statistically significantly superior to placebo.
- Study 041513 was an extension to 52 weeks of Study 041023 without placebo control (patients previously on placebo received asenapine). Study 041023 was validated by its active control and showed efficacy greater than placebo for asenapine 5 mg bd but not 10 mg bd. The data from both doses of asenapine was not separated in the study report. There was no hypothesis testing only summary statistics were presented for efficacy endpoints. The primary endpoint was the time to failure to maintain effect for those patients who had at least a 30% decrease from baseline in PANSS at the end of the acute phase. In the extension period the PANSS total score at the end point for those continually on asenapine rose (that is, deteriorated) by 1.9 from 62.4 (88 patients), while that for haloperidol decreased by -4.1 from 64.4 (41 patients). Baseline score at the start of 04123 was 86.1 for asenapine and 87.0 for haloperidol. There were 51 patients (of 65, 78%) on asenapine 5-10 mg bd and 24 patients (of 29, 83%) on haloperidol who had an initial episode of loss of effect during this extension trial. Median survival times for subjects continuing on active treatment from the feeder studies were 31 days for subjects treated with asenapine 5-10 mg bd and 85 days for subjects treated with haloperidol 2-8 mg bd. These results strongly suggest that asenapine is less effective than haloperidol in maintenance treatment of schizophrenia however there was no statistical comparison between the active treatments.

The numbers completing the longer term use studies were small.

The study designs met the requirements of the TGA-adopted EU guideline.[39] The fixed doses of 5 mg and 10 mg in Study 041021 were justified on the basis of Study 041004 and an unidentified safety study using up to 20 mg bd. However there were some matters of concern in that multiple centres were involved with each centre assessing relatively few patients and some of the endpoints definitions were subjective. Thus studies 041512 and 041513 defined failure to maintain effect to include any of:

- A dose increase to improve clinical response in a destabilized subject
- The patient's schizophrenic symptomatology has deteriorated
- Discontinuation due to lack of efficacy
- AE/SAE of worsening of schizophrenia

While Study A 7501012 defined a relapse or impending relapse to include:

- In the opinion of the investigator, the subject's symptoms of schizophrenia had deteriorated to such an extent or the risk of violence to self or others or suicide had

increased so that 1 or more of the following measures was necessary or had occurred:

- Required at least an additional 2 mg or greater lorazepam (or equivalent) per day as compared to the highest open-label dose of the monotherapy phase;
- Addition of open-label antipsychotic medication or mood stabilizers;
- Addition or increase in the dose of antidepressant medication;
- Increase in the level of psychiatric care (e.g., supervised living, day hospital care);
- Hospitalization or increase in the level of hospitalization;
- An arrest or imprisonment for objectionable behaviour;
- Electroconvulsive therapy;
- Other.

Bipolar disorder

Acute treatment of mania or mixed episodes in monotherapy

Of the 2 studies were submitted, one (A7501005) that was validated by olanzapine, showed a clinically significant difference in YMRS total score at 3 weeks (5.3) between asenapine and placebo. However, the other study (A7501004) at 3.7 did not quite reach the clinically significant difference of 4 as defined by the non-inferiority margin in study A7501006. Further, there was a significant treatment by centre interaction. When the relevant centres were excluded from analysis there was either no difference from placebo or no clinically significant difference in efficacy. On the data provided olanzapine appears marginally better than asenapine however there were no statistical comparisons between active treatments.

Maintenance of clinical improvement in monotherapy

In their statistical analysis of the primary endpoint for Study A7501006, the YMRS score was adjusted for each subject to account for the non-inferiority margin of 4 points on the YMRS scale; the score used in the analysis for the olanzapine groups was the unadjusted, raw YMRS total score. The sponsor should be required to justify why this adjustment was performed.

Justification of the choice of non-inferiority margin was also requested as it appears wide and larger than the mean difference from placebo seen in the acute treatment studies. This would have the effect of reducing the ability of the study to detect differences between asenapine and olanzapine.

The treatment by centre interaction present in Study A751004 persisted in this study due to the same study sites. The significance of this interaction is unclear.

Study A7501007 had no statistical analysis of the principal parameter used in other studies YMRS total score. This was primarily a safety study however long-term efficacy of asenapine compared with olanzapine was assessed as a secondary objective. Mean changes from baseline to trial endpoint in YMRS total score were minus 5.8 for asenapine vs -26.1 for olanzapine. Responder and remitter rates were also similar for the 2 actives. This study had a very high withdrawal rate with few subjects completing the full 52 weeks of exposure. The sponsor has claimed that in this study that "time to response failure" among those who responded to treatment was statistically significantly longer in the asenapine group than in the olanzapine group ($p = 0.0127$). This was not accepted because in determining "time to response failure" the source table uses as the number at risk, not the number of responders but the ITT population some of whom, having not responded, would not be at risk of response failure.

Acute treatment of mania or mixed episodes in combination with lithium or sodium valproate

Study A7501008 was submitted to support this claim. There was no active comparator to validate the study. While statistically superior to placebo, the efficacy results were smaller than seen with asenapine monotherapy (at 3 weeks difference LSMs = 2.4 and 12 weeks difference LSMs = 3.4). This may reflect a more resistant population as these subjects had not adequately responded to monotherapy lithium or valproate. Confirmatory analyses did not consistently demonstrate statistical significance from placebo but all trended towards asenapine as being more effective than placebo when in combination with either lithium or valproate. Remitter rates and CGI-BP were statistically significantly in favour of asenapine.

Maintenance of clinical improvement in combination with lithium or sodium valproate

Study A7501009. Among the study participants the difference between those receiving asenapine and those on placebo favoured asenapine at Week 12 by 0.9 and by Week 52 patients who had asenapine added to their lithium or valproate did worse than those without it by 2.0.

This study was small and had substantial differences with reasons for discontinuation between the placebo and asenapine groups. Discontinuation due to withdrawal of consent, loss to follow-up and lack of efficacy were more frequent in the placebo group while discontinuation due to adverse events was more frequent in the asenapine group. Only 13 subjects in each group completed the 52 weeks and among that small sample there was an apparent trend towards those taking placebo doing better, however given the high withdrawal rates and small numbers of subjects this result is irrelevant to a determination of longer term efficacy.

The numbers completing the studies plus extension were small.

Clinical safety

Patient exposure to asenapine 5-10 mg bd was 1301 subjects for at least 6 months and 779 for at least 12 months, meeting the guideline requirements for patient long term exposure.

Overall discontinuations due to AEs for asenapine (14.2%) were comparable to placebo (12.6%) and discontinuations due to lack of efficacy for asenapine (9.7%) were lower than for placebo (15.9%). Discontinuations due to worsening of the disease were high (7.8%) for asenapine compared to olanzapine (3.2%) and risperidone (0).

The AEs and SAEs were generally comparable with comparators.

The increase in prolactin levels are discussed under *Pharmacodynamics*.

Extrapyramidal symptoms, weight gain, suicidality, prolonged QTc, pyrexia and neuroleptic malignant syndrome are discussed under *Evaluator's overall conclusions on clinical safety*

Some of the AEs occurring post-treatment (placebo incidence > 2 x the incidence in the continuing asenapine treatment) included insomnia (13.5%), weight decreased (8.3%), hallucination (6.8%), agitation (5.7%), delusion (5.7%), irritability (3.6%), schizophrenia, paranoid type (3.6%) and hallucination, auditory (3.6%).

Asenapine has not been systematically studied in animals or humans for its abuse potential or its ability to induce tolerance or physical dependence.

No specific information is available on the treatment of overdose with asenapine

Benefit risk assessment

Benefits

Schizophrenia

In relation to acute treatment of schizophrenia, the balance of these studies does not favour 5 mg bd being more efficacious than placebo in acute treatment of schizophrenia. Furthermore, 10 mg bd asenapine was not shown to be more efficacious than placebo in acute treatment of schizophrenia.

In relation to the prevention of relapse, the demonstration of efficacy was limited to those patients who were able to be successfully stabilised on asenapine open-label therapy. Given that efficacy of asenapine in acute treatment of schizophrenia had not been adequately demonstrated it is difficult to see how asenapine could be used for prevention of relapse in the selected population in which its efficacy has not been demonstrated.

The sponsors submitted this study as evidence for the maintenance of clinical improvement and the same argument applies.

In the extension studies, the results strongly suggest that asenapine is less effective than haloperidol in maintenance treatment of schizophrenia however there was no statistical comparison between the active treatments.

Bipolar disorder

The non-inferiority margin of 4 points on the YMRS scale chosen in Study A7501006 appears quite wide and as such would have the effect of reducing the ability of the study to detect differences between asenapine and olanzapine. It is larger than the mean difference from placebo seen in 2 of the acute treatment studies, raising the question as to whether the differences are clinically significant.

The numbers completing the studies plus extension were small.

Thus the balance of studies for the acute treatment of mania or mixed episodes is one study clearly supportive and one equivocal. The monotherapy maintenance studies have one study, the analysis of which is questioned and one study that was primarily a safety study with few

completers, that showed that those who did so were responders and remitters with a similar high incidence in both groups, which would be expected, the only other statistical analysis of a study parameter was rejected.

The acute treatment of mania or mixed episodes in combination therapy at the primary LOCF endpoint showed a statistical but small difference from placebo unsupported by the OC results, with no statistical difference in the low number of responders (34% asenapine vs 27%) i.e. the study is not clearly supportive. The combination therapy maintenance study is not supportive.

The sponsors submitted 2 references for olanzapine in acute bipolar mania: Tohen et al (1999), which showed a response rate for olanzapine of 48.8% vs 24.2% for placebo and Tohen et al (2007) with response rates of 65% vs 43%.

Risks

Overall discontinuations due to worsening of the disease were high: (7.8%) for asenapine compared to olanzapine (3.2%) and risperidone (0).

The AEs and SAEs were generally comparable with comparators:

- asenapine increased prolactin levels more often than placebo but less than most other comparators.
- Extrapyramidal symptoms had a higher incidence of AEs for asenapine than olanzapine and risperidone in the trials but they were lower than with haloperidol.
- Weight increase by≥ 7% was lowest for asenapine 5 -10 mg except for haloperidol.
- Suicidality when assessed across the studies by the incidence of suicide attempts was higher than placebo in all medication groups though the numbers were small.
- Prolonged QT_c was highest (0.8%) on asenapine 5-10 mg and analysis revealed n exposure response relationship.
- Pyrexia was lowest on 35(1.1%) on asenapine 5-10 mg, except for placebo.

Some AEs of interest did not occur frequently enough in the studies for realistic comparison to be made. Clearly with the infrequent events continuing watch is required.

Some of the AEs occurring post-treatment (placebo incidence > 2 x the incidence in the continuing asenapine treatment) included insomnia (13.5%), weight decreased (8.3%), hallucination (6.8%), agitation (5.7%), delusion (5.7%), irritability (3.6%), schizophrenia, paranoid type (3.6%) and hallucination, auditory (3.6%).

That the incidence of QT_C prolongation was the highest with asenapine is a matter of concern, (a small effect of asenapine on QTc prolongation was found in study A7501001 according to the exposure response analysis).

The studies' reports and summary tables sometimes review both OC and LOCF results, sometimes only one of them. OC will, especially in long term trials, when analysed at the last study visit will look at those with good response, the others having left the study beforehand. LOCF will, especially in short term placebo controlled trials, tend to favour the test drug and comparator, as placebo patients are more likely to leave the study from lack of efficacy, while those on the test drug or comparator are more likely to leave from AEs (that is, the drug is still acting at the time of last observation).

Balance

The PKs show wide inter and intra patient variability, making prescribing the correct dosage more difficult for the physician and the patient more likely to suffer loss of effect or some of the exposure related adverse effects.

The mode of administration may offer advantages to the patient who has difficulty swallowing but the process of administration is likely to take a longer period of observation to ensure patient compliance. Preventing a manic patient from swallowing the medication does not appear to have been a problem in the studies.

For the patient with acute schizophrenia on balance asenapine does not offer efficacy, nor does the evidence show it is useful for maintenance or prevention of relapse.

For the patient with an acute manic or mixed episode of bipolar disorder asenapine does on balance offer some evidence of efficacy as monotherapy but is unlikely to produce clinically significant improvement in combination with lithium or valproate for similar acute episodes. Nor does it show efficacy patients with such episodes of bipolar disorder in the long term.

For patients there is less likelihood of some adverse effects compared with alternative drugs (weight increase, raised prolactin levels) while there is an increased likelihood of others (extrapyramidal symptoms, QT_c prolongation [both of which are exposure related]). While patients can maintain their own observations of the former, QT_c prolongation will require monitoring by the physician.

Of concern to physician and patient is that the discontinuations due to worsening of the disease was relatively high (17, 4.5%) for asenapine compared to olanzapine (4, 1%) and placebo (9, 4%) in short term bipolar trials; while in long term trials that for asenapine rose to 6.2% vs 0 for olanzapine.

Conclusions

The overall benefit risk balance of asenapine is positive only for the acute treatment of manic or mixed episodes of bipolar disorder, provided the physician monitors QT_c interval.

The balance was not positive for the other proposed indications.

It was recommended that asenapine be registered for:

The treatment of acute mania or mixed episodes associated with bipolar disorder

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

The ongoing safety concerns were identified by the sponsor as shown in Table 45.

Table45: Summary of ongoing safety concerns

Important identified risks	EPS Weight gain Somnolence and sedation Patients with severe hepatic impairment
Important potential risks	NMS Rhabdomyolysis Seizures Hyperprolactinaemia Cardiovascular effects: QT prolongation, orthostatic hypotension Neutropenia
Important missing information	Pregnancy and lactation Pediatric patients Elderly

The OPR reviewer noted that there have been reports of atypical antipsychotics being used in children with behavioural disturbances associated with autism. This has led to concerns about the volume of use of these medicines in children in residential care facilities. Given that the risk of such paediatric off-label use is common to all of the atypical antipsychotics, the proposed PI warning statement that asenapine is not recommended for use in children and adolescents below 18 years of age is considered sufficient as a routine risk minimisation activity.[51] It is assumed that off-label use as a whole will be appropriately monitored by routine pharmacovigilance activities and reported in future PSURs.[52]

In principle there was no objection to the sponsor implementing the proposed application of routine pharmacovigilance activities for all the specified ongoing safety concerns and the application of an additional pharmacovigilance activity for the missing information in elderly patients. However, the specified ongoing study is not considered to be part of the planned clinical studies in the pharmacovigilance plan, therefore the related study protocol has not been reviewed. Nevertheless an update on the progress/results/analysis of this study will be expected in future PSURs.

Routine risk minimisation activities will include warnings or notification of undesirable effects in the Australian PI for all the specified ongoing safety concerns, except for 'Rhabdomyolysis' and 'Neutropenia' as there was no apparent direct association between asenapine exposure and the development of these adverse drug reactions. This was

[51] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

[52] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

considered generally acceptable as it would appear that the safety profile of asenapine is consistent and comparable with those of already approved atypical antipsychotic medicines.

The reviewer made some recommendations with regard to the proposed PI but these are beyond the scope of this AusPAR

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There were no issues which were likely to preclude registration.

Nonclinical

There were no nonclinical objections to registration. The evaluator noted that adequate toxicity studies were conducted and characterised by observations consistent with pharmacological activity but with little target organ toxicity being identified. Safety pharmacology studies indicated a potential for adverse cardiovascular effects, including orthostatic hypotension and prolonged QTc intervals.

No nonclinical studies were conducted with asenapine in combination with lithium or sodium valproate however use of asenapine in combination therapy for bipolar disorder has been proposed. No oncogenic responses were observed in the long-term rodent carcinogenicity studies despite a potential for prolactin elevation being demonstrated in male rats, consistent with dopamine receptor binding.

Clinical

Pharmacology

Asenapine is a racemic mix of R and S enantiomers that are not significantly different from racemic asenapine with respect to antidopaminergic, antiserotonergic, adrenolytic and antihistaminic properties. It was initially developed as an oral formulation but this was discontinued in favour of a sublingual tablet due to low oral bioavailability caused by extensive first-pass metabolism. Two studies examined absolute bioavailability which was 34.8% (95%CI 31.6 – 38.7%).

Three formulations were used in clinical trials. The commercial formulation was shown to be bioequivalent to the formulation used in clinical trials.

Mean C_{max} , after a single 5 mg sublingual dose, ranged from 3.00 ng/mL to 6.85 ng/mL across studies with a weighed mean C_{max} of 4.22 ng/mL. Median t_{max} ranged from 0.5 to 1.5 hours across studies with all overall median of 1.0 hours. At steady state after sublingual doses of 5 mg bd mean C_{max} was 3.58 ng/mL and median t_{max} was 1.0 hours. Food taken immediately after dosing had little effect on the PK of asenapine. The effect of 150 mL of water taken 2, 5 and 10 minutes after a sublingual dose was examined and small effects (reduction in C_{max} of 17% and AUC of 18%) were found at 2 minutes and lesser effects at 5 minutes. AUC increases somewhat less than linearly with increasing dose within the recommended dose range. The clinical evaluator considered this may be due to limitations in the absorption capacity from the oral mucosa, leading to higher proportions of the dose being swallowed with increasing dose.

Volume of distribution was estimated at 1719 L in one study and 1748 L in another. Asenapine is highly protein bound (95-98.7%). Very little drug is excreted unchanged in urine, 5-16% is excreted in faeces. It is a high hepatic extraction ratio drug and is metabolised by multiple pathways primarily to N-desmethylasenapine, asenapine N+-

glucuronide and N-desmethylasenapine-N-carbamoylglucuronide. Both enantiomers of asenapine are weak inhibitors of CYP2D6 and to lesser extent CYP1A2, CYP2C19 and CYP3A4.

No significant differences in PK parameters were seen between Japanese and Caucasian subjects. Asenapine exposure in adolescents, smokers and those with renal impairment was similar to that of adults aged 18 to 57 years in clinical trials. Limited PK data from 33 elderly patients with psychosis showed a mean increase in AUC of 30% compared with adults in other studies. N-desmethylasenapine concentrations in these elderly patients were almost double those in adult patients. Increasing weight increased clearance by 0.15% per kg. Mild and moderate hepatic impairment had a limited effect on PK but severe hepatic impairment (Child-Pugh C) resulted in a 5.5 fold increase in AUC for bound drug and a 7.7 fold increase in unbound drug.

Asenapine was associated with QT interval prolongation in multidose studies. This was not clearly dose dependent in Study A7501001 which was designed to examine QT prolongation. Asenapine doses of 5 mg, 10 mg, 15 mg and 20 mg bd were associated with mean QTcF increases of 2.6 msec, 10.5 msec, 6.4 msec and 5.2 msec respectively. In the combined Phase 2/3 studies QTcF prolongation to > 500 msec was reported in 0.3% of subjects given placebo, 0.8% of subjects given asenapine 5-10 mg bd and 0.7% of subjects given olanzapine 5- 20 mg daily. In that cohort no subjects given asenapine up to 20 mg had QT prolongation≥ 60 msec from baseline.

Increased prolactin was seen in a high dose study where subjects received up to 48 mg asenapine bd. In study 25506, a pilot single rising dose study in which 4 different doses of asenapine (0.7, 1.5, 3 and 4.5 mg) were administered via intravenous infusion over 30 minutes to 8 healthy subjects, with 2 subjects receiving each dose. This study was stopped because one subject, given the lowest planned dose, collapsed in asystole while sitting having his BP recorded 45 minutes after the start of the infusion. Subsequent cardiac investigations and cardiological opinion revealed no predisposing or post event cardiac pathology. Orthostatic hypotension and somnolence were seen in some subsequent studies of sublingual asenapine. In the combined Phase 2/3 clinical trial population, 37% of subjects given asenapine 5-10 mg had shifts to elevated prolactin and 20% had prolactin levels at least 4 x ULN compared with 46% with elevations and 31% with levels at least 4x ULN for subjects given olanzapine.

Efficacy

Schizophrenia

Acute treatment

Four studies were submitted to support acute treatment (of up to 6 weeks) of schizophrenia. The primary endpoint in all 4 studies was a comparison between each asenapine dose group and placebo of the mean change from baseline in the Positive and Negative Symptom Scale (PANSS) total score. The "responder rate" (the proportion of subjects with ≥ 30% reduction from baseline in total PANSS score) was a secondary endpoint. Of these 4 studies, 2 demonstrated a statistically significant difference from placebo for at least one dose of asenapine. In only one of these studies did both asenapine and the active comparator show a statistically significant difference from placebo for the primary efficacy endpoint (Study 023) but in that study statistical significance of the higher dose of asenapine was not demonstrated. None of the studies presented a statistical comparison between asenapine and active comparators. No combined analysis of the results of these 4 studies was presented but after receiving the clinical evaluation report the sponsor presented a combined analysis.

Study participants had a current diagnosis of schizophrenia and a minimum PANSS total score of at least 60 at screening and baseline. They were also required to have previously responded positively to an antipsychotic medication other than clozapine. A total of 1277 subjects were included in the ITT analyses of these studies. Results for the primary endpoint and responder rates for each of these studies are presented in Tables 10 and 11 (Study 023), 12 and 13 (004), 14 and 15 (021) and 16 (022).

It was clear that Study 022 was a failed study in which no actives showed superiority over placebo and will not be considered further. This study used flexibly dosed asenapine (5 or 10 mg bd). The 3 studies not using flexibly dosed asenapine showed no indication of dose response for the primary endpoint. The difference from placebo in mean reduction in PANSS score across the 3 studies examining the 5 mg bd dose ranged from minus 3.0 to minus 10.59 and was statistically significantly better than placebo in 2 of the 3 studies. The difference from placebo in mean reduction in PANSS across the 2 studies in which the 10 mg bd dose was examined ranged from minus 2.4 to minus 4.2 and was statistically significant in neither of these studies. The difference from placebo in responder rates for the asenapine 5 mg bd dose ranged from minus 12.2% to 15.6% in the 2 studies in which statistical analysis of this secondary endpoint was presented. Both these results were statistically significant favouring asenapine 5 mg bd. For the 10 mg bd dose the differences from placebo in responder rates were 15.8% in Study 023 and 11.8% in Study 021, with only the 15.8% difference being statistically significant.

Maintenance of clinical improvement

The above studies were followed by 3 extension studies examining maintenance of clinical improvement. Study subjects were to receive continuing study drug for up to 12 months.

Study 502 was an extension of study 004. The population base was very small (n=33), the discontinuation rate high and the active comparator olanzapine remained no more effective than placebo. The study therefore did not provide useful information.

Study 512 was an extension of studies 021 and 022. A selected population of responders was enrolled from the base studies, asenapine was flexibly dosed at either 5 mg bd or 10 mg bd. In this study, median times (95%CI) to loss of effect were: asenapine 29(13, 85) days; olanzapine 29(9, 87) days and placebo/asenapine 42(16, 169) days. The number of patients with a loss of effect in the asenapine 5-10 mg bd group was 42/46 (91.3%) and in the olanzapine group was 32/36 (88.9%). Given the small study numbers and very high relapse rate on medication this study cannot reasonably be considered to support use of asenapine in maintenance treatment of schizophrenia.

Study 513 was an extension of study 023 again only the selected population of responders were considered for the primary analysis of maintenance of effect. The active comparator was haloperidol 2- 8 mg bd. Only 66 (35.7%) subjects completed the study. Sixteen (17.4%) subjects given asenapine withdrew due to insufficient therapeutic effect and 9 (9.8%) due to lack of efficacy compared with 4 (9.3%) withdrawing due to insufficient therapeutic effect and 3 (7%) due to lack of efficacy given haloperidol. A total of 51/65 (78%) subjects given asenapine and 24/29 (83%) given haloperidol had an initial loss of effect during this study. Median survival times for subjects continuing on active treatment from the feeder studies were 31 days (95%CI 28, 140) for subjects treated with asenapine 5-10 mg bd and 85 days (95%CI 15.0, 118.0) for subjects treated with haloperidol 2-8 mg bd. By Week 52 the only subjects still on study who were responders at baseline and who had not suffered a loss of effect were 5 given asenapine and 1 given haloperidol.

Prevention of relapse

One study (012) was presented in which subjects received open label asenapine for up to 4 weeks cross-titration from prior antipsychotic medication, followed by at least 22 weeks monotherapy with asenapine then up to 26 weeks of double-blind treatment with either asenapine 5-10 mg bd or placebo. The primary objective was to determine time to relapse or an impending relapse in schizophrenia in subjects who had received treatment with asenapine for 26 weeks. Subjects had received at least 1 year of continuous antipsychotic treatment for schizophrenia and were clinically stable prior to enrolment. When 115 subjects had confirmation of relapse or impending relapse the study was to be terminated. A total of 382 subjects were included in the ITT analysis. The rate of relapse was 11.05% in the asenapine group and 45.79% in the placebo group during double-blind treatment. The relative risk of experiencing a relapse in the asenapine group compared with the placebo group was 0.26 ($p<0.0001$).

An analysis of effect on persistent negative symptoms in maintenance of clinical improvement (22 weeks initially) was performed. In the 3 studies in which this was assessed (studies 25543, A7501013 and 25544) asenapine was not statistically significantly different from the active comparator, olanzapine. These were not equivalence studies. Superiority of one treatment over the other was not demonstrated.

Response to Clinical Evaluation Report

Following receipt of the Clinical Evaluation Report the sponsor met with TGA representatives to provide a response to the report. It was stated that Study 004 was considered to be a Phase 2 study by the EMEA and a pivotal study by the FDA. A metaanalysis of the 4 short term studies considered to be pivotal (including 004) was presented. This metaanalysis combined results from the 5 mg and 10 mg asenapine doses. In this analysis the reduction from baseline in PANSS vs placebo was minus 3.7 (95%CI -5.9 to -1.5; p= 0.0011). For the combined comparators (olanzapine, risperidone and haloperidol) the reduction from baseline in PANSS vs placebo was -4.1 (95%CI -6.5 to -1.7; p = 0.0010).

Other combinations of these studies were also pooled and presented as sensitivity analyses – one to exclude the failed study, one to exclude Study 004 and another excluding both the failed study and Study 004. All of these analyses showed a statistically significant reduction in PANSS from baseline vs placebo for asenapine. Pooled results for the 30% responder rates were also presented. For the 4 pivotal studies the number needed to treat (NNT) to achieve a patient with a ≥30% improvement was 10.2 for asenapine and 12.0 for the combined comparators. Sensitivity analyses were not presented for this endpoint.

Bipolar 1 Disorder

Six studies in patients with acute mania or mixed episodes associated with Bipolar 1 Disorder were submitted. Studies 004 and 005 were 3-week double-blind period, randomised, placebo and active (olanzapine)-controlled studies of nearly identical design. Subjects completing those studies could participate in Study 006 which permitted continuing treatment for a further 9 weeks. Asenapine as adjuvant therapy to lithium or valproate was examined in Study 008. The final 2 studies (007 and 009) assessed maintenance of effect for up to 52 weeks and enrolled subjects who had completed either Study 006 or 008. The usual asenapine dose in these studies was 10 mg bd but dose titration down to 5 mg bd was permitted in some studies.

The short term studies assessed adult subjects with manic or mixed episodes associated with Bipolar 1 Disorder than must have commenced within 3 months of screening. The primary measure of efficacy was the Young Mania Rating Scale (YMRS), a validated instrument for

assessing mania on a scale from 0-60 with higher scores indicating more severe symptoms. Subjects were required to have a minimum YMRS score of 20 and a history of at least one prior moderate to severe mood episode. Subjects with a history of rapid cycling were excluded.

After an up to 7 day single-blind placebo run in period during which patients received either placebo or olanzapine, the active treatment commenced with placebo, asenapine 10 mg bd or olanzapine 15 mg od in a 1:2:2 ratio. Thereafter down titration of asenapine to 5 mg bd and up or down titration of olanzapine between 5 and 20 mg od based on efficacy and tolerability was permitted. Lorazepam was permitted for treatment of agitation during screening and for the first 7 days only. The primary efficacy endpoint was change from baseline to Day 21 on the YMRS total score (LOCF). The primary comparison was asenapine vs placebo.

A total of 488 subjects were treated in Study 004 and 489 in Study 005. In each study approximately 70% in each treatment group had acute mania and 30% an acute mixed episode. Across groups in the 2 studies mean YMRS total score at baseline ranged from 28.3 to 29.7. The mean changes in YMRS scores from baseline for each treatment group are shown in Tables 27 (004) and 24 (005).

Secondary endpoints included 50% responder rate and change from baseline to end of double-blind period in Clinical Global Impression-BP severity. Both asenapine and olanzapine were statistically significantly superior to placebo for both these endpoints in Study 005. In Study 004 asenapine did not reach statistical significance for 50% responder rate compared with placebo with a responder rate at Day 21 of 42.6% for asenapine and 34% for placebo. The responder rate for olanzapine was 54.7%. Both asenapine and olanzapine were superior to placebo for CGP-BP in that study.

Study 006 was a 9-week extension study to Studies 004 and 005, designed to demonstrate non-inferiority of the maintenance of effectiveness of asenapine compared with olanzapine in the treatment of acute mania in subjects with manic or mixed episodes associated with Bipolar 1 Disorder for up to 12 weeks. Subjects who were on active treatment continued on the same treatment. Subjects previously receiving placebo were blindly allocated to receive asenapine. The primary efficacy endpoint was the change from baseline YMRS of the feeder study to Week 12. The non-inferiority margin was 4 points on the YMRS. The primary analysis was of the PP dataset.

A total of 504 subjects received at least one dose of double-blinded trial medication during the 9-week extension study, 181 had previously received asenapine, 229 olanzapine and 94 placebo in the 3 week acute treatment studies. The PP dataset included only those subjects who were continuing either asenapine or olanzapine. The 95% CI for the difference in change in YMRS score from baseline to Week 12 was not presented. Instead a p-value based on the difference in the LS means, calculated as asenapine-olanzapine was provided. The YMRS total score was reduced by 4 points prior to calculating change from baseline for the asenapine group only. The analysis is based on the difference in the adjusted change from baseline score in the asenapine group versus the unadjusted score in the olanzapine group. The difference between groups for the primary analysis was 0.8 (reduction of 17.1 for olanzapine vs 16.3 for asenapine; $p < 0.0001$). The confidence intervals for the difference between olanzapine and asenapine were not reported.

The results for the primary efficacy criteria (PP population) for Study 006 are shown in Table 30.

The LOCF ITT analysis for the difference in mean change from baseline to Week 12 in YMRS score was minus 20.1 (n=175) for asenapine and minus 21.3 (n=222) for asenapine.

The responder rate for this population was 76.6% for asenapine and 82% for olanzapine (p= 0.0841), again no confidence intervals for the difference were provided.

Efficacy of asenapine in maintenance of effect in subjects with Bipolar 1 Disorder who experienced an episode of acute mania or a mixed episode was examined in Study 007. This was a 40-week continuation of study 006. A total of 218 subjects entered the study and 133 completed. Reduction in mean YMRS score was maintained in both groups at end of study and the responder rates were over 97% for both the asenapine and olanzapine treatment groups at end of study.

The use of asenapine as an adjuvant preparation in subjects taking either lithium or sodium valproate who had inadequate control during acute manic or mixed episodes associated with Bipolar 1 Disorder was examined in Study 008. Subjects were required to have a YMRS score of at least 20 at screening and baseline and to have been continuously treated with lithium or sodium valproate for at least 2 weeks prior to screening.

Double-blinded asenapine or placebo was flexibly dosed (asenapine 5 or 10 mg bd) for up to 12 weeks. A total of 326 subjects were randomised with 116 (36%) completing the double-blind period. Approximately 60% had an acute manic episode and 40% a mixed episode. Mean YMRS scores at baseline were 28.2 for subjects given placebo and 20.0 for those given asenapine. LS mean reduction in YMRS at the end of Week 12 (ITT, LOCF) was 9.3 for subjects given placebo and 12.7 for subjects given asenapine (p=0.0073). The responder rates (ITT, LOCF) at the end of Week 12 were 34.4% for placebo vs 47.7% for asenapine (p=0.0152).

Longer term treatment (an additional 40 weeks) of asenapine as adjuvant therapy was examined in Study 009. Only 77 subjects were enrolled (41 asenapine; 36 placebo) with 34 (44.2%) completing the study. 13 subjects in each group were available for the observed cases analysis at week 52 of treatment. There was no statistical analysis of efficacy results. The LOCF results showed greater mean reductions in YMRS scores for those taking asenapine compared with placebo but results were reversed for the observed cases group at Week 52. It was not clear that the continued addition of asenapine improved the outcome for subjects taking lithium or sodium valproate beyond 12 weeks.

Safety

A total of 4565 subjects received at least one dose of sublingual asenapine: 3159 received the proposed dose of 5-10 mg bd in Phase 2/3 studies and 779 subjects received asenapine for more than 52 weeks; 454 in the schizophrenia studies and 41 in the bipolar mania studies. The most frequently reported adverse events in the combined Phase 2/3 studies were: somnolence (11.0%), weight increased (7.7%), sedation (7.5%), akathisia (6.7%), Parkinsonism (3.5%) and oral hypoaesthesia (3.3%).

Serious adverse events were reported in 15.5% of subjects given asenapine compared with 17.5%- 11.3% in subjects given antipsychotic comparators and 10.1% in subjects given placebo. Nineteen deaths (1.26/ 100 exposure years) occurred in subjects given asenapine compared with one death (0.69/ 100 patient years) in subjects given placebo and from 0-2.89/ 100 patient years with comparator antipsychotics. The highest incidence of death was with haloperidol. The most common adverse event leading to death was suicide, (12 in total, 8 given asenapine [0.2%], 4 given olanzapine [0.4%]). Other subjects given asenapine who died were reported to have epiglottitis (1), pulmonary embolism (2), pneumonia (1), cardiac failure (2), metastatic lung cancer (1) and neonatal drug exposure (1).

A total of 17.5% of subjects given asenapine withdrew due to adverse events (7.4% due to serious adverse events) compared with from 13-23.3% for comparator antipsychotics and

13.5% for placebo. The most frequent serious adverse events in subjects given asenapine were related to the conditions being treated and included: schizophrenia, depression, mania, suicidal ideation and psychotic disorder. Other serious adverse events not clearly due to the conditions being treated were: syncope (0.2%), dystonia (0.1%), hyponatraemia (0.1%), rhabdomyolysis (0.1%) and neuroleptic malignant syndrome (0.1%).

Asenapine was associated with dizziness and postural dizziness with an incidence of 18.8% and 8.1% respectively for subjects in the combined Phase 2/ 3 studies. Pre-syncope, syncope and vasovagal syncope occurred in 3.5%, 1.5% and 1.1% of subjects respectively. The incidences of orthostatic hypotension and syncope were 0.4% each and were similar to those of olanzapine.

Asenapine had no clearly apparent adverse effects on haematology parameters. Changes in LFTs were minor and generally consistent or less than occurred with comparator antipsychotic medications. There were no treatment-related trends observed in glucose and lipid parameters based on mean and median changes from baseline, however there was a mean increase of 11.8 pmol/L in fasting insulin for subjects given asenapine. The increase in fasting insulin was less than occurred in subjects given olanzapine (23.8 pmol/L). Asenapine increased prolactin levels but to a lesser extent than olanzapine.

Subjects given asenapine had a higher incidence of extrapyramidal symptoms than those given olanzapine or risperidone and but less than of subjects given haloperidol. In the long term studies the overall incidence of extrapyramidal symptoms was 16% for subjects given asenapine, compared with 7.7% and 16.2% for olanzapine in the long term studies for schizophrenia and bipolar mania respectively.

Rhabdomyolysis was reported in 4 subjects given asenapine and 1 given olanzapine. All subjects had several risk factors for rhabdomyolysis (polydipsia, water intoxication, hyponatraemia, seizure, fall, prolonged immobilisation and/ or alcohol withdrawal). Three additional serious cases of hyponatraemia without rhabdomyolysis occurred in subjects given asenapine. In 2 of these cases the subjects had excessive water intake. Two of these subjects had seizures. It was considered that the hyponatraemia and seizures were related to polydipsia as a symptom of schizophrenia rather than an adverse effect of asenapine. Seizures occurred in 8/3457 subjects given asenapine (0.2%) compared with 4/1139 (0.4%) given olanzapine and 1/115 (0.9%) given haloperidol.

Weight increases of ≥ 7% body weight occurred in 12.6% of subjects given asenapine in the combined short term studies compared with 14.6% given risperidone, 31.7% given olanzapine and 8.4% given haloperidol. In the long term studies in subjects with Bipolar 1 Disorder weight increases ≥ 7% occurred in 12.5% of subjects given asenapine and in 33.2% given olanzapine. The mean increase in this long term study was 2 kg for subjects given asenapine and 4.5 kg in subjects given olanzapine. In the long-term studies in subjects with schizophrenia or bipolar disorder given asenapine weight increases ≥ 7% occurred in 12.5% with a mean increase of 0.6 kg (clinical safety summary).

Risk Management Plan

The Risk Management Plan (RMP) evaluator noted that the sponsor updated the EU RMP on 10 June 2010 and requested this be submitted in full, rather than the table of changes to the April 2009 version which was included in the submission. There appear to be no safety issues in the previous RMP or in the updated information submitted which would preclude registration.

Risk-Benefit Analysis

Delegate Considerations

Schizophrenia

The demonstration of efficacy in the acute treatment studies was limited and inconsistent. There was no evidence of a dose response. The only Phase 3 study using the proposed flexible dose regimen was a failed study. In the studies considered pivotal (studies 023, 004 and 021) the 5 mg bd dose was superior to placebo for the primary efficacy endpoint in 2 studies (023 and 004) and for the major secondary endpoint of 30% response rate in 2 studies (023 and 004). The 10 mg bd dose was not superior to placebo for the primary efficacy endpoint in any of the pivotal studies. It was superior to placebo for a 30% response rate in one of the 2 pivotal studies in which it was assessed. The major evidence to support the 10 mg bd dose is the *post hoc* metaanalysis of all 4 pivotal trials (including the failed study) in which asenapine was statistically significantly better than placebo for both the primary efficacy endpoint and for the 30% responder rate. In that metaanalysis the differences from placebo were quite small. Of particular concern was the relatively large number of subjects required to be treated to observe a clinically significant response, taken as the responder rate (30% reduction from baseline in total PANSS score). The Delegate did not consider this sufficient evidence to support approval of the 10 mg bd dose regimen for the treatment of acute schizophrenia.

Maintenance of effect assumes that the initial efficacy in treatment of acute schizophrenia is satisfactory. There were 3 studies using flexibly dosed asenapine. The study population was limited to subjects who responded in the 4 acute treatment studies. Subject numbers were small and discontinuation rates very high, leading to few subjects being eligible for assessment of maintenance of effect. Studies 502 and 512 had too few subjects to provide useful information. Study 513 provided the best evidence of efficacy however median survival times for subjects continuing on active treatment from the feeder studies were 31 days (95%CI 28, 140) for subjects treated with asenapine 5-10 mg bd and 85 days (95%CI 15.0, 118.0) for subjects treated with haloperidol 2-8 mg bd. This difference was not statistically significant, however there was a clear trend in favour of haloperidol.

Given the trend towards inferiority of flexibly dosed asenapine in a small study against an active comparator and the lack of data on the 5 mg bd dose as a maintenance treatment the Delegate did not propose to approve asenapine for maintenance of effect in patients with schizophrenia. Flexibly dosed asenapine was better than placebo in prevention of relapse in subjects who had been stable on alternative antipsychotic medication but given that the Delegate did not consider the 10 mg dose of asenapine to have adequately demonstrated efficacy for acute treatment or maintenance treatment it is difficult to see a role for asenapine in prevention of relapse. Ideally the dose in this study should have been the dose in which efficacy in acute treatment was demonstrated.

A restricted indication for reduction in persistent negative symptoms (PNS) could not be considered without a prior satisfactory demonstration of efficacy in schizophrenia. In addition the 3 studies which examined efficacy in reduction in PNS were not adequately designed to determine this effect as a "stand alone" indication.

The Delegate considered that there is just sufficient evidence to approve asenapine for acute schizophrenia at a dose of 5 mg bd.

Bipolar 1 Disorder

Efficacy in the treatment of acute manic or mixed episodes in adults with Bipolar 1 Disorder for initial treatment was well demonstrated for both monotherapy asenapine and as an

adjuvant to either lithium or sodium valproate. The statistical treatment in Study 006 (monotherapy maintenance) was not usual for a non-inferiority study. The sponsor was requested to justify the selection of 4 YMRS points as the non-inferiority margin and to submit the 95% CI for difference for the reduction from baseline to Week 12 in mean YMRS scores for both the PP and ITT population groups to clarify the extent of difference between asenapine and olanzapine in maintenance of effect.

The effect of asenapine in prevention of recurrence of manic or mixed episodes has not been assessed. The TGA-adopted EU guideline distinguishes between prevention of relapse (following an acute episode) and prevention of recurrence.[40] Prevention of recurrence requires that subjects be in full remission at the start of study. The indications should reflect efficacy in prevention of relapse rather than in *maintenance of improvement* as has been proposed by the sponsor because *maintenance of improvement* is likely to be confused with the usual usage of maintenance as both for prevention of recurrence and of relapse. Efficacy of the long term use of asenapine as an adjuvant to lithium or sodium valproate was not adequately demonstrated. Use of asenapine as monotherapy in the prevention of relapse to 12 months is better supported and appears as efficacious as olanzapine.

Asenapine has little effect on prolactin levels and less effect metabolic parameters than most atypical antipsychotic medicines. It is associated with more extrapyramidal effects than risperidone and olanzapine. Weight gain occurs but to a lesser extent than with olanzapine. Other adverse effects associated with atypical antipsychotic medicines such as sedation, neuroleptic malignant syndrome, seizures and orthostatic hypotension were also apparent with asenapine.

As a sublingual dose form it is not clear if patients would take asenapine sublingually or tend to swallow it. Careful patient selection and instruction is likely to be required. The tablet should be held in the mouth until it dissolves completely and no food or liquid taken for 10 minutes after the tablet is placed under the tongue.

The Delegate proposed to approve Saphris for *acute treatment of schizophrenia in adults.* The recommended dose is 5 mg bd.

The Delegate further proposed to approve Saphris 5 mg and 10 mg sublingual tablets for:

Treatment of acute manic or mixed episodes associated with Bipolar 1 Disorder as monotherapy or in combination with lithium or sodium valproate; and for

Prevention of recurrence of manic or mixed episodes in Bipolar 1 Disorder as monotherapy

The Delegate proposed to reject Saphris for prevention of relapse and maintenance of clinical improvement during continuation therapy in patients with schizophrenia due to insufficient evidence of efficacy.

The advice of the ACPM was particularly requested on:

1. Whether asenapine should be approved for use in acute schizophrenia given the lack of evidence of a dose response relationship.
2. Whether it is appropriate to approve asenapine for acute treatment of schizophrenia when there is inadequate evidence for use of asenapine for ongoing management following acute episodes.

Response from Sponsor

The sponsor addressed the matters raised by the Delegate.

Acute treatment of schizophrenia with asenapine 5 mg and 10 mg bd

The asenapine 5 mg bd dose was demonstrated to be superior to placebo for the primary efficacy variable (Change from baseline [CFB] of PANSS total score) in two independent fixed dose trials in acute schizophrenia (Studies 004 and 023). In the fixed dose trials this 5 mg bd dose was also superior to placebo in the secondary efficacy variable (>30% PANSS responders) in three trials (004, 021 and 023). The difference from placebo in responder rates for the asenapine 5 mg bd dose ranged from 15.6% to 22.2% in the two studies in which statistical analysis of this secondary endpoint was presented. The dose of 10 mg bd did not meet the primary efficacy endpoint in the LOCF analysis of the performed trials. However, the 10 mg bd fixed dose arm in trial 023 showed similar efficacy on the primary endpoint (CFB of PANSS total score of -4.2 points compared to placebo, which missed statistical significance in the LOCF analysis but was significant in the MMRM analysis, p=0.037) and also produced significantly higher rates of PANSS responders than placebo (51/105 (48.6%) vs 40/122 (32.8%), p=0.015).

Meta-analyses of the trials in acute schizophrenia were performed using the combined doses of 5 mg and 10 mg bd and these meta-analyses were submitted to the TGA in response to the clinical evaluation report. They demonstrate that Saphris at the combined doses of 5 mg and 10 mg bd is significantly superior to placebo for the primary efficacy parameter of CFB of PANSS total score (-3.7; 95% CI -5.9 to -1.5; p =0.0011) and the effect size is comparable to the active controls used in the same trials (combined comparators olanzapine, risperidone and haloperidol -4.1; 95% CI -6.5 to -1.7; p = 0.0010). For these same trials, the NNT to achieve a response (defined as at least 30% improvement) in a patient was 10.2 for asenapine and 12.0 for the combined comparators.

Similar results were obtained when response rates (>30% PANSS responders) were analysed in the dose range of 5-10 mg bd for Saphris in comparison to placebo and referencing active controls from the same clinical trials. The Delegate acknowledges in the overview that the "major evidence to support the 10 mg bd dose is the *post hoc* metaanalysis of all 4 pivotal trials (including the failed study) in which asenapine was statistically significantly better than placebo for both the primary efficacy endpoint and for the 30% responder rate".

While the sponsor agreed that the 10 mg bd dose did on average not lead to an increased clinical effect in the acute schizophrenia studies, a clear-cut dose response relationship has generally not been well established for atypical antipsychotics either. A review from Kinon et al. (2004) concluded: "A challenge in the treatment of schizophrenia is our limited knowledge of the effective dose-response relationships of these agents".[53] Since individual sensitivity to wanted and unwanted effects may vary between individuals for unknown reasons, clinicians have to match in clinical practice the dose of any antipsychotic agent to the individual needs of the patient, attempting to optimise the benefit-risk on an individual patient level. The clinical data for asenapine suggest that for some patients a dose higher than 5 mg bd can be of clinical benefit. The sponsor therefore proposed that asenapine 5 mg bd should be the recommended starting dose for treatment of schizophrenia, with the option for clinicians to increase the dose up to asenapine 10 mg bd, if a dose increase seems clinically warranted by the treating physician.

Long-term treatment of schizophrenia with asenapine 5 mg and 10 mg bd

The TGA-adopted EU guideline discusses several approaches to demonstrate maintenance of efficacy in schizophrenia.[54] Section 2.4 specifically states that "Relapse prevention studies

[53] Kinon BJ et al. Dose response and atypical antipsychotics in schizophrenia. CNS Drugs 2004; 18: 597-616.
[54] EMEA, Committee for Proprietary Medical Products (CPMP), 26 February 1998. Note for Guidance on the

may be used to show that the effect of medicinal products is maintained". Section 4.2 follows to discuss methods to assess efficacy in "Relapse prevention (maintenance therapy): The expected attrition rate should be taken into account for power calculation. Time to relapse could be analysed and there also should be a direct comparison between treatment arms in terms of proportion patients who relapsed." Section 6.4.2 "Maintenance therapy" elaborates on trial design issues. The guideline states: "Another possibility is a so-called relapse prevention study, in which responders to the acute treatment are included and randomized into a medication and a placebo group and for which rate of or time to relapse is used as criterion for efficacy. However, when this design is used, the duration of the acute therapy period probably needs to be longer than 6 weeks and it may be useful to stabilize the patients first during an open treatment period."

The design of Study A7501012 has been conducted according to the guidelines. The sponsor emphasised that during the 26 weeks of open label stabilization, subjects were treated to stabilization on a flexible dose of Saphris 5-10 mg bd, not on alternative antipsychotic medication. Previous antipsychotic medication had previously been tapered off, while Saphris was introduced already before the start of the 26 weeks long term open label stabilization period.

In this study, 700 patients who were previously treated with other antipsychotics were included in the trial and switched to open label flexible dose treatment with Saphris 5-10 mg bd for a period of 26 weeks. A total of 386 met the criteria of stabilization after 26 weeks on asenapine 5-10 mg bd and were randomized to the double blind, placebo controlled withdrawal part of the trial. A sizable number of patients was stabilized and maintained on the dose of 10 mg bd (77.8 %). The rate of relapse was 11.05% in the asenapine group and 45.79% in the placebo group during the double-blind treatment. The relative risk of experiencing a relapse in the asenapine group compared with the placebo group was 0.26 ($p < 0.0001$). Therefore, the primary endpoint of the trial was clearly met, Saphris was significantly superior to placebo (Figure 11).

Study A7501012 provides robust evidence for the claim of maintenance of efficacy in schizophrenia and is the main supportive evidence for maintenance therapy in schizophrenia with Saphris. Study A7501012 was the basis of evidence for the approval of an sNDA provided for the maintenance treatment of schizophrenia granted by the FDA.

In summary, the results of Study A7501012 strongly support the efficacy of Saphris as maintenance therapy in schizophrenia. Therefore the sponsor proposed approval of Saphris for "Treatment of schizophrenia, with efficacy established in two 6-week clinical trials and one maintenance trial in adult patients with schizophrenia".

Treatment of Persistent negative symptoms of schizophrenia with asenapine

Dedicated studies were performed to investigate the use of asenapine 5 mg and 10 mg bd in the treatment of persistent negative symptoms compared with olanzapine. Although the primary efficacy variable of superiority versus olanzapine was not met, asenapine did demonstrate an improvement over baseline for up to 12 months treatment similar to olanzapine. This study also supports the long-term use of asenapine 5 mg and 10 mg bd in the treatment of schizophrenia.

Treatment of Bipolar 1 Disorder with asenapine

The Delegate requested that the sponsor justify the selection of 4 YMRS points as the non-inferiority margin that was used in Study A7501006. In summary, this aspect was discussed

Clinical Investigation of Medicinal Products in the Treatment of Schizophrenia, CPMP/EWP/559/95.

with members of an Advisory Board and these clinical experts concluded that a margin of 4 points would constitute a fair and relevant non-inferiority margin, which was half of the difference between the YMRS entry criterion of 20 and the YMRS remitter criterion of 12.

The Delegate also requested the sponsor to submit the 95% CI for difference for the reduction from baseline to week 12 in mean YMRS scores for both the PP and ITT population groups to clarify the extent of difference between asenapine and olanzapine in maintenance of effect. The raw data was provided. The Analysis of Covariance (ANCOVA) with factors of treatment and pooled investigator's site and baseline value as covariate was used. From the data observed, the asenapine group and olanzapine group performed similar in reduction of the YMRS total score in this study for both ITT and PP population, as well as for both LOCF and OC analysis.

In summary, asenapine 5 mg bd was demonstrated to be superior to placebo in the acute treatment of schizophrenia for the primary efficacy variable (CFB of PANSS total score) in two independent studies and superior to placebo for the secondary efficacy variable (>30% PANSS responders) in three independent studies. The results for asenapine 10 mg bd trended in the same direction but did not reach statistical significance however a significant result for the secondary efficacy variable (>30% PANSS responders) was noted in Study 023. The meta-analysis of the 4 acute studies in schizophrenia using all available data (both asenapine 5 mg and 10 mg bd and data from a failed study) demonstrated a significant treatment effect for asenapine over placebo on the primary and secondary efficacy variables and an effect similar in magnitude to the pooled comparators. The relapse prevention trial was conducted with a significant stabilization period on asenapine followed by randomization to asenapine and placebo and the results confirm the superiority of asenapine over placebo (the relative risk of experiencing a relapse in the asenapine group compared with the placebo group was 0.26). Thus the data presented for asenapine 5 mg and 10 mg bd supports the acute and long-term maintenance treatment of schizophrenia patients.

The Delegate has concurred with the sponsor's view on the use of asenapine for the treatment of patients with Bipolar 1 Disorder. The sponsor believes that the wording of the proposed indication below appropriate reflects the data that was evaluated and assessed by the TGA.

In conclusion, the sponsor proposed approval for the indications:

• *treatment of schizophrenia in adults including maintenance therapy*

• *treatment of acute manic or mixed episodes associated with Bipolar 1 Disorder in adults and maintenance of clinical improvement during the manic episode as monotherapy or in combination with lithium or sodium valproate*

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended approval of the submission for the indication:

The treatment of schizophrenia in adults with a recommended dose of 5 mg bd.

For the treatment of acute, manic or mixed episodes associated with Bipolar 1 Disorder as monotherapy or in combination with lithium or sodium valproate with a recommended dose of 5 or 10 mg bd.

For prevention of relapse of manic or mixed episodes in Bipolar I Disorder as monotherapy with a recommended dose of 5 or 10 mg bd.

The ACPM also recommended changes to the Product Information (PI) and Consumer Medicines Information (CMI) which are beyond the scope of this AusPAR.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Saphris containing asenapine (as maleate) 5 mg and 10 mg sublingual wafer blister pack, indicated for:

Treatment of schizophrenia in adults

Treatment of acute manic or mixed episodes associated with Bipolar 1 Disorder in adults as monotherapy or in combination with lithium or sodium valproate

Prevention of relapse of manic or mixed episodes in Bipolar 1 Disorder in adults as monotherapy or in combination with lithium or sodium valproate

As a condition of registration, the full implementation of the Risk Management Plan version 02 dated April 2009, as agreed with the Office of Product Review, must be implemented.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

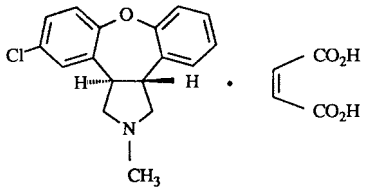
AUSTRALIAN PRODUCT INFORMATION

SAPHRIS®

(asenapine maleate)

NAME OF THE MEDICINE

Asenapine maleate is chemically identified as (3a*R*,12b*R*)-rel-5-chloro-2,3,3a,12b-tetrahydro-2-methyl-1*H*-dibenz(2,3:6,7)oxepino[4,5-c]pyrrole (2*Z*)-2-butenedioate (1:1) and has the following structural formula:



Molecular formula: $C_{17}H_{16}ClNO \cdot C_4H_4O_4$ (and enantiomer)

Molecular weight: 401.84

CAS number: 85650-56-2

DESCRIPTION

SAPHRIS is a novel antipsychotic, belonging to the dibenzo-oxepino pyrroles. It has antagonist activity on the dopamine 2 (D_2) and serotonin (5-HT)-2A receptors.

The solubility of asenapine (active entity) in water is 3.7 mg/mL, in 0.1M HCl is 13 mg/mL and in aqueous buffers of pH 4.0 and 7.0 the solubility is 3.8 mg/mL and 3.0 mg/mL, respectively. The pKa of asenapine is 8.6 (determined in water/methanol). Asenapine has a log P (n-octanol/water) of 4.9 for the neutral species and 1.4 for the cationic species.

SAPHRIS is available as 5 mg and 10 mg wafers containing 5 mg asenapine (7.03 mg asenapine maleate) and 10 mg asenapine (14.06 mg asenapine maleate), respectively. Each wafer of SAPHRIS also contains gelatin and mannitol.

PHARMACOLOGY

Pharmacodynamics

The mechanism of action of asenapine, as with other drugs having efficacy in schizophrenia and bipolar disorder, is not fully understood. However, based on its receptor pharmacology, it is proposed that the efficacy of asenapine is mediated through a combination of antagonist activity at D_2 and 5-HT_{2A} receptors. Actions at other receptors e.g., 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2C}, 5-HT_6, 5-HT_7, D_3, and α_2-adrenergic receptors, may also contribute to the clinical effects of asenapine.

Pharmacokinetics

<u>Absorption</u>

Following sublingual administration, asenapine is rapidly absorbed with peak plasma concentrations occurring within 0.5 to 1.5 hours. The average peak plasma concentrations at steady state of 5 and 10 mg twice daily were 3.6 ng/mL and 7.0 ng/mL respectively. The absolute bioavailability of sublingual asenapine at 5 mg is 35%. Increasing the dose from 5 to 10 mg twice daily (a two-fold increase) results in less than linear (1.7 times) increases in both the extent of exposure and maximum concentration. The absolute bioavailability of asenapine when swallowed is low (< 2% with an oral tablet formulation). The intake of water several (2 or 5) minutes after asenapine administration resulted in decreased (19% and 10%, respectively) asenapine exposure. Therefore, eating and drinking should be avoided for 10 minutes after administration (see DOSAGE AND ADMINISTRATION).

Distribution

Asenapine is rapidly distributed and has a large volume of distribution (approximately 1700L), indicating extensive extravascular distribution. Asenapine is highly bound (95-97% at 1-500ng/mL) to plasma proteins *in vitro*, including albumin and α1-acid glycoprotein.

Metabolism

Asenapine is extensively metabolised. Oxidative metabolism by cytochrome P450 isoenzymes (predominantly CYP 1A2) and direct glucuronidation by UGT1A4 are the primary metabolic pathways for asenapine. In an *in vivo* study in humans with radio-labelled asenapine, the predominant drug-related entity in plasma was asenapine N^+-glucuronide; others included N-desmethylasenapine, N-desmethylasenapine N-carbamoyl glucuronide, and unchanged asenapine in smaller amounts. SAPHRIS activity is primarily due to the parent drug.

Asenapine is a weak inhibitor of microsomal CYP2D6 activity. Asenapine does not cause induction of CYP1A2 activity and slightly increased CYP3A4 activity at high concentrations 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 PRECAUTIONS – Interactions with other medicines).

Elimination

Asenapine is a high clearance drug, with a clearance after intravenous administration of 52 L/h. In a mass balance study, the majority of the radioactive dose was recovered in urine (about 50%) and faeces (about 40%), with only a small amount excreted in faeces (5-16%) as unchanged drug. 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.

Special Populations

Renal Impairment

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.

Hepatic Insufficiency

The pharmacokinetics of asenapine were similar among subjects with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment and subjects with normal hepatic function. In subjects with severe hepatic impairment (Child-Pugh C), a 7-fold increase in asenapine exposure was observed (see Dosage and administration – hepatic impairment).

Elderly

Interim results from 33 subjects aged 65-85 years indicate approximately 30% higher exposure to asenapine in elderly patients compared to adult patients.

Adolescents

At the 5 mg twice daily dose level, the pharmacokinetics of asenapine in adolescents (12 to 17 years of age, inclusive) is similar to those observed in adults. In adolescents, the 10 mg twice daily dose did not result in increased exposure to asenapine compared to 5 mg twice daily.

Smoking

A population pharmacokinetic analysis indicated that smoking, which induces CYP1A2, has no effect on the clearance of asenapine. In a dedicated study, concomitant smoking during administration of a single 5 mg sublingual dose had no effect on the pharmacokinetics of asenapine.

Gender

A population pharmacokinetic analysis indicated that there is no evidence of gender-related differences in the pharmacokinetics of asenapine.

Race

A single dose pharmacokinetic study did not demonstrate any significant differences in pharmacokinetic parameters between Japanese and Caucasian healthy subjects. Additionally, in a population pharmacokinetic analysis, no clinically relevant effects of race on the pharmacokinetics of asenapine were found.

CLINICAL TRIALS

Schizophrenia

Acute Schizophrenia

The efficacy of SAPHRIS in the treatment of schizophrenia was investigated in three fixed-dose, short-term (6 weeks), randomised, double-blind, placebo- and active-controlled trials of patients who met DSM IV criteria for schizophrenia and were having an acute exacerbation of their schizophrenic illness. The primary efficacy rating scale was the Positive and Negative Syndrome Scale (PANSS), which assesses the symptoms of schizophrenia. Secondary efficacy endpoints included each of the PANSS subscales (PANSS positive, negative and general psychopathology subscales), the PANSS subscales based on the Marder factor analysis and the Clinical Global Impression (CGI). **Study 041004** was a trial (n=174)

comparing SAPHRIS (5 mg twice daily) to placebo with risperidone (3 mg twice daily) as the active control. **Study 041023** was a trial (n=448) comparing two fixed doses of SAPHRIS (5 and 10 mg twice daily), to placebo with haloperidol (4 mg twice daily) as the active control. **Study 041021** was a trial (n=386) comparing two fixed doses of SAPHRIS (5 and 10 mg twice daily) to placebo with olanzapine (15 mg once daily) as the active control. The results for the efficacy variables (change from baseline in PANSS total score and 30% responder rates) are presented in the following tables.

Study 041004

Variable	Placebo (N=60)	Asenapine 5mg bid (N=58)	Risperidone 3mg bid (N=56)
PANSS (Mean ± SE)			
Baseline	92.43 ± 1.93	96.48 ± 2.16	92.18 ± 2.05
Visit 6/Endpoint	87.17 ± 2.81	80.62 ± 2.79	81.25 ± 3.02
Endpoint Change	-5.27 ± 2.30	-15.86 ± 2.62	-10.93 ± 2.67
Difference in mean endpoint change from placebo		-10.59 p = 0.002	-5.66 p = 0.1186
PANSS Responders n (%)	15 (25)	22 (38)	22 (39)
Difference from placebo in responder rate		13%	14%

Study 041023

Variable	Placebo (N=122)	Asenapine 5mg bid (N=109)	Asenapine 10mg bid (N=105)	Haloperidol 4mg bid (N=112)
PANSS (Mean + SD)				
Baseline	88.9 ± 11.67	89.2 ± 12.01	89.1 ± 12.88	88.6 ± 12.15
Endpoint	78.4 ± 19.88	73.3 ± 21.39	74.4 ± 20.42	73.5 ± 19.33

Endpoint Change (range)	-10.4 ± 18.05	-15.9 ± 17.69	-14.6 ± 19.31	-15.1 ± 16.29
Difference in mean endpoint change from placebo		-5.5 P = 0.029	-4.2 P = 0.068	-4.7 P = 0.0342
PANSS Responders n (%)	40 (32.8)	60 (55.0)	51 (48.6)	48 (42.9)
Difference from placebo in responder rate		22.2% P = 0.005	15.8% P = 0.015	10.1% P = 0.0927

Study 041021

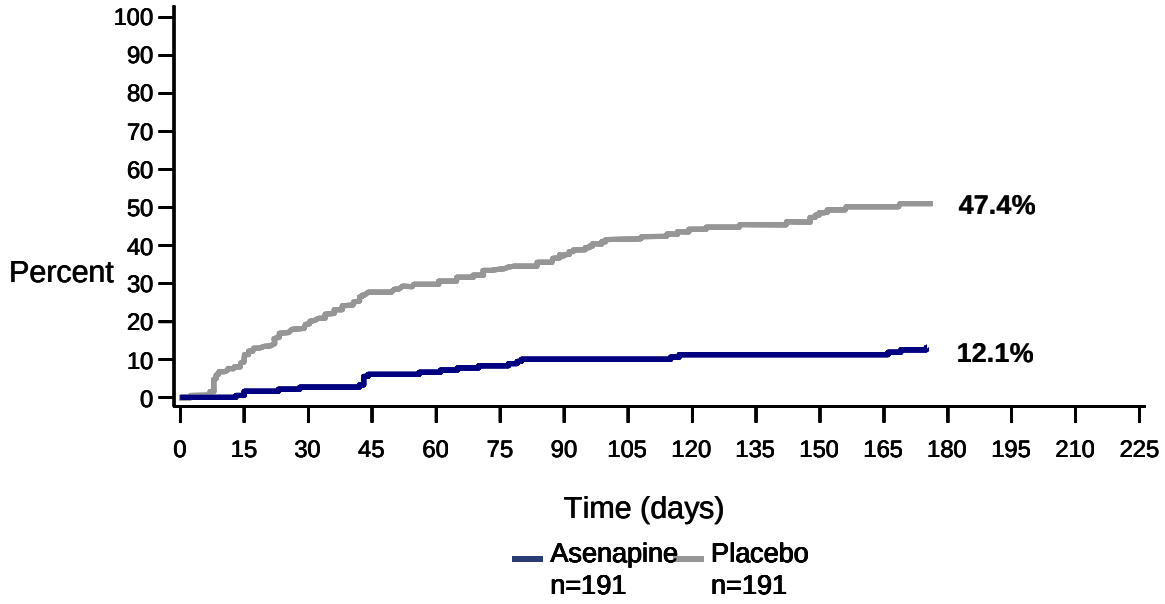
Variable	Placebo (N=93)	Asenapine 5mg bid (N=102)	Asenapine 10mg bid (N=96)	Olanzapine 15mg (N=95)
PANSS (Mean ± SD)				
Baseline	94.6 ± 12.69	91.7 ± 15.47	94.4 ± 13.58	93.7 ± 12.93
Endpoint	83.8 ± 19.82	78.1 ± 19.63	81.3 ± 20.13	78.0 ± 18.01
Endpoint Change (range)	-10.7 ± 17.00	-13.7 ± 17.24	-13.1 ± 18.49	-15.7 ± 16.15
Difference in mean endpoint change from placebo		-3.0 p = 0.1278	-2.4 p = 0.3046	-5.0 p = 0.0168
PANSS Responders n (%)	21 (22.6)	39 (38.2)	33 (34.4)	39 (41.1)
Difference from placebo in responder rate		15.6% p = 0.0199	11.8% p = 0.0796	18.5% p = 0.0019

Maintenance in Schizophrenia

Study A7501012. This study was a randomized, placebo-controlled, double-blind, multicentre, multinational clinical trial evaluating the efficacy and safety of sublingually administered SAPHRIS (5 or 10 mg twice daily) compared to placebo in the prevention of relapse in subjects with schizophrenia. A total of 700 patients entered the open-label treatment with SAPHRIS for up to 26 weeks. Of these, a total of 386 patients met criteria for stabilization on SAPHRIS and were randomised to treatment in the 26-week double-blind placebo-controlled phase of the trial.

SAPHRIS was significantly more effective than placebo in preventing relapse, as measured by the endpoint of the trial estimated through Kaplan-Meier curves. At the 26 week endpoint, 47% of the placebo-treated patients relapsed, compared with only 12% of the asenapine-treated patients (p<0.0001) (Figure 1).

Figure 1: Kaplan-Meier estimation of percent relapse/impending relapse as determined by the investigator (Intent-to-treat)



Bipolar 1 Disorder

Acute treatment of manic or mixed episodes

Two similarly designed 3-week, randomised, double-blind, placebo and active-controlled (olanzapine) monotherapy trials involving 488 (Study A751004) and 489 (Study A751005) patients, respectively, with acute manic or mixed episode of bipolar I disorder with or without psychotic features, investigated the efficacy of SAPHRIS compared to placebo in the reduction of manic symptoms over 3 weeks. The primary efficacy end point was the reduction from baseline in YMRS mean change from BL score and for SAPHRIS a statistically significant effect was noted as early as Day 2, and was maintained until the last trial visit (Day 21) when compared to placebo. The main efficacy results are presented in the following Tables.

Table 1. Efficacy results (LOCF-ITT) for Study A751005.

YMRS mean change from BL score	Placebo	Asenapine	Olanzapine

	(n=103)	(n=189)	(n=188)
Day 21			
LS mean change from baseline (SE)	- 5.5 (1.01)	- 10.8 (0.75)[a]	- 12.6 (0.76)[a]
% responders	25.2	42.3[b]	50.0[a]
% remitters	22.3	40.2[c]	39.4[d]

Responders: a 50% decrease from baseline in YMRS total score
Remitters: have a YMRS total score of 12 or lower
[a] P < 0.0001; [b] P = 0.0049, [c] P = 0.0020; [d] P = 0.0041 (all compared to placebo)

Table 2. Efficacy results (LOCF-ITT) for Study A751004.

YMRS mean change from BL score	Placebo (n=94)	Asenapine (n=183)	Olanzapine (n=203)
Day 21			
LS mean change from baseline (SE)	- 7.8 (1.11)	- 11.5 (0.80)[b]	- 14.6 (0.76)[a]
% responders	34.0	42.6	54.7[c]
% remitters	30.9	35.5	46.3[d]

Responders: a 50% decrease from baseline in YMRS total score
Remitters: have a YMRS total score of 12 or lower
[a] P < 0.0001; [b] P = 0.0065, [c] P = 0.0011; [d] P = 0.0159 (all compared to placebo)

Maintenance of Effect:

A 9-week extension trial (Study A751006; n=181 for asenapine and n=229 for olanzapine) was conducted to demonstrate non-inferiority of the maintenance of effectiveness of SAPHRIS compared with olanzapine for up to 12 weeks. The primary efficacy endpoint was the change from baseline YMRS score to week 12. SAPHRIS was shown not to be statistically (PP: 1.1 with 95% CI -0.47 to 2.78; ITT: 1.2 with 95% CI -0.42 to 2.81) inferior to olanzapine in the treatment of subjects with a manic or mixed bipolar episode.

Combination therapy with lithium or sodium valproate

A 12-week randomised, double-blind, placebo-controlled, flexible dose trial (Study A751008) examined the efficacy of SAPHRIS (5 mg as the starting dose with the option to uptitrate to 10 mg) when administered concurrently with lithium or sodium valproate compared with lithium or sodium valproate monotherapy. The primary efficacy endpoint was the change from baseline to Day 21 (3 weeks) in the YMRS score (LOCF-ITT). Multiple secondary parameters were investigated including YMRS responder and remitter rates. The results are presented below up to 84 days (12 weeks) of treatment (Table 3).

Table 3. Efficacy results (LOCF-ITT) for asenapine combination therapy with lithium or sodium valproate in comparison with lithium or sodium valproate monotherapy (Study A751008).

YMRS mean change from BL score	Placebo (n=163)	Asenapine (n=155)	p-value
Day 21			
LS mean change from baseline (SE)	- 7.9 (0.76)	- 10.3 (0.79)	0.0257
% responders	27.0	34.2	0.1634
% remitters	21.5	33.5	0.0158
Day 84			
LS mean change from baseline (SE)	- 9.3 (0.89)	-12.7 (0.92)	0.0073
% responders	34.4	47.7	0.0152
% remitters	30.1	43.2	0.0148

Responders: a 50% decrease from baseline in YMRS total score
Remitters: have a YMRS total score of 12 or lower

The efficacy of combination therapy beyond 12 weeks has not been demonstrated.

INDICATIONS

SAPHRIS is indicated in the:

- treatment of schizophrenia in adults
- treatment of acute manic or mixed episodes associated with Bipolar 1 Disorder in adults as monotherapy or in combination with lithium or sodium valproate
- prevention of relapse of manic or mixed episodes in Bipolar 1 Disorder in adults as monotherapy or in combination with lithium or sodium valproate

CONTRAINDICATIONS

SAPHRIS is contraindicated in:

- Patients who are hypersensitive to any component of the wafer or to asenapine

PRECAUTIONS

Elderly patients with dementia-related psychosis:

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death compared to placebo. A meta-analysis of 17 placebo controlled trials with dementia related behavioural disorders showed a risk of death in

the drug treated patients of approximately 1.6 to 1.7 times that seen in placebo treated patients. The clinical trials included in the meta-analysis were undertaken with Zyprexa (olanzapine), Abilify (aripiprazole), Risperdal (risperidone) and Seroquel (quetiapine). Over the course of these trials averaging about ten weeks in duration, the rate of death in drug treated patients was about 4.5% compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g. heart failure, sudden death) or infectious (e.g. pneumonia) in nature. SAPHRIS is not approved for the treatment of patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome:

Neuroleptic Malignant Syndrome (NMS), characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated serum creatine phosphokinase levels, has been reported to occur with antipsychotics, including SAPHRIS. Additional clinical signs may include myoglobinuria (rhabdomyolysis) and acute renal failure.

If a patient develops signs and symptoms indicative of NMS, SAPHRIS must be discontinued.

Seizures:

In clinical trials, cases of seizure were occasionally reported during treatment with SAPHRIS. Therefore, SAPHRIS should be used with caution in patients who have a history of seizure disorder or have conditions associated with seizures.

Suicide:

The possibility of a suicide attempt is inherent in schizophrenia and bipolar disorder; close supervision of high-risk patients should accompany treatment. Prescriptions for SAPHRIS should be written for the smallest quantity of wafers consistent with good patient management in order to reduce the risk of overdose.

Weight increase:

In the combined short-term and long-term schizophrenia and bipolar mania trials, the mean weight change for patients treated with asenapine was 0.8 kg. The mean body weight change from baseline to endpoint in the placebo-controlled short-term schizophrenia trials was 1.1 kg for SAPHRIS, 0.1 kg for placebo, and 2.4 kg for olanzapine. The proportion of subjects with clinically significant weight gain (>7% weight gain from baseline to endpoint) in the short-term schizophrenia trials was 5.3% for asenapine-treated subjects compared to 2.3% for placebo. In the placebo-controlled short-term bipolar mania trials, mean weight changes were 1.3 kg for SAPHRIS, 0.2 kg for placebo, and 2.3 kg for olanzapine. The proportion of subjects with clinically significant weight gain in the short-term bipolar mania trials was 6.5% for asenapine-treated patients compared with 0.6% for placebo.

In the open-label phase of Study A7501012 the mean change in body weight from baseline to open-label endpoint was 0.5 kg. Clinically relevant weight gain (> 7% from baseline) occurred in 7.0% of the subjects, while clinically relevant weight loss occurred in 4.3%. In the double-blind phase, mean change in body weight from double-blind baseline to double-blind endpoint was -1.2 kg in the placebo treatment group and 0.0 kg in the asenapine treatment group. Clinically relevant weight gain in

the double-blind phase occurred in 3.7% of the asenapine-treated subjects and in 0.5% of the placebo-treated subjects, while clinically relevant weight loss occurred in 3.2% of the asenapine subjects and in 9.6% of placebo subjects. There were no subjects in either the asenapine or placebo group who discontinued from the study due to weight increased or weight decreased.

In the long-term trials, the mean body weight changes from baseline to endpoint for SAPHRIS were 0.6 kg and 2.0 kg (schizophrenia and bipolar mania trials, respectively). The mean body weight changes in these trials for olanzapine were 3.7 kg and 4.5 kg (schizophrenia and bipolar mania trials, respectively).

Orthostatic Hypotension:

SAPHRIS may induce orthostatic hypotension and syncope, especially early in treatment, probably reflecting its α1-adrenergic antagonist properties. Elderly patients are particularly at risk for experiencing orthostatic hypotension. In clinical trials, cases of syncope were occasionally reported during treatment with SAPHRIS. As with other atypical antipsychotics, SAPHRIS should be used with caution in elderly patients and patients with known cardiovascular disease (history of myocardial infarction or ischaemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions which would predispose patients to hypotension (dehydration, hypovolaemia, and treatment with antihypertensive medications).

Tardive Dyskinesia:

Medicines with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia characterised by rhythmical, involuntary movements, predominantly of the tongue and/or face. In clinical trials, cases of tardive dyskinesia were occasionally reported during treatment with SAPHRIS. The onset of extrapyramidal symptoms is a risk factor for tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear in a patient on SAPHRIS, discontinuation of treatment should be considered.

SAPHRIS should be prescribed in a manner that is most likely to minimise the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

Hyperprolactinaemia:

Like other drugs that antagonise dopamine D_2 receptors, SAPHRIS can elevate prolactin levels, and the elevation can persist during chronic administration. Hyperprolactinaemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhoea, amenorrhoea and gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinaemia when associated with hypogonadism may lead to decreased bone density in both female

and male subjects. In SAPHRIS clinical trials, the incidence of adverse events related to abnormal prolactin levels were 0.4% versus 0% for placebo.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent in vitro, a factor of potential importance if the prescription of these drugs is considered in a patient with previously-detected breast cancer. Neither clinical studies nor epidemiological studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive.

Leukopenia, Neutropenia, and Agranulocytosis:

In clinical trials and postmarketing experience, events of leukopenia/neutropenia have been reported temporarily related to antipsychotic agents, including SAPHRIS. Agranulocytosis (including fatal cases) has been reported with other agents in the class.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should have their complete blood count (BC) monitored frequently during the first few months of therapy and SAPHRIS should be discontinued at the first signs of decline in WBC in the absence of other causative factors.

Patients with neutropenia should be carefully monitored for fever ot other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < 1000/mm^3) should discontinue SAPHRIS and have their WBC followed until recovery.

QT interval:

Clinically relevant QT prolongation does not appear to be associated with asenapine. Caution should be exercised when SAPHRIS is prescribed in patients with known cardiovascular disease or family history of QT prolongation, and in concomitant use with other medicines thought to prolong the QT interval.

The effects of asenapine on the QT/QTc interval were evaluated in a dedicated QT study. This trial involved asenapine doses of 5 mg, 10 mg, 15 mg and 20 mg twice daily and placebo, and was conducted in 151 clinically stable patients with schizophrenia with electrocardiographic assessments throughout the dosing interval at baseline and steady state. At these doses, asenapine was associated with increases in QTc interval ranging from 2 to 5 msec compared to placebo. No patients treated with SAPHRIS experienced QTc increases $\geq$ 60 msec from baseline measurement, nor did any patient experience a QTc of $\geq$ 500 msec.

Electrocardiogram (ECG) measurements were taken at various time points during the SAPHRIS clinical trial program (5 mg or 10 mg twice daily doses). Post-baseline QT prolongations exceeding 500 msec were reported at comparable rates for asenapine and placebo in these short-term trials.

Hyperglycaemia and Diabetes Mellitus:

Hyperglycaemia or exacerbation of pre-existing diabetes has occasionally been reported during SAPHRIS treatment. In clinical trials with SAPHRIS, there were no

significant differences in the incidence rates of hyperglycaemia-related adverse events compared to placebo. However, in short term clinical studies there was a mean increase in fasting insulin of 11.8 pmol/L for subjects given asenapine. The increase in fasting insulin was less than occurred in subjects given olanzapine (23.8 pmol/L). Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

Dysphagia:

Oesophageal dysmotility and aspiration have been associated with antipsychotic treatment. Cases of dysphagia were occasionally reported in patients treated with SAPHRIS.

Body temperature regulation:

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic medicines. From the clinical trials, it is concluded that clinically relevant body temperature dysregulation does not appear to be associated with asenapine. Appropriate care is advised when prescribing SAPHRIS for patients who will be experiencing conditions that may contribute to an elevation in core body temperature e.g. exercising strenuously, exposure to extreme heat, receiving concomitant medicinal products with anticholinergic activity or being subject to dehydration.

Patients with severe hepatic impairment:

Asenapine exposure is increased 7-fold in patients with severe hepatic impairment (Child-Pugh C). Therefore, SAPHRIS is not recommended in such patients.

Extrapyramidal Symptoms (EPS):

From the short-term (6 week) schizophrenia trials there appears to be a dose-response relationship for akathisia in patients treated with asenapine, and for parkinsonism there was an increasing trend with higher doses.

In the long term trials the overall incidence of EPS for subjects treated with SAPHRIS 5-10 mg twice daily was approximately 16% for both the schizophrenia population (olanzapine 7.7%); and the bipolar mania population (olanzapine 16.2%).

Use in pregnancy (Category B3)

There are no adequate data from the use of SAPHRIS in pregnant women. Asenapine was not teratogenic in rats or rabbits at oral or intravenous doses that resulted in estimated drug exposures up to 11 (rat, based on plasma AUC) or 24 (rabbit, based on body surface area) times the expected human values with the maximum recommended dose. Reproductive toxicity studies were conducted using oral and intravenous routes, rather than the sublingual route used clinically. Increases in pre- and post-implantation losses were observed in some studies in rats, with pre-implantation loss increased after oral doses that resulted in estimated

exposures (based on AUC) 3 times that expected in humans at the maximum recommended dose.

In rats treated intravenously from early gestation to weaning, increased early mortality and reduced weight gain were seen in pups at maternal doses resulting in exposures (based on AUC) approximately 3 fold that expected in humans at the maximum recommended dose. A cross-fostering study suggests that the increased pup mortality was mainly due to prenatal drug effects.

Use in lactation

Asenapine and/or its metabolites were excreted in the milk of rats during lactation. It is not known whether asenapine and/or its metabolites are excreted in human milk. It is recommended that women receiving SAPHRIS should not breast feed.

Paediatric Use

SAPHRIS is not recommended for use in children and adolescents below 18 years of age, due to a lack of sufficient data on safety and efficacy.

Genotoxicity

Asenapine was not genotoxic in *in vitro* (bacterial reverse mutation, mammalian cell forward mutation, chromosomal aberration, sister chromatid exchange) and *in vivo* (rat micronucleus) tests.

Carcinogenicity

Long term carcinogenicity studies with subcutaneous administration were conducted in mice and rats. Doses used resulted in estimated drug exposures (based on plasma AUC) that were up to 3-4 fold the expected human value with the maximum recommended dose. No oncogenic responses to asenapine treatment were observed.

Effects on fertility

Fertility in rats was unaffected by oral asenapine administration that resulted in an estimated drug exposure (based on plasma AUC) 11 fold that expected in humans with the maximum recommended dose.

Interactions with other medicines

Given the primary CNS effects of asenapine (see ADVERSE EVENTS), caution should be used when it is taken in combination with other centrally acting drugs. Patients should be advised to avoid alcohol while taking SAPHRIS.

<u>Potential for other medicines to affect SAPHRIS</u>

Asenapine is cleared primarily through direct glucuronidation by UGT1A4 and oxidative metabolism by cytochrome P450 isoenzymes (predominantly CYP1A2). The potential effects of inhibitors and an inducer of several of these enzyme pathways on asenapine pharmacokinetics were studied (Table 4). With the exception of fluvoxamine (strong CYP1A2 inhibitor), none of the interacting drugs resulted in clinically relevant alterations in asenapine pharmacokinetics.

Table 4: The potential effects of inhibitors and an inducer of CYP enzyme pathways on asenapine pharmacokinetics

Coadministered drug (Postulated effect on CYP450/UGT)	**Dose schedules**		**Effect on asenapine pharmacokinetics**		**Recommendation**
	Coadministered drug	**Asenapine**	**C_{max}**	**$AUC_{0-\infty}$**	
Fluvoxamine (CYP1A2 inhibitor)	25 mg twice daily for 8 days	5 mg Single Dose	+13%	+29%	Coadminister with caution*
Paroxetine (CYP2D6 inhibitor)	20 mg once daily for 9 days	5 mg Single Dose	–13%	–9%	No SAPHRIS dose adjustment required *[see potential for SAPHRIS to affect other medicines]*
Imipramine (CYP1A2/2C19/3A4 inhibitor)	75 mg Single Dose	5 mg Single Dose	+17%	+10%	No SAPHRIS dose adjustment required
Cimetidine (CYP3A4/2D6/1A2 inhibitor)	800 mg twice daily for 8 days	5 mg Single Dose	–13%	+1%	No SAPHRIS dose adjustment required
Carbamazepine (CYP3A4 inducer)	200mg twice daily for 4 days 400 mg twice daily for 15 days	5 mg Single Dose	–16%	–16%	No SAPHRIS dose adjustment required
Valproate (UGT1A4 inhibitor)	500 mg twice daily for 9 days	5 mg Single Dose	2%	–1%	No SAPHRIS adjustment required

*The full therapeutic dose of fluvoxamine would be expected to cause a greater increase in asenapine plasma concentrations

Potential for SAPHRIS to affect other medicines

Because of its α1-adrenergic antagonism with potential for inducing orthostatic hypotension (see PRECAUTIONS), SAPHRIS may enhance the effects of certain antihypertensive agents.

In vitro studies indicate that asenapine weakly inhibits CYP2D6. Following coadministration of dextromethorphan and asenapine in healthy subjects, the ratio of dextrorphan/dextromethorphan (DX/DM) as a marker of CYP2D6 activity was measured. Indicative of CYP2D6 inhibition, treatment with asenapine 5 mg twice daily resulted in a fractional decrease in DX/DM ratio to 0.43. In the same study, treatment with paroxetine 20 mg daily decreased the DX/DM ratio to 0.032. In a separate study, coadministration of a single 75 mg dose of imipramine with a single 5 mg dose of asenapine did not affect the plasma concentrations of the metabolite desipramine (a CYP2D6 substrate). Coadministration of a single 20 mg dose of paroxetine (a CYP2D6 substrate and inhibitor) during treatment with 5 mg asenapine

twice daily in 15 healthy male subjects resulted in an almost 2-fold increase in paroxetine exposure. *In vivo* asenapine appears to be at most a weak inhibitor of CYP2D6. However, asenapine may enhance the inhibitory effects of paroxetine on its own metabolism.

Therefore, SAPHRIS should be coadministered cautiously with drugs that are both substrates and inhibitors for CYP2D6.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Asenapine may cause somnolence and sedation. Therefore, patients should be cautioned about operating machinery, including motor vehicles, until they are reasonably certain that SAPHRIS therapy does not affect them adversely.

ADVERSE EFFECTS

SAPHRIS has been administered in clinical trials to approximately 4500 subjects, including more than 3150 patients in phase 2/3 trials with schizophrenia or manic episodes associated with bipolar I disorder. In the table below, all treatment-related adverse events that have an incidence of ≥ 2% have been listed from the phase 2/3 schizophrenia and bipolar mania trials (Table 5).

Table 5: Treatment – related adverse events for all phase 2/3 trials. Combined schizophrenia and bipolar disorder studies. (≥ 2%) (All subjects treated group)

System organ class **Preferred term**		**Placebo n=1064**	**Asenapine 5 - 10mg bid n=3159**	**Olanzapine 5 - 20mg QD n=1139**
Gastrointestinal disorders				
	Nausea	42 (3.9)	106 (3.4)	29 (2.5)
	Hypoaesthesia oral	5 (0.5)	103 (3.3)	3 (0.3)
	Dry Mouth	15 (1.4)	55 (1.7)	54 (4.7)
	Constipation	28 (2.6)	49 (1.6)	24 (2.1)
General disorders and administration site conditions				
	Fatigue	18 (1.7)	87 (2.8)	53 (4.7)
Investigations				
	Weight increased	6 (0.6)	239 (7.6)	212 (18.6)
	Alanine aminotransferase increased	6 (0.6)	37 (1.2)	23 (2.0)
Metabolism and nutrition disorders				
	Increased appetite	6 (0.6)	53 (1.7)	47 (4.1)
Nervous system disorders				
	Somnolence	21 (2.0)	339 (10.7)	113 (9.9)
	Sedation	36 (3.4)	237 (7.5)	140 (12.3)
	Akathisia	22 (2.1)	195 (6.2)	47 (4.1)
	Dizziness	29 (2.7)	131 (4.1)	50 (4.4)
	Headache	58 (5.5)	126 (4.0)	65 (5.7)
	Parkinsonism	10 (0.9)	100 (3.2)	15 (1.3)
	Tremor	13 (1.2)	70 (2.2)	14 (1.2)
Psychiatric disorders				
	Insomnia	57 (5.4)	207 (6.6)	47 (4.1)
	Anxiety	30 (2.8)	108 (3.4)	18 (1.6)
	Schizophrenia	27 (2.5)	87 (2.8)	21 (1.8)
	Agitation	25 (2.3)	76 (2.4)	15 (1.3)

bid = twice daily; QD = once daily

Asenapine has anaesthetic properties. Oral hyperaesthesia and oral paraesthesia may occur directly after administration and usually resolve within 1 hour.

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with SAPHRIS including swollen tongue and swollen throat (pharyngeal oedema). The local anaesthetic properties of asenapine should be considered as a possible alternative etiology for the oropharyngeal symptoms.

DOSAGE AND ADMINISTRATION

Schizophrenia

The recommended dose range of SAPHRIS is 5 mg to 10 mg twice daily. SAPHRIS should be administered at an initial daily dose of 5 mg twice daily. An increase in dose to 10 mg twice daily is recommended only after clinical assessment. In controlled trials, there was no suggestion of added benefit with a higher dose of 10 mg twice daily 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 (see Clinical Trials).

Acute and maintenance treatment of manic or mixed episodes in Bipolar 1 Disorder

The recommended starting dose of SAPHRIS as monotherapy is 10 mg twice daily. The dose can be reduced to 5 mg twice daily, according to clinical assessment.

For combination therapy a starting dose of 5 mg twice daily is recommended. Depending on the clinical response and tolerability in the individual patient, the dose can be increased to 10 mg twice daily. SAPHRIS has not been adequately assessed for the long term treatment of patients with Bipolar 1 Disorder. It has shown efficacy in the prevention of relapse of manic or mixed episodes when used as monotherapy or in combination with lithium or sodium valproate for up to 12 weeks. When used as monotherapy or in combination with lithium or sodium valproate, it is generally recommended that responding patients be continued beyond the acute response. If SAPHRIS is used for extended periods in Bipolar 1 Disorder, the long-term risks and benefits of the drug for the individual patient should be periodically re-evaluated.

Method of administration:

The wafer should not be removed from the blister until ready to take it. Use dry hands when handling the wafer. Do not push the wafer through the wafer pack. Do not cut or tear the wafer pack. Peel back the coloured tab and gently remove the wafer. Do not crush the wafer.

To ensure optimal absorption, place the SAPHRIS wafer under the tongue and allow it to dissolve completely. The wafer will dissolve in saliva within seconds. Do not chew or swallow the SAPHRIS wafers. Do not eat or drink for 10 minutes.

When used in combination with other medication, SAPHRIS should be taken last.

Treatment with SAPHRIS is not advised in patients who are unable to comply with this method of administration as the bioavailability of asenapine when swallowed is low (<2% with an oral tablet formulation).

Elderly

SAPHRIS should be used with care in the elderly. Limited data on safety and efficacy are available in patients 65 years of age or older (see PHARMACOLOGY – Special Populations).

Renal Impairment

No dosage adjustment is required for patients with renal impairment.

Hepatic Impairment

No dosage adjustment is required for patients with mild to moderate hepatic impairment. In subjects with severe hepatic impairment (Child-Pugh C), a 7-fold increase in asenapine exposure was observed. Thus, SAPHRIS is not recommended in patients with severe hepatic impairment (see PHARMACOLOGY – Special Populations).

Children

Use of SAPHRIS in children below the age of 18 is not recommended, due to lack of sufficient data on efficacy and safety. Limited safety data with SAPHRIS are available in adolescent patients. A pharmacokinetic study was performed in adolescent patients (see PHARMACOLOGY – Special Populations).

OVERDOSAGE

Few cases of overdose were reported in the asenapine program. Reported estimated doses were between 15 and 400 mg. In most cases it was not clear if asenapine had been taken sublingually. Treatment-related adverse events included agitation and confusion, akathisia, orofacial dystonia, sedation, and asymptomatic ECG findings (bradycardia, supraventricular complexes, intraventricular conduction delay).

No specific information is available on the treatment of overdose with SAPHRIS. There is no specific antidote to SAPHRIS. The possibility of multiple drug involvement should be considered. Cardiovascular monitoring is necessary to detect possible arrhythmias and management of overdose should concentrate on supportive therapy, maintaining an adequate airway oxygenation and ventilation, and management of symptoms. Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulations may worsen hypotension in the setting of SAPHRIS-induced alpha blockade). In case of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

PRESENTATION AND STORAGE CONDITIONS

SAPHRIS 5 mg contains 5 mg of asenapine as maleate. It is a round wafer, white to off-white in colour with “5” debossed on one side.

SAPHRIS 10 mg contains 10 mg of asenapine as maleate. It is a round wafer, white to off-white in colour with “10” debossed on one side.

SAPHRIS is available in blister packs of 20, 60 and 100 wafers.

Not all pack sizes may be available.

Store below 30°C.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

Schedule 4

Date of TGA approval

7 March 2011

Therapeutic Goods Administration

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