EMA/CHMP/583011/2010

Evaluation of Medicines for Human Use

Assessment report

Sycrest

International Nonproprietary Name: asenapine

Procedure No. EMEA/H/C/001177

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant N.V. Organon submitted on 05 May 2009 an application for Marketing Authorisation to the European Medicines Agency for Sycrest, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the Agency/CHMP on 24 January 2008.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

The application submitted is a complete dossier:

composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.1.1. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006 the application included an Agency Decision P/233/2009 for the following condition(s):

Schizophrenia

on the agreement of a paediatric investigation plan (PIP)

Bipolar I disorder

on the agreement of a paediatric investigation plan (PIP)

The PIP is not yet completed because studies contained in the paediatric investigation plan have been deferred.

1.1.2. Licensing status:

The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Ian Hudson Co-Rapporteur: Cristina Sampaio

1.2. Steps taken for the assessment of the product

- The application was received by the Agency on 5 May 2009.
- The procedure started on 27 May 2009.
- The Rapporteur's Initial Assessment Report was circulated to all CHMP members on 24 August 2009. The Co-Rapporteur's Initial Assessment Report was circulated to all CHMP members on 21 August 2009.
- During the meeting from 21-24 September 2009, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 September 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 December 2009.
- The summary report of the inspections carried out at the following three investigator's sites in the US and in Thailand between 29 October and 19 November 2009 was issued on 8 December 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 4 February 2010.
- During the CHMP meeting from 15 – 18 February 2010, the CHMP agreed on a List of Outstanding Issues to be addressed in writing and in an oral explanation by the applicant.
- The applicant submitted the written responses to the CHMP List of Outstanding Issues on 19 March 2010.
- During the CHMP meeting on 19 May 2010, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- The Rapporteurs circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 9 June 2010.
- During the meeting from 21-24 June 2010, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Sycrest on 24 June 2010. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 22 June 2010.
- The CHMP opinions were forwarded in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 1 September 2010.

2. Scientific discussion

2.1. Introduction

Asenapine is claimed to be a novel psychopharmacologic agent with high affinity and potency for blocking dopamine, serotonin, α-adrenergic and histamine receptors, and no appreciable activity at muscarinic cholinergic receptors. The mechanism of action of asenapine, like other atypical antipsychotics is believed to be mediated through a combination of antagonist activity at 5-HT2A and D2 receptors.

The following indications were initially applied for: treatment of schizophrenia, treatment of manic episodes associated with bipolar I disorder.

In adults, the recommended dose can range from 5 mg to 10 mg twice daily.

Sycrest (asenapine) is a fast dissolving tablet for sublingual administration containing asenapine in the form of maleate salt as active substance. The product contains 5mg or 10mg asenapine in gelatin and mannitol.

Schizophrenia is a severe, disabling disorder that affects about 1% of the world's population. According to DSM-IV-TR, the diagnosis of schizophrenia requires the presence of at least two of the following symptoms over a period of at least one month: delusion, hallucinations, disorganised speech, catatonic or grossly disorganised behaviour, negative symptoms. Furthermore, additional unspecific symptoms (often termed prodromal or residual symptoms) are required to be present for at least 6 months. In addition, the clinical symptoms are required to be associated with a significant social/occupational dysfunction, often in the sense of a decline in performance. In a majority of individuals, schizophrenia is a chronic disorder in the sense that individuals experience disabling symptoms over long periods of time after initial onset, which typically occurs in early adulthood. Complete remission is probably not common in this disorder. In addition to the positive symptoms (such as delusions and hallucinations) and negative symptoms (such as alogia, affective flattening or avolition), which are listed as diagnostic criteria in DSM-IV-TR, many patients also experience various cognitive deficits as well as symptoms of depression and anxiety. Moreover, schizophrenia is a disorder associated with a high risk of suicidality, with a frequently reported modal rate of suicide rate being approximately 10%. Classical antipsychotic drugs typically show efficacy in the treatment of positive symptoms but not in all patients. They are generally less effective in the treatment of negative symptoms and tend to cause troubling extrapyramidal motor symptoms, which often strongly limit their acceptance among patients. Atypical antipsychotics are associated with a lower frequency of this important side effect but they cause other adverse effects that limit their use in some patient populations, such as elevated prolactin levels, agranulocytosis, cardiac side effects or excessive weight gain. There are therefore still substantial unmet needs in the treatment of schizophrenia.

Bipolar disorder is a chronic, typically cyclic mood disorder with a lifetime prevalence of approximately 0.8% to 1.6% (DSM-IV-TR). The disorder is characterized by the occurrence of episodes of significantly altered mood, which may be manic, depressive (meeting criteria for major depressive episode), or mixed. Bipolar I disorder is characterized by the occurrence of at least one manic or mixed episode according to the criteria of DSM-IV-TR. The duration of a manic episode can extend from days to months. Typical symptoms of a manic episode include abnormally and persistently elevated or irritable mood accompanied by inflated self-esteem, ideas of grandiosity, decreased need for sleep, increased drive, logorrhoea, or flight of ideas. Manic patients are at increased risk to engage in unrestrained buying sprees, sexual indiscretions or foolish business investments. Patients with

mixed episodes experience rapidly alternating moods meeting the criteria for both a manic and major depressive episode over a prolonged period of time of at least one week. Individuals with bipolar I disorder have a substantially elevated risk of suicidality, with 10-15% of affected individuals finally committing suicide (DSM-IV-TR). Treatment of bipolar I disorders comprises an effective treatment of manic or mixed symptoms as well as treatment of bipolar depression, which differs substantially from the treatment of unipolar depression due to the increased risk of a switch into mania. Moreover, an important long term goal is mood stabilization, ideally in the state of euthymia. For the treatment of manic symptoms, a variety of drug treatment options have been used in the past decades. Lithium and antiepileptic drugs such as valproate or carbamazepine have demonstrated antimanic effects. Typical antipsychotics have frequently been used to control manic symptoms; their use however, was often limited by the occurrence of EPS. More recently, atypical antipsychotics have increasingly been used successfully and approved to treat manic episodes associated with bipolar I disorder.

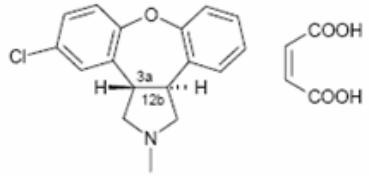
2.2. Quality aspects

2.2.1. Introduction

Sycrest contains asenapine in the form of maleate salt as active substance. The drug product formulation is a fast dissolving tablet for sublingual administration .The bioavailability after sublingual dosing is much higher (approximately 35%) than after oral dosing (<2% in tablet formulation). The product contains 5mg or 10mg asenapine in gelatin and mannitol and is administered twice daily.
Sycrest 5 mg and 10 mg tablets are presented as white to-off-white circular tablets, with '5' and '10', respectively, embossed on one side. The different tablet strengths are distinguishable from each other by the tablet markings, which is acceptable given the nature of the product.
The product is packaged in peelable cold form aluminium/aluminium blisters in cartons of 20, 60 or 100 sublingual tablets per carton.

2.2.2. Active substance

The chemical name of the active substance is (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). The molecular formula of active substance is $C_{17}H_{16}ClNO.C_4H_4O_4$, its relative molecular mass 401.84 and its structural formula is shown below.



Asenapine maleate is a white to off-white non hygroscopic powder, slightly soluble in water, sparingly soluble in 0.1 M HCl. Two polymorphic forms have been found. One of them is the more stable form at ambient temperature and is the desired one. Asenapine maleate contains two chiral centres at C3a and C12b and is a racemate (R,R and S,S). The pH of a saturated asenapine solution in water is 4.2 at 23.5 ^{o}C, its pKa is 8.6 (protonated free base) and its logP is 4.9 (neutral species) and 1.4 (cationic species).

2.2.2.1. Manufacture

The manufacturing process of asenapine maleate comprises three steps that yield the desired polymorph. If required, reprocessing is foreseen in accordance with defined criteria and in line with ICH Q7.
The process parameters for all steps including the purification step of the manufacturing process for asenapine maleate are not considered to be critical and are easily controlled within the proven acceptable ranges (PAR). The PARs were sufficiently established.

2.2.2.2. Specification

The drug substance specification includes tests for appearance (visual), identification (IR, HPLC), polymorphic form (X-RPD), assay (HPLC), impurities (HPLC), residual solvents (GC), heavy metals (ICP-AE), sulphated ash (Ph Eur), and particle size distribution (LDS).
Results from 31 development batches and 26 post development batches of asenapine maleate were presented. The most recent 4 batches were manufactured wholly in accordance with the current manufacturing process at the current manufacturing site. Full compliance with the current proposed specification is confirmed for these batches. In addition the results of all other batches are acceptable and consistent with respect to the analytical parameters tested. No significant variations between the individual asenapine maleate batches manufactured via the commercial process have been observed.

2.2.2.3. Stability

Four batches of active substance, manufactured according to the proposed commercial manufacturing process, have been entered into long-term (25 °C/60% RH), intermediate (30 °C/65% RH) and accelerated (30 °C/75% RH) stability studies, in accordance with ICH conditions. Samples were stored in packaging representative of that proposed for long-term storage. 36 months of long-term and intermediate data, and results from completed (6 months) accelerated studies are presented. Samples were observed to meet the proposed specification throughout the studies, under all storage conditions
A photostability study was conducted on one batch according to ICH Q1B guideline. After light exposure assay, colour, water content, polymorphic form and particle size show no change. Analysis of samples indicates the formation of a small amount of degradation. As this degradation was not observed in long term studies and the container closure system provides some protection from light, no protection from light other than storage in the container closure system is proposed.
Forced degradation studies to asenapine maleate powder and solutions using active substance from one batch were performed. The results of the studies support the possible degradation pathway.
In accordance with EU GMP guidelines[1], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMEA.

In conclusion the proposed retest period and storage conditions are acceptable.

2.2.3. Finished Medicinal Product

2.2.3.1. Pharmaceutical Development

Initial development examined a conventional oral solid dosage form, however, low bioavailability (<2%) caused by extensive first-pass metabolism dictated that another route be adopted, and it was

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

decided to follow the sublingual route. The experience of the finished product manufacturer was utilised in the development of sublingual tablets, through a freeze-dried matrix of gelatin and mannitol. The suitability of methods used to monitor tablet disintegration and dissolution has been thoroughly investigated during development.
All clinical batches were demonstrated to meet the disintegration specification and showed similar dissolution profiles.
Asenapine maleate salt was selected for use in Sycrest drug product due to good chemical stability, sufficiently high melting point, good purifying effect upon crystallization, and acceptable solubility in water.
Asenapine maleate drug substance is not readily susceptible to heat, pH, light, or oxidative agents.
One of the two identified polymorphic forms is the desired form for use in the product, due to its better stability at ambient temperatures. The polymorphic form is controlled in the active substance. Tablets formulated with the other form were demonstrated not to be bioequivalent to those prepared with the desired form (study 041009). Development work showed that the dissolved drug substance is quickly frozen and lyophilized, allowing for amorphous asenapine to be present in the final drug product. The drug substance that does not dissolve in the matrix remains crystalline in the final drug product.
Widely used, pharmacopoeial excipients are employed. The use of gelatin and mannitol in the formulation of products of the same technology is well-established. Compatibility between the active substance and the excipients has been demonstrated adequately. Bioequivalence between batches manufactured with gelatin from different sources was demonstrated (study A7501015).
The different tablet strengths are distinguishable from each other by the tablet markings, which is acceptable given the nature of the product.
Optimisation of manufacture was performed with development batches of various batch sizes including the commercial batch size.
Extensive investigation into the development of the manufacturing process is reported, with a full consideration of critical manufacturing parameters and justification of the established target parameters and acceptable ranges.
While many aspects of the manufacturing process are common to all products employing the same freeze-dried matrix technology, and other parameters are defined during qualification of the equipment concerned, a number of parameters/conditions require specific evaluation and optimisation. Satisfactory justification for the process parameters adopted for commercial scale manufacture has been provided.
The selection of the packaging type is based on the experience of the finished product manufacturer and the requirements relating to the production process and protective properties for the finished product. The cold-form aluminium blister packs provide adequate protection from moisture. The suitability of the proposed packaging is confirmed by stability studies, see IV.8, below.

'Sycrest' 5 mg & 10 mg tablets are presented as white to-off-white circular tablets, with '5' and '10', respectively, embossed on one side.

The development of the formulation, based on the finished product manufacturer's proprietary 'Zydis' technology, in which the active substance is mixed in a solution of gelatin and mannitol, and subsequently dispensed by weight into blister pockets before freeze-drying and blister sealing, is described in detail. Relevant properties of the active substance have been considered and critical manufacturing parameters investigated and defined

The manufacturing process is adequately described, with appropriate controls in place. The manufacturing process may be considered as a 'standard process' on the basis of the manufacturer's prior experience.

Analytical methodology has been validated adequately.

2.2.3.2. Adventitious agents

Gelatin used in Sycrest is of animal origin. The supplier has been issued with Ph Eur Certificates of Suitability by the EDQM, in relation to compliance with TSE requirements.

2.2.3.3. Manufacture of the product

The manufacturing process is considered to be a standard manufacturing process comprising: mixing of asenapine maleate into an aqueous solution of gelatin and mannitol and dosed by volume into cold-formed aluminum blister pockets, freezing the suspension within the pockets subsequently drying by subliming the ice in a freeze dryer; the dried product in the blister pockets is then sealed by application of a lidding foil.
The manufacturing process development work identified the critical steps in the manufacture. Discussion of each of these steps, and the controls in place to ensure conditions are fulfilled is provided.
The manufacturing process of Sycrest tablets is such that the tablets are produced in their primary packaging. Since tablets are formed in situ in the blisters, robustness during manufacture is not required, as no mechanical handling of the tablets occurs during production. For this reason, handling of bulk tablets will not occur, making tablet strength irrelevant as an in-process control, hence the specification for appearance may be considered as sufficient and representative of a suitable degree of handling.

2.2.3.4. Product specification

The release and shelf-life specifications of the finished product include tests and limits for appearance (visual), identification (HPLC-diode array), assay (HPLC), impurities (HPLC), uniformity of dosage units (Ph Eur, only at release), disintegration time (Ph Eur) and water content (Ph Eur).
Release testing of Sycrest includes a test for appearance. The tablets have to be removed intact from the blister in order to meet the requirements for appearance. This removal is representative for the handling of the tablets by patients.
It is also considered that sufficient evidence has been provided to demonstrate that testing for microbiological quality may be excluded from the finished product specification. Batch analytical results were presented for a number of development batches up to commercial scale of each strength. Full compliance with the proposed specification is demonstrated. Only one impurity was detected above the reporting threshold in some batches of the 5 mg strength. This impurity however is stated to be a major metabolite of the active substance and, hence, may be regarded as fully qualified toxicologically.

2.2.3.5. Stability of the product

Stability studies have been performed on three pilot scale batches of each strength with samples stored in the proposed commercial packaging at ICH recommended long-term (25 °C/60% RH), accelerated conditions (40 °C/75% RH), and in addition under intermediate conditions at elevated humidity (30 °C/75% RH), under refrigeration (5 °C/ambient RH) and at elevated temperature

(50 °C/ambient RH). Samples were tested with regard to appearance, disintegration, water content, assay and degradation products in accordance with the specification and also for microbiological quality, dissolution performance, polymorphic characterisation and tablet diameter.
Data are presented for completed studies for up to 36 months at 25 °C/60% RH, 30 °C/75% RH and 5 °C/ambient RH, up to six months at 40 °C/75% RH an dup to three months at 50 °C/ambient RH.
No significant deterioration in product quality was recorded in the stability studies under any of the conditions tested. Appearance and disintegration time remained unchanged throughout. Increases in water content were detected with time. However, the observed increase in water content of the tablets was shown not to have any noticeable effect on tablet appearance or disintegration performance and can, therefore, be considered as non-critical to tablet quality.
The individual graphical representations of the assay results for each batch, with regression analysis extrapolating to 5 years, predict continued compliance with the proposed assay specification limits.
Increases in levels of degradation products are apparent with time; these are more marked for the 5 mg strength. Similar degradant levels were observed under both long-term and intermediate conditions. The individual graphical representations of the impurities results for each batch, with regression analysis extrapolating to 5 years, predict continued compliance with the proposed impurity specification limits for each of the specified impurities and for total impurities. No changes in microbiological quality, dissolution or tablet diameter were apparent throughout studies under any conditions. No change in polymorphic form was observed.

Photostability
A single pilot scale batch of each strength was entered into a photostability study under light conditions in accordance with ICH recommendations.
Samples were tested in accordance with the proposed specification with regard to appearance, disintegration, water content, assay and degradation products and also for tablet diameter and dissolution performance. Increases in the levels of one impurity were recorded for the directly exposed tablets, which suggest a degree of sensitivity of the product to light. No significant changes were observed for any of the parameters studied for the unopened blister samples; it is concluded that the primary packaging provides adequate protection from light.

Based upon the stability data provided, the proposed shelf-life and storage conditions are considered acceptable.

In accordance with EU GMP guidelines, any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMEA.

2.2.4. Discussion and Conclusions on chemical, pharmaceutical and biological aspects

The quality of Sycrest sublingual tablet is adequately established. Information on development, manufacture and control of the drug substance has been presented in a satisfactory manner. The quality of the active substance is considered sufficiently described and adequately supported by data. Sufficient chemical and pharmaceutical documentation relating to development, manufacture and control of the drug product has been presented. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.
Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

2.3. Non-clinical aspects

Pivotal toxicology studies were performed according to Good Laboratory Practices (GLP), as stated by the applicant.

2.3.1. Introduction

Asenapine, and its known/putative metabolites and enantiomers have been evaluated in a series of *in vitro* and *in vivo* pharmacological tests used for characterization of antipsychotic agents. Studies included in vitro (receptor binding and function) and in vivo (regional neuronal activation, neurotransmitter efflux, receptor regulation and behavioural analysis).

2.3.2. Pharmacology

2.3.2.1. Primary pharmacodynamic studies

The binding profile of asenapine has revealed high affinity for a range of human serotonin, dopamine, noradrenaline and histamine receptor subtypes. In particular, asenapine had subnanomolar affinity for several human 5-HT receptor subtypes (pKi): 5-HT2C (10.5), 5-HT2A (10.2), 5-HT7 (9.9), 5-HT2B (9.8), and 5-HT6 (9.6). Subnanomolar affinity was also observed for (pKi): α2B-adrenergic (9.5) and dopamine D3 (9.4) receptors. Asenapine had an appreciable affinity for histamine H2 receptors (pKi: 8.2) but not for muscarinic receptors.

Following autoradiographic analysis, 1nM [3H]-asenapine demonstrated varying degrees of specific binding in the majority of coronal sections throughout the rostro-caudal extent of the rat brain, especially in the cortex and choroid plexus associated with high serotonin receptor density.

Asenapine acts as an antagonist at serotonin, dopamine, noradrenaline and histamine receptors. It potently blocked agonist- induced activation of the following studied receptors (pKB): 5-HT2A (9.1), 5-HT2B (9.9), 5-HT2C (9.0), 5-HT1A (7.4), 5-HT1B (8.1), 5-HT6 (8.0), 5-HT7 (8.5), D2 (9.1), D3 (9.1), α2A (7.3), α2B (8.3), α2C (6.8) and H1 (8.4). This profile is different than other atypical antipsychotics which did not show appreciable antagonism at 5-HT6 and α2-adrenergic receptors (PKB<5).
Asenapine potentiated NMDA receptor in isolated rat medial prefrontal cortex (mPC) slice preparation, evoking electrophysiological responses in mPFC pyramidal cells. However the magnitude of potentiation was reduced at higher concentrations (7.5, 10, and 100nM) and no appreciable binding affinity for NMDA receptors has been shown.

Asenapine occupied serotonin, dopamine, noradrenaline and histamine receptors studied in different regions of rat brain with a distinct rank of order of potency (ED50, mg/kg, subcutaneous): 5- HT2A (0.005)> 5-HT2C (0.02)> α1 (0.077), D2 (0.1), H1 (0.11), α2 (0.13), >D3 (1.1), D1 (1.3)>5-HT1A (6.5).

Following studies in rat striatum and cortex using the irreversible antagonist Nethoxycarbonyl- 2-ethoxy-1,2-dihydroquinoline, asenapine (0.25 mg/kg, intraperitoneal=i.p) preferentially occupied 5-HT2 receptors (84%) as compared to D1 (7%) or D2 (44%). Asenapine (0.1 mg/kg) showed time and exposure related increase in D2 receptor occupancy. Plasma levels of 0.48 ng/ml and 1.24 ng/ml were necessary for 50% receptor occupancy of the 5-HT2A (ED50: 0.011 mg/kg) and D2 (ED50: 0.016 mg/kg. The range for plasma levels to achieve 60 – 80% D2 receptor occupancy, was 1-3 ng/ml.

Following acute intravenous administration of asenapine (0.001-1 mg/kg) to anaesthetised rats at central 5-HT2A, 5-HT1A, α2-adrenergic and D2 receptors mediated effects on monoamine neurone firing activity. Asenapine blocked the inhibitory effects of the 5-HT2A (ED50: 0.075 mg/kg) and the α2 adrenergic receptor activation (ED50: 0.085 mg/kg) on the noradrenergic locus coeruleus neurone firing. Dopaminergic neurone activity in ventral tegmental area was blocked by asenapine (ED50 :0.040 mg/kg). Asenapine did not show any evidence of 5-HT1A receptor blocking activity on dorsal raphe serotonergic neurone firing. However, local microionotophoretic application of asenapine in the dorsal raphe or CA3 neurones of the hippocampus revealed partial agonist activity at the 5-HT1A receptor.

Following subcutaneous (s.c) repeated dose administration of asenapine (28 days, twice daily=BID, injection) in rat, dose-dependent and regionally specific effects on serotonin, dopamine and ionotropic glutamate receptor subtypes were observed. D2 receptor binding density in mPFC, nucleus accumbens, hippocampus at 0.03 and 0.1mg/kg were increased while the same effect was only observed at higher dose (0.3 mg/kg) in the caudated putamen region. D1 and D4 receptor binding density was also increased at 0.1 and 0.3 mg/kg but no effect on D3 receptor binding density was observed in any region of the brain investigated. At all doses, 5-HTA2A receptor binding density were decreased in the mPFC and dorsolateral cerebral cortex. Increased 5-HTA1 receptor binding density was observed in mPFC, dorsolateral cerebral cortex and hippocampus at 0.1 and 0.3 mg/kg but no effect on 5-HT2C receptor binding density was observed in any region of the brain investigated. At all doses, asenapine produced regionally selective increases in α1 and α2 adrenoceptor binding density in the mPFC and dorsolateral frontal cortex. In relation to effects on ionotropic glutamate receptor binding density, asenapine significantly decreased NMDA/MK-801 modulatory site receptor binding in the nucleus accumbens and caudate putamen at all doses and the AMPA receptor binding in the hippocampus at 0.3 mg/kg.

Following autoradiographic analysis using [33P]-labelled probes specific for c-fos mRNA , asenapine showed neuronal activation in mPFC, amygdaloid nucleus and striatum but also in the parietal cortex, medial hippocampal CA2 field and medial habenula.

Asenapine significantly increased dopamine efflux in the mPFC and hippocampus following acute administration at 0.05, 0.1 and 0.5 mg/kg and in the nucleus accumbens, only at 0.5 mg/kg. It also increased acetycholine efflux in the mPFC and hippocampus at 0.1 and 0.5 mg/kg but no effect was observed in nucleus accumbens. Noradrenaline release in the mand hippocampus was observed at 0.05 and 0.1 mg/kg but there was no increased effect on serotonin (medial prefrontal cortex or hippocampus), glutamate (medial prefrontal cortex or nucleus accumbens) or GABA (medial prefrontal cortex or nucleus accumbens) levels at 0.1 mg/kg. Subchronic administration of asenapine (0.1 mg/kg, 14 days) also increased dopamine and acetycholine efflux in the mPFC and hippocampus.

Asenapine inhibited the behavioral effects (head shakes, penile erections, forepaw treading) of various serotonergic ligands in rats (ED50: in mg/kg, s.c.) by blocking the following receptors: 5-HT2A (0.001), 5-HT2C (0.02) and 5-HT1A (0.08). It also antagonised apomorphine-induced climbing in mice (0.02 - 0.04) and D2, D1 receptor agonists – induced circling behaviour in rats.

Asenapine (0.05, 0.1, 0.2 mg/kg, s.c.) also produced a dose- related suppression of conditioned avoidance response in rats with an ED50 of 0.12 mg/kg. Only 0.1 and 0.2 mg/kg doses of asenapine produced significant inhibition at 20 and 90 minutes post treatment. The dose required for about 80% inhibition was between 0.1-0.2 mg/kg. Asenapine also showed preferential inhibition of locomotor activity in stimulated by low doses of amphetamine (1mg/kg, s.c) compared to high doses of amphetamine (3 mg/kg, s.c) with minimum effective doses (MEDs) of 0.03 and 0.1 mg/kg

respectively. Asenapine reversed apomorphine-induced disruption of prepubile inhibition with MED of 0.03 mg/kg, s.c. Effects on spontaneous locomotor activity in mice were seen at relatively higher doses (0.3-0.4 mg/kg, s.c) with asenapine (ED50: 0.4 mg/ kg, s.c).

Following s.c administration in mice and/or rat models, asenapine has not shown antidepressant-like activity at dose of 0.025 - 0.1 mg/kg nor anxiolytic like activity at 0.001 - 0.3 mg/kg.

Following sc administration of asenapine in rats model, the deficit in cognitive behavioural flexibility was attenuated at 0.075 mg/kg, while no effect was observed at lower doses. Asenapine also attenuated the D-amphetamine induced deficit in cued reversal learning task at the same dose. The procognitive effects of asenapine at different tested doses, in treated phencyclidine rats and monkeys models were maintained after repeated administration.

Following i.p repeated administration of asenapine (0.06, 0.2, 0.6 mg/kg, BID) in rats ahnedonia model, chronic mild stress was reduced. However a decrease in sensitivity to the rewarding effects of electrical stimulation of ventral tegmental area in rats was observed at 0.1 mg/kg.

Individual enantiomers of asenapine have shown similar human receptor binding properties to asenapine (50:50 mixture) and potency for blocking 5-HT2A, 5-HT2C, 5-HT1A, D2, D1 receptor ligands mediated behavioural responses in mice and rats. However, metabolites have shown lower receptor binding properties compared to asenapine. A lower potency than asenapine was also observed in some metabolites (N-glucuronideasenapine and N-desmethyl-asenapine). The 11-O-sulphated-asenapine metabolite has shown inability to cross the blood brain barrier.

2.3.2.2. Secondary pharmacodynamic studies

No studies described specifically as secondary pharmacodynamic have been performed with asenapine. Available supportive data are derived from primary pharmacodynamics studies and these were considered sufficient to characterise the pharmacodynamic profile of asenapine.

2.3.2.3. Safety pharmacology program

CNS system

Following single intramuscular (i.m) administration of asenapine in monkeys previously sensitised to neuroleptics, locomotor activity dose-dependently decreased from 0.025 mg/kg onwards. Asenapine produced moderate syndromes of dystonia and bradykinesia that were dose-dependent from 0.025 mg/kg onwards. Decreased reactivity to environmental stimuli was not present until dystonia and bradykinesia were observed. There were mild slow tongue protrusions at baseline that decreased in frequency by about 50% at highest doses. Asenapine produced mild chewing mouth movements. There were no effects on lip movements or stereotyped behavior. and no effects on eye blinking, sedation or arousal were observed with asenapine.

Cardiovascular system

The main haemodynamic effects of intravenous asenapine were a decrease in arterial blood pressure and orthostatic hypotension in several species. In these *in vivo* studies, asenapine also displayed marked anti-histaminergic properties while no effects on cholinergic or β-adrenergic systems were observed.

In conscious dog, orally administered asenapine induced dose-dependent negative inotropic and positive chronotropic effects accompanied by ECG changes (QTc interval prolongation), orthostatic

hypotension on tilt with marked tachycardia. Sublingually administered asenapine had fewer side-effects even at doses yielding similar asenapine plasma levels. The effects after sublingual administration were dose-dependent tachycardia in the absence of negative inotropy and hypotension. Furthermore, after passive tilt, modest orthostatic hypotension was observed accompanied by an augmented orthostatic rise in heart rate. Sublingual administration of the two asenapine enantiomers [the (S)-enantiomer and the (R)-enantiomer] showed the same cardiovascular profile as racemic asenapine.

Asenapine has shown to have a greater potential to modify arterial blood pressure and heart rate whilst the metabolite (N-desmethylasenapine) may possess more negative inotropic activity in dogs. Asenapine appeared to block α1 adrenoceptors whilst the metabolite was at least 10 times less potent than asenapine in dogs and rats.

Asenapine and N-desmethyl asenapine have produced a concentration-dependent inhibition of hERG current (IC50 = 0.3 and 0.7 μM; IC20 = 42 nM and 0.2 μM) in transfected HEK293 cells. A lower activity of N+-glucuronide asenapine on hERG current inhibition has been observed (IC50 = 9.3 μM; IC20 = 2.3 μM). A decrease in action potential duration was induced by asenapine in canine Purkinje fibers. This effect was dose-dependent and more pronounced under low stimulation rates (0.33 Hz) than under normal stimulation rates (1Hz). It was also associated with a decrease in the plateau of action potential involving mainly calcium channel current. QTc interval data from the above mentioned study in conscious dogs revealed that the QTcF (Fridericia's correction) and QTcVdW (van de Water's correction prolongation) was minimal (approximately 15 msec higher than controls at low dose) after oral administration and the increases did not appear to be dose-dependent. After sublingual administration, no statistically significant prolongation of the QTcF and QTcVdW intervals relative to controls was observed.

Respiratory system
Asenapine induced a transient central respiratory depressive effect (increase in tidal volume, expired volume, enhanced pause), 20 minutes after subcutaneous administration of 5mg/kg, s.c in rats. The no effect level was 1.5 mg/kg with an estimated Cmax of 100 ng/ml.

Other systems
Asenapine has been shown a 2.5 fold stronger local anaesthetic activity as compared to lidocaine in isolated toad sciatic nerve (Xenopus laevis).

In immature rats, a slight effect of asenapine on adrenal and thyroid gland weights was observed but there were neither mineralocorticosteroidal activity nor antiestrogenic effects. In immature rabbits, neither a progestational activity nor anti-progrestational activity was observed. However, a significant increase in prolactin plasma level was induced by asenapine after single subcutaneous administration in rats.

Short-lasting effects on the intestinal system after intravenous (i.v.) administration in guinea pigs and acute ulcerogenic activity following single oral (p.o.) administration in rats were reported but no effect in gastrointestinal motility in rats was observed.

2.3.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were carried out with asenapine. The available supportive data were based on clinical studies and were considered sufficient to characterize the drug interaction profile of asenapine.

2.3.3. Pharmacokinetics

The metabolism and pharmacokinetics of asenapine were investigated using five animal species: mouse, rat, rabbit, dog and monkey. Asenapine was rapidly but highly variably absorbed (tmax ranging from 0.4 - 1.9 h) following sublingual administration in dogs, showing a higher bioavailability than after oral administration. In another study in dogs, Cmax was reached within 0.05 - 0.25 h after dosing. The exposure to asenapine was linearly dependent upon dose, except for high oral doses. No apparent sex related difference in asenapine pharmacokinetics was noted in rats and dogs. No pharmacokinetic differences were observed between the enantiomers in dogs and man. In mice , rats and rabbits higher plasma levels (up to 1.9 fold) of the (+) enantiomer were observed as compared to the (-) enantiomer.

The apparent volume of distribution of asenapine following intravenous administration was larger than the total body water (0.7 L/kg) in rats (10L/kg), rabbits (5-7 L/kg) and dogs (7L/kg). Tissue distribution of radioactivity throughout the body was noted in rats with transfer of radioactivity across the blood brain and placental barriers. In rabbits, transfer of radioactivity across the placental barrier was also noted. In rats, the tissues with the greatest uptake were the liver, kidney cortex, eye choroid and lacrimal gland. Extensive distribution of radioactivity in selected tissues was also observed in dogs (tongue, gall bladder, liver, lungs, pancreas, the gastrointestinal (GI) tract, esophagus, skin and eyes). There was no retention in melanin containing tissues (eye, skin) of rats and dogs. CNS penetration of asenapine and it N-desmethyl metabolite was shown in rats and monkeys, with ready partition into the brain tissue. However, there was no transfer of radioactivity across the blood brain barriers of the 11-hydroxy-sulfate metabolite. Asenapine and its metabolites (N-desmethyl and 11-hydroxy-sulfate) had relatively reversible high binding to animal and human plasma proteins in vitro (> 97%) and did not distribute extensively into red blood cells (20-30%). Asenapine and its N-desmethyl metabolites appeared to be a weak substrate of the protein P-glycoprotein transporter (P-gp), in transfected MDCK- (MDR1 gene) cells.

In all species, metabolic pathways for asenapine initially involved N-oxidation, N-demethylation and N-glucuronidation. N-demethylation followed by formation of the carbamoyl glucuronide or followed by N-formylation, mono-hydroxylation followed by conjugation, di-hydroxylation followed by conjugation on one or two of the hydroxy group were found in all species except in rats. In plasma, different metabolites were found in all species, predominant metabolite was the N+-glucuronide asenapine in humans while N desmethyl and/or N-oxide asenapine were predominantly found in dogs, rats and rabbits and mice. In plasma, 11- Hydroxysulfate metabolite was found in rats. Repeated administration of asenapine resulted in an increased CYP2E1 and/or CYP1A2 (and to a lesser extent CYP1A1, CYP1A2, CYP2B1/CYP2B2) activities in rats. CYP2C11 and CYP3A1 activities were decreased in male rats. In vitro studies with human hepatocytes demonstrated inhibition of CYP2D6 and CYP1A2 and induction of CYP1A2 and CYP3A4 (only at very high concentrations above the therapeutic range).

Asenapine related material was mainly excreted in the faeces (35-70%) with a smaller amount in the urine (5-11%) after sublingual dosing in dogs .Asenapine and/or its metabolite(s) were also excreted in the milk of rats.

2.3.4. Toxicology

2.3.4.1. Single dose toxicity

Acute toxicity studies were performed in both rats and dogs using oral and intravenous routes. In rats, mortality occurred within 24 hours after oral administration (to 48 hours for some female rats). Median lethal dose in rats ranged from 110 to 178 mg/kg. No deaths were noted in dogs after oral dosing (up to 200 mg/kg) and in rats by intravenous route (up to 21 mg/kg). Both rats and dogs showed clinical signs of CNS deterioration (e.g convulsions, reduced motor coordination, reduced activity/ventral recumbency, stereotype behaviour). Rats had superficial erosions in the glandular stomach epithelium.

2.3.4.2. Repeat dose toxicity (with toxicokinetics)

Repeated dose toxicity studies were conducted using the oral route of administration in both rats and dogs for 4 and 13 weeks (dogs only) and to 52 week duration (rats and dogs). In rats, doses were ranging from 6.5 to 75 mg/kg (13 weeks) and from 0.3- 10.8 mg/kg, (52 weeks). In dogs, doses were ranging from 20 to 80 mg/kg (4 weeks) 1.25- 20 mg/kg (13 weeks) and 0.1- 3.6 mg/kg (52 weeks). Additional toxicity study was performed in dogs by intravenous route (39 weeks, dose ranging from 0.1 to 0.6 mg/kg) as the maximum tolerated dose was not reached in the oral 52 week study. In addition, a juvenile rat study was also conducted at dose ranging from 0.4 to 3.2 mg/kg (Day 14 of age to day 56).

Following asenapine oral administration, adverse clinical signs varied by species. Evidence of partial recovery of these effects was noted.

In rats, notable effects observed consisted of reduced motor activity, miosis, palpebral ptosis, dose-related decrease in body weight and food consumption in males, body weight decrease and increase in food consumption in females and deteriorated bodily condition. Biochemistry analysis showed small reductions in blood glucose, cholesterol and triglycerides. In addition, blood urea-N and creatinine values were slightly increased, accompanied by increased urinary volume but without histopathological changes. Deaths occurred at high doses.

In dogs, treatment related effects included miosis, reduced activity, motor in-coordination, tremors, abnormal behaviour and increased heart rate. At doses ≥ 20 mg/kg only, some animals had reduced food intake and lost weight. Inhibition of spermatogenesis was observed at 40 mg/kg and higher. In females, disturbance of the estrus cycle and increased secretory activity of mammary glands were also observed. There was a lack of reversibility of the effect on the estrus cycle related morphology of the uterus compared to that of the mammary gland. Dose- and time-dependent hepatic changes were observed, varying from various degrees of liver cell damage, accompanied by inflammatory cell reactions. Liver enzyme activities in blood reflected liver lesions. Accumulation of grayish-brownish intrahepatocellular pigment was noted. No deaths occurred.

In dogs, high i.v doses induced severe clinical signs and body weight loss. The main treatment related effects were hypoactivity, excitation and compulsive disorder which generally occured within 10 minutes after injection. ECG changes were also noted at all doses. No deaths occurred.

Toxicokinetic data collected in dog studies (oral and intravenous) showed that the half-life of asenapine was sufficiently long to reach a steady-state with a twice daily dosage regimen. There was no PK difference by gender after single or multiple dosing. A linearity was observed between AUC and the dose.

2.3.4.3. Genotoxicity

The mutagenicity of asenapine was evaluated in vitro in an Ames test, DNA repair test, and in a gene mutation assay in mouse lymphoma cells. The clastogenic potential was evaluated in vitro in human lymphocytes and in vivo in a rat micronucleus test. All of these studies had negative results.

Two tested degradation products induced structural chromosomal aberrations in vitro in human blood lymphocytes. However, these were negative in the Ames test and did not show evidence of clastogenicity or DNA damage in a rat bone marrow micronucleus test and a Comet assay.

2.3.4.4. Carcinogenicity

The oncogenic potential of asenapine was assessed in mice and rats following subcutaneous administration. Asenapine did not exhibit any organ specific, systemic or local tumorigenic potential. In mice, dose-related increase in morbidity/mortality was noted with associated clinical lesions at different sites (skin/appendage, uro-genital tract , gastrointestinal) and haemolympho-reticular tumours. Fasciitis/fibrosis was suggestive of minor local response but no macroscopic findings of carcinogenicity were found. A higher incidence of cardiomyopathy was seen at high doses for both males (0.5-5 mg/kg) and females (0.5-7.5 mg/kg). No treatment-related increases in tumours in the skin/subcutis, or injection sites were reported. In rats, treatment dose-dependent effects were increased subcutaneous fibrosis at the injection sites, increased incidence of aggregation of foamy macrophages in lungs (NOAEL 1.2 mg/kg/day) and hypertrophied follicular epithelium in thyroid glands (NOAEL for males 0.3 mg/kg/day, for females 1.2 mg/kg/day). An increased incidence of cystic/haemorrhagic (cortical) degeneration in adrenal glands was noted in males at 1.2 and 5.0 mg/kg/day. The incidence and severity of diffuse C-cell hyperplasia in the thyroid glands was dose-dependently decreased. Asenapine has shown to reduce the incidence of a number of types of tumours (benign mammary tumours and pituitary pars distalis tumours in females, fatal pituitary pars distalis tumours and injection site fibromas in males, adrenal phaeochromocytomas, squamous cell tumours and histiocytic sarcoma) for both sexes.

2.3.4.5. Reproduction Toxicity

The effect of asenapine on fertility and early embryonic development was assessed in male and female rats and in female rabbits. Asenapine did not impair fertility in rats. After oral dosing at 0.5 mg/kg in rats, asenapine caused reduced reproductive performance and retardation of skeletal development of fetuses. From 2.5-15 mg/kg, significant adverse effects on reproductive performance and offspring development occurred including embryotoxicity (increased post-implantation loss, decreased foetal weights, and delayed ossification) and mortality. The embryotoxic effects were also observed via intravenous route in rats. Increased neonatal mortality was noted among offsprings of female rats treated during gestation and lactation, this was most likely related to impairment of the pups than altered nursing behaviour. In rabbits, oral administered asenapine adversely affected the body weight at 15 mg/kg and caused embryotoxicity. The embryotoxic effects were not observed in rabbits dosed i.v. Asenapine did not reveal any signs of teratogenecity in both studied species.

2.3.4.6. Local Tolerance

Asenapine was not irritating to the oral cavity but did cause mild to moderate clinical signs (e.g hypersalivation, stereotype behavior) in dogs.

2.3.4.7. Other toxicity studies

Asenapine did not cause any sign of anaphylaxis and/or hypersensitivity in guinea pigs. It was non-phototoxic in the 3T3-NRU assay.

2.3.5. Ecotoxicity/environmental risk assessment

An ERA according to CHMP guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00, June 2006) was submitted. The physiochemical properties of asenapine are: Molecular mass: 401.84; solubility in water, 3.7 mg/ml; Log Kow (neutral): 4.9 and Log Kow (acid): 1.4.
In Phase I, based on a maximum daily dose of 20 mg asenapine, a worst-case Predicted Environmental Concentration in surface water (PECsw) of 0.1 µg/l was calculated using default values. In addition, Asenapine was shown to be not ready biodegradable and the Aerobic and Anareobic transformation study in aquatic sediment systems (OECD 308) demonstrated significant shifting (> 10 % after or at 14 days) of asenapine to the sediment therefore further effect testing of sediment organisms. The CHMP concluded that a Phase II (Tiers A and B) was required prior any final conclusions on the ERA could be reached. In addition, endocrine disrupting effects were also observed for asenapine in mammals and reproductive effects on aquatic species could not be excluded. The CHMP was of opinion that the applicant should conduct a Phase II, Tier A and B studies and a study for potential endocrine disrupting effects.

2.3.6. Discussion on non-clinical aspects

The pharmacological studies adequately characterised the properties and principal effects of asenapine as well as potential harmful effects on vital organ systems. Receptor binding and functional studies in several in vitro and in vivo models demonstrated that asenapine has a combination of antagonist activities at D2 and 5-HT2A , and also 5-HT1A, 5-HT1B, 5- HT2C, 5-HT6, 5-HT7, D3, and α2 adrenergic receptors.

Several animal models demonstrated the potential usefulness of asenapine as an antipsychotic drug. Asenapine showed effects in models of cognitive dysfunction and anhedonia which may have relevance to the ability of asenapine to diminish cognitive and negative/ affective symptoms associated with schizophrenia. There was also correlation between doses showing in vivo receptor activity and neurochemical or neurobehavioural effects. It seems that potent blockade of serotonin, dopamine and noradrenaline receptor is primarily involved in mediating the effects of asenapine on behavioral tests predictive of antipsychotic activity.

The safety pharmacology identified mainly CNS (e.g dystonia, bradykinesia) cardiac (e.g decrease in arterial blood pressure, orthostatic hypotension) and endocrine effects (e.g hyperprolactinaemia) as possible targets for asenapine regarding potential adverse effects in man.

The results of pharmacokinetic studies in animals showed: rapid oral absorption; moderate tissue distribution (but crossed the blood brain and placenta barriers), high protein binding and high systemic clearance. Asenapine drug related material is excreted both in urine and faeces and notably in milk.

The majority of the findings in the repeated dose toxicity studies were related to the pharmacological activity of asenapine. Clinical signs of CNS deterioration (e.g sedation; reduced motor activity/coordination) and prolactin-mediated effects on mammary glands and oestrus cycle disturbances were observed. In addition, hepatotoxicity was observed at high dose in dogs that was was not observed after chronic intravenous administration. Asenapine had also some affinity to

melanin-containing tissues. histopathological examination did not reveal any signs of ocular toxicity. Furthermore, asenapine was non phototoxic in a vitro test.

There was no evidence of genotoxicity in a standard package of tests.

In carcinogenicity studies in rats and mice using the s.c route of administration, no increases in tumour incidences were observed.

Asenapine did not impair fertility in rats and was not teratogenic in rat and rabbit. Embryotoxicity was found in reproduction toxicology studies using rats and rabbits. Asenapine caused mild maternal toxicity and slight retardation of foetal skeletal development. Following oral administration to pregnant rabbits during the period of organogenesis, asenapine adversely affected body weight at the high dose of 15 mg/kg twice daily. At this dose foetal body weight decreased. When asenapine was administered intravenously to pregnant rabbits, no signs of embryotoxicity were observed. In rats, embryofoetal toxicity (increased post-implantation loss, decreased foetal weights, and delayed ossification) was observed following oral or intravenous administration during organogenesis or throughout gestation. Increased neonatal mortality was observed among the offspring of female ratstreated during gestation and lactation. Increased neonatal mortality was noted among offsprings of female rats treated during gestation and lactation, this was most likely related to impairment of the pups than altered nursing behaviour.

Finally, the environmental impact of asenapine needed further evaluation and additional studies. The applicant committed to carry out such studies as a post-approval commitment.

2.4. Clinical aspects

2.4.1. GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

At the CHMP's request, a GCP inspection was carried out at 3 of the 74 investigational sites of study A7501008 (investigators' sites located in the US and Thailand). Some critical findings relating to missing documents were identified, however the overall conclusions of the inspection recommended that these data could be used for the evaluation of the present application.

2.4.2. Pharmacokinetics

The Phase I clinical pharmacology program has been conducted in healthy volunteers and patients with schizophrenia using oral or sublingual formulations. The development of the oral formulation was discontinued because of its low bioavailability (<2%) caused by extensive first-pass metabolism. In addition to the Phase I studies, the pharmacokinetics of asenapine have been investigated in two pooled analyses across the pharmacokinetic data of a range of clinical trials.

Plasma concentration of asenapine and its analysed metabolites was determined using GC/MS, LC/MS , or LC/MS/MS methods in the PK studies. Pharmacokinetic parameters were determined using non compartmental models. Population PK analyses were conducted using nonlinear mixed effects modeling methodology (NONMEM).

2.4.2.1. Absorption

Asenapine was rapidly absorbed upon sublingual administration with peak plasma concentration occurring within 0.5 to 1.5 hours. The absolute bioavailability of sublingual asenapine at 5 mg was 35% whereas when swallowed was very low (<2% with an oral tablet formulation). Asenapine and its N-desmethyl metabolites appeared to be a weak substrate of P-gp. Minor differences were noted at different sites in the oral cavity, with a greatest extent of absorption via the buccal route as compared to the supralingual route. During concomitant water intake, Cmax and AUC of asenapine decreased by 21 and 19 % after 2 minutes and by 12 and 10 % after 5 minutes. During concomitant food intake, AUC of asenapine immediately decreased by 21-22%. The SPC recommends that eating and drinking should be avoided for 10 minutes after administration. Concomitant smoking following sublingual administration had no effect on the pharmacokinetics of asenapine.

Bioequivalence between 5 mg sublingual tablet applied for and the formulation used during phase III studies was demonstrated. No bioequivalence was conducted with 10 mg tablet applied for.

2.4.2.2. Distribution

Following intravenous administration, asenapine had a large volume of distribution (1731 L), indicating extensive extravascular distribution and reflecting its high lipophilicity. Asenapine is highly bound (95%) to human plasma proteins including albumin and α1- acid glycoprotein.

2.4.2.3. Elimination

Asenapine had a high hepatic 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. Its metabolites (N+-glucuronide, Ndesmethyl and 11-O-sulfate) showed similar elimination profile indicating that no accumulation of one of these metabolites is to be expected. The terminal half life was approximately 24 hours.

2.4.2.4. Dose proportionality and time dependencies

The pharmacokinetics was approximately dose proportional for up to 5mg twice daily (bid), the exposure thereafter increased less than in proportion to the dose. Increasing the dose from 5 to 10 mg twice daily (a two-fold increase) resulted in less than linear (1.7 times) increases in both the extent of exposure and maximum concentration. During twice-daily dosing, steady-state was attained within 3 days. Overall, steady-state asenapine pharmacokinetics were similar to single-dose pharmacokinetics.

2.4.2.5. Special populations

Population pharmacokinetic analyses and specific phases I studies evaluating renal and hepatic functions, paediatric and elderly populations and the effect of race, gender and age were conducted.

Specific studies were conducted in subjects with moderate to severe renal impairment at 0.3 and 5 mg sublingual single dose. There was no significant difference in AUC or Cmax after 5 mg dose between subjects with mild to moderate renal impairment and control subjects. There were no data in severe renal impairment.

Specific studies were conducted in subjects with mild, moderate and severe hepatic impairment at 0.3 and 5 mg sublingual single dose. There was no significant difference after 5 mg dose in total or unbound AUC of asenapine or its metabolites (N-desmethyl, N+ glucuronide) between subjects with mild to moderate hepatic impairment and control subjects. However, total and unbound AUC of asenapine were significantly increased by 5.3 and 7 times higher in severe hepatic impairment subjects. Total exposure of its metabolites was also increased in those subjects.

In elderly patients (between 65 and 85 years of age), AUC and Cmax were increased by approximately 30 % as compared with younger adults after 5 and 10 mg BID doses.

A specific study was conducted in Caucasian and Japanese subjects to evaluate the effect of race. There were no significant differences observed between Caucasian and Japanese after 5 mg single or bid doses. However, population PK analysis showed a decrease in mean clearance of black subject by 13.8% as compared to other ethnic origins.

In adolescent patients (12 to 17 years), AUC and Cmax increased at dose ranging from 1mg to 5 mg bid and this increased exposure was less than proportional to the dose. A lower exposure was noted at higher dose (10 mg bid).

Population pharmacokinetic analyses did not reveal any significant effect of gender nor age. Apart from a shorter estimated lag time in patients as compared to healthy volunteers, while their absorption rate was estimated to be approximately 50 % lower, no pharmacokinetic differences could be observed between these 2 populations.

2.4.2.6. Pharmacokinetic interaction studies

In vitro studies suggested inhibition of CYP2D6 and CYP1A2 and induction of CYP1A2 and CYP3A4 (only at very high concentrations above the therapeutic range). The potential interactions were studied for the following drugs: fluvoxamine (CYP1A2 inhibitor), imipramine (CYP1A2/2C19/3A4 inhibitor), cimetidine (CYP3A4/2D6/1A2 inhibitor), carbamazepine (CYP3A4/1A2 inducer) and valproate (UGT inhibitor), dextrometorphan and paroxetine (CYP2D6 substrate/inhibitor).

Study 2552545

This was an open-label, randomized, two parallel group, multiple dose,interaction trial between asenapine, paroxetine and dextromethorphan in healthy male volunteers.

In sequence A, paroxetine (20 mg) was given on Day 1. After one day of placebo dosing,1 mg asenapine (BID) was given on Day 4, followed by 3 mg (BID) on Day 5 and 5 mg (BID) on Days 6-16. On Days 12 and 14, single doses of dextromethorphan (30 mg) and paroxetine (20 mg) respectively were co-administered. In sequence B, after a placebo asenapine dosing on Day 1, asenapine (5 mg) was given at Day 2. Paroxetine 20 mg once daily was given for 9 days (Day 7-15). On Day 11, dextromethorphan (30 mg single dose) was co-administered. On Days 12 and 13, placebo asenapine and asenapine (5 mg single dose) were co-administered respectively.

Seventeen subjects were included in sequence A, of whom 13 subjects (24-55 years) completed this sequence. Thirty subjects were included in sequence B, of whom twenty-six subjects (18-51 years) completed this sequence. Results showed a considerable increase of paroxetine plasma concentrations upon co-administration of asenapine. On average the AUC0-∞ as well as the Cmax of paroxetine were almost 2-fold higher after the combination treatment as compared tothe paroxetine alone treatment. Vice versa, a drug interaction effect of paroxetine was absent on the AUC and slightly present on the Cmax of asenapine. On average the Cmax of asenapine was 13% lower after the combination treatment as compared to the asenapine alone treatment. The N-desmethylasenapine plasma concentrations were also slightly increased upon co-administration of paroxetine. Mean decreases in DX/DM ratio of approximately 2.5 and 30 times were observed, for asenapine and paroxetine confirming CYP2D6 inhibition by both compounds.

Study 2552646

This was an open-label, randomized, three-period crossover interaction study between imipramine and asenapine in healthy male subjects.

There were six groups of 4 subjects each. Each of the six possible treatment sequences was allocated to a group. The three following treatments were given within the same subject with a washout period of at least 1 week between successive drug administrations: 5 mg single sublingual dose of asenapine (treatment A), 75 mg single oral dose of imipramine (Treatment B), treatment A+B (treatment C).

Results showed extensive metabolism of imipramine by CYP2D6 and other cytochromes. An effect was observed of imipramine on the peak asenapine plasma concentration (Cmax). On average the Cmax of asenapine was 17% higher after the combination treatment as compared to the asenapine alone treatment. No drug interaction effect of imipramine on extent of exposure (AUC) to asenapine was observed. In addition, no drug interaction effect of imipramine on the PK parameters of N-desmethylasenapine was present. The rate and extent of exposure to imipramine was not altered by co-administration of asenapine.

Study 2552847

This was an open-label, interaction study to investigate the effect of steady state carbamazepine on the single dose pharmacokinetics of 5 mg asenapine in healthy male subjects

Twenty four healthy male subjects (18-45 years), received a single sublingual dose of asenapine before and during treatment with carbamazepine. A single sublingual dose of 5 mg of asenapine was administered once on Day 1 and once on Day 20. Carbamazepine was orally administered on Days 4-7 as 200 mg BID and on Days 8-22 as 400 mgBID.

An effect of carbamazepine on the pharmacokinetics was present for asenapine as well as for the metabolites N-desmethylasenapine and asenapineN+-glucuronide. On average the AUC0-∞ of

asenapine was 16% lower after the combination treatment as compared to the asenapine alone treatment. For N-desmethylasenapine, the AUC0-∞ was 30% lower after the combination treatment as compared to the asenapine alone treatment and for asenapine N+-glucuronide 16% lower. The effects on Cmax were similar to those on AUC for asenapine and N-desmethylasenapine. The 6β–hydroxycortisol/free cortisol ratio in urine during treatment (day 19) was approximately 4 times as high as on Day -1 during treatment (Day 19) to pre-treatment (Day -1) confirming the inducing effect of carbamazepine on CYP3A4.

Study 2552948

This was an open label, randomized, two-way cross-over trial in 24 healthy male subjects (18-45 years), in which a single dose of asenapine was sublingually administered without (treatment A) and during treatment with cimetidine (treatment B).

The following treatments were given in a two-period/two-sequence cross-over fashion, with a washout period of at least 2 weeks between successive treatment periods: single sublingual dose of 5 mg asenapine on Day 1 (treatment A), multiple oral doses of 800 mg BID cimetidine during Days 1-7 with a single sublingual dose of 5 mg asenapine on Day 5 (treatment B). On Days -1 and 3 during treatment B, subjects received a single oral dose of 100 mg caffeine and 30 mg dextromethorphan.

An effect of cimetidine on AUC and Cmax was present for N-desmethylasenapine, and to a lesser extent for asenapine, N+-glucuronide whereas for asenapine no drug interaction was observed. On average the N-desmethyl asenapine AUC0-∞ was 2.2 times as high after the combination treatment and the Cmax 1.5 times as high as compared to the asenapine alone treatment. During treatment, paraxanthine/caffeine, dextrorphan/ dextromethorphan hydroxycortisol/free cortisol ratios decreased by 36% (plasma), 75% (urine) and 23% (urine), respectively confirming observed inhibitory effects of cimetidine on CYP1A2, CYP2D6 and CYP3A4.

Study 04103349

This was an open label, randomized, two-period, 2 sequences, cross-over trial in 26 healthy male subjects (18-55 years), in which a single dose of asenapine was administered alone or simultaneously with multiple doses of fluvoxamine. In addition a single dose of caffeine was administered alone and simultaneously with multiple doses of fluvoxamine.

The following treatments were given in a two-period crossover, randomized fashion with a washout of at least 1 week between the two treatment periods: a single sublingual dose of 5 mg asenapine on Day 1 (treatment A), multiple doses of 25 mg fluvoxamine BID on Days 1-7 with a single sublingual dose of 5 mg asenapine on Day 5 (treatment B)

During treatment B, subjects received a single oral dose of 100 mg caffeine on Days -1 and 3.

An effect of fluvoxamine on the pharmacokinetics of asenapine was present as well as for the metabolites N-desmethylasenapine and asenapine 11-Osulfate. Fluvoxamine administered simultaneously with asenapine increased the mean extent of exposure (AUC) to asenapine with 29% and the mean asenapine peak concentration (Cmax) with 13%. In addition, it doubled the mean N-desmethylasenapine AUC but had no effect on N-desmethyl Cmax. The mean asenapine 11-O-sulfate AUC after the combination treatment was decreased with 29% and the mean asenapine 11-O-sulfate Cmax was 2.5 times lower as compared to the asenapine alone treatment.

During treatment (day3), paraxanthine/caffeine, ratio decreased was decreased 5.4 times as compared to pre-treatment (day-1) confirming observed inhibitory effects of fluvoxamine on CYP1A2.

Study 2552750

This was an open label, randomized, two-way cross-over trial in 24 healthy male subjects (18-55 years), in which a single dose of 5 mg asenapine was sublingually administered alone (treatment A) and during treatment with valproate 500 mg BID orally for 9 days (treatment B). There was a washout of at least 2 weeks between successive treatment periods.

No drug interaction was observed for the PK parameters Cmax and AUC of asenapine and for the Cmax of N-desmethylasenapine. However, a drug interaction effect of valproate on the PK parameters Cmax and AUC was present for asenapine N+-glucuronide and on the AUC for N-desmethylasenapine. On average the AUC0-∞ and the Cmax of asenapine N+-glucuronide were respectively 7.4 and 6.6 times lower after the combination treatment as compared to the asenapine alone treatment. For N-desmethylasenapine, the AUC0-∞ was 30% lower after the combination treatment as compared to the asenapine alone treatment.

2.4.2.7. Pharmacokinetics using human biomaterials

Not applicable

2.4.3. Pharmacodynamics

2.4.3.1. Mechanism of action

As for other atypical antipsychotics the efficacy of asenapine in the claimed indications is proposed to be mediated, at least in part, through a combination of antagonist activity at D2 and 5-HT2A receptors. The applicant claimed that asenapine has a unique human receptor binding profile with the highest affinity for blocking serotonin receptors, followed by dopamine and alpha-adrenergic receptors. It is said to display minimal affinity for muscarinic receptors. In addition to the assumption of efficacy mediated via D2 and 5-HT2A receptors, the applicant claims that actions at other receptors (e.g., 5-HT2C, 5-HT6, 5-HT7 5-HT1A, 5-HT1B, D3, and α2-adrenergic receptors) may be associated with improvements in cognition, and negative and affective symptoms.

In general, however, the exact mechanism of action of asenapine, as with other drugs with efficacy in schizophrenia and bipolar disorder, is unknown.

2.4.3.2. Primary and Secondary pharmacology

Three clinical studies were conducted (2 in healthy subjects, 1 in patients with schizophrenia) to investigate the D2-dopamine and 5HT2A- receptors binding of asenapine using Positron Emission Tomography (PET).

In study 25510 (n=3), following administration of a single sublingual dose of placebo followed, at least one week later, by a single sublingual dose of 100 µg asenapine, D2 receptor occupancy in the putamen at 2.5h post-dosing of the three healthy males was 12%, 20% and 23%, respectively. The 5-HT2A receptor occupancy by asenapine in the frontal cortex at 4.5h post-dosing was 15%, 15%, and 30%, respectively.

In study 25516 (n=6), following titrated administration of sublingual dose of asenapine (up to 300 µg BID) over three days in healthy males, mean D2-receptor occupancy was 31 % (29%) in the putamen (caudate nucleus) at 2 h post-dosing in four subjects and 25% (31%) 3.5 h post-dosing in two

subjects. The occupancy decreased after this time point reaching 16% (18%) at 6 h, 5% (7%) at 12 h and 5 % (3%) at 24 h post dosing.

In study 041007 (n=8), 6 subjects received BID asenapine doses of 2.4 mg (n = 1), 4.0 mg (n = 1) and 4.8 mg (n = 4), and in two subjects were on placebo. The individual percentages of central D2 occupancy for asenapine subjects ranged from 68-93% at approximately 2-6 h after dosing, with the majority of subjects having ≥90% occupancy. After a dose of 4.8 mg, an average occupancy percentage of 79 % was obtained at approximately 3-4 h after dosing. This percentage decreased to 66 % at 8 h after dosing and 38 % at 15 h after dosing. Peak occupancy in the subject at 2.4mg (93 %, subject 1015) was equally high as for subjects on 4.8 mg; this could be attributed to the relatively high plasma levels of asenapine observed in this individual.

Pharmacokinetic-pharmacodynamic modeling indicated striatal D2 occupancy by asenapine to be directly related to plasma concentrations. At plasma concentrations of 0.72 ng/mL on average 50% of D2 receptors occupancy was shown. A further analysis using phase II trial data showed dose-dependency for asenapine D2 receptor occupancy (dose range 0.1 – 4.8 mg).

No secondary pharmacology studies were performed in humans.

2.4.4. Discussion and conclusions on clinical pharmacology

The pharmacokinetic profile (absorption, distribution, metabolism and elimination) of asenapine has been adequately characterised. No major PK differences were observed between healthy volunteers and patients with schizophrenia.

Bioequivalence between 5 mg sublingual tablet applied for and the formulation used during phase III studies was demonstrated. No bioequivalence was conducted with 10 mg tablet applied for. Based on the available data and feasibility concerns, the CHMP accepted that no bioequivalence was conducted with 10 mg tablet applied for.

No dose adjustment is required for patients with renal impairment and patients with mild to moderate hepatic impairment. However, there is no experience with asenapine in severe renal impairment (patients with a creatinine clearance less than 15 mL/min). and asenapine is not recommended in patients with severe hepatic impairment due to an observed 7-fold increase exposure in these patients. In elderly patients (between 65 and 85 years of age), exposure to asenapine is approximately 30 % higher than in younger adults. At the 5 mg twice daily dose level, asenapine pharmacokinetics in adolescent patients (12 to 17 years of age, inclusive) are similar to those observed in adults. In adolescents, the 10 mg twice daily dose did not result in increased exposure compared to 5 mg twice daily.

Except for fluvoxamine, none of the interacting drugs medicinal products resulted in clinically relevant alterations in asenapine pharmacokinetics. During combined administration with a single dose of asenapine 5 mg, fluvoxamine 25 mg BID resulted in a 29 % increase in asenapine AUC. The full therapeutic dose of fluvoxamine would be expected to produce a greater increase in asenapine plasma concentrations. Therefore, caution concerning co-administration of both asenapine and fluvoxamine is reflected in the SPC.

2.4.5. Clinical efficacy

The following indications were initially applied for: treatment of schizophrenia, treatment of manic episodes associated with Bipolar I disorder. The clinical development program is discussed below per indication.

SCHIZOPHRENIA

The clinical development program comprised a total of 20 trials, of which 17 were completed and three were ongoing as of the data cut-off date of 01 December 2008. The completed studies (except study 041590[1]) are summarised in Tables 1-3 for completed Phase II, completed Phase III, and ongoing studies.

Main studies are as follows:

- Three phase II short-term 6-week, randomized, double-blind placebo controlled trials (**041002, 041013, 041004**) in subjects with schizophrenia;
- Three phase III short-term 6-week, randomized, double-blind placebo controlled trials. Two were of fixed dose design (**041021, 041023**) and the other employed a flexible dose of 5-10mg BID (**041022**) in subjects with schizophrenia;
- A 52 week randomized placebo controlled relapse prevention trial (**A7501012**).
- A 52 week flexible dose study (**25517**) using olanzapine as active comparator in patients with schizophrenia or schizoaffective disorder. Trial **22520** was its double- blind extension.
- A 26 week flexible dose study (**25543**) using olanzapine as active comparator in patients schizophrenia with predominant persistent negative symptoms. Trial **25544** was its 26 weeks double-blind extension.

Trials **041512** and **041513** were double-blind, flexible-dose, active-controlled, 1-year extensions to the short-term phase III trials (041021/041022 and 041023, respectively).

The remaining studies (**041500, 041505, 041502**) were 1-year fixed double blind extensions of the phase II trials (041002, 041013 and 041004, respectively). A brief summary of results from studies 041500 and 041502 is provided, considering the small sample sizes of phase II extension trials.

[1] open-label humanitarian study for subjects who had successfully completed one of the short-term phase II trials and its extension and who were assessed by the investigator as potentially benefiting from continued therapy at the same dosage.

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

Trial / design	Trial Dates	Number of subjects evaluable for efficacy												
		Asenapine								Olanzapine		Risp	Halo	Placebo
		200 µg BID	400 µg BID	800 µg BID	1600 µg BID	2400 µg BID	5 mg BID	10 mg BID	5-10 mgBID	15 mg QD	10-20 mg QD	3 mg BID	4 mg BID	
Phase II														
041002 / DB, PC, AC, FD DF, 42-d	May 1998-May 2000	58	55	59								57		54
041013 / DB, PC, FD, DF, 42-d	Feb 2000 - Jun 2001				54	54								62
041004 / DB, PC, DF, AC, FD, 42-d	Aug 2001-May 2002						58					56		60
041500: extension to 041002 / DB, PC, AC, FD, DF, 1-yr[a]	June 1998-Nov 2000	(8)	(6)	(14)								(13)		(8)
041502: extension to 041004 / DB, PC, AC, FD, 1-yr[a]	Oct 2001-May 2003						(15)					(17)		(7)
041505: extension to 041013 / DB, PC, FD, DF, 1-yr[a]	June 2000-Jan 2002				(10)	(10)								(8)
Total number of evaluable phase II subjects in feeder (extension) trials by dose group [a]		**58 (8)**	**55 (6)**	**59 (14)**	**54 (10)**	**54 (10)**	**58 (15)**					**113 (30)**		**176 (23)**

Source: 041002 CTR Table 8, 041013 CTR Table 9, 041004 CTR Table 9, 041500 CTR Table 4, 041502 CTR Table 3, 041505 CTR Table 7.

a Numbers and totals (in parentheses) include subjects who completed a short-term trial and were enrolled and treated in an extension trial.

AC = active control; BID = twice daily; d= day; DB = double blind; DF = dose-finding; FD = fixed dose; Halo = Haloperidol; PC = placebo control; QD = once daily; Risp = Risperidone; yr = year.

Table 2 Overview of completed phase III trials in the asenapine schizophrenia clinical development program (Intent-to-Treat)

Trial / design	Trial Dates	Number of subjects evaluable for efficacy										
		Asenapine					Olanzapine			Haloperidol		Placebo
		5 mg BID	10 mg BID	5-10 mg BID	Placebo/ 5-10 mg BID	5-10 mg BID /Placebo	15 mg QD	10-20 mg QD	5-20 mg QD	4 mg BID	2-8 mg BID	
041022 / DB, PC AC, Flex D, 42-d	Feb 2005–Feb 2006			85				85				89
041021 / DB, PC, AC, FD, 42-d	May 2005-May 2006	102	96				95					93
041023 / DB, FD, PC, AC, 42-d	Jun 2005-Sep 2006	109	105							112		122
25517 / DB, AC, FlexD / 52-wk	Sep 2003-Feb 2006			869				297				
041512: extension to 041021 & 041022 / DB, AC, Flex D, 52-wk	April 2005-June 2007			(81)	(52)				(59)			
25520: extension to 25517 / DB-SB-OL, Flex D, 52-wk+	Oct 2004-Oct 2006			(267)				(147)				
041513: extension to 041023 / DB, AC, Flex D, 52-wk	Sep 2005-Oct 2007			(88)	(47)						(41)	
25543 / DB, AC, Flex D, 26-wk	May 2005-Jun 2007			216					217			
25544: extension to 25543 / DB, AC, Flex D, 26-wk	Jun 2006-Dec 2007			(122)					(157)			
A7501012 / DB, PC, Flex D[a], 52-wk	May 2005-Jul 2008			191		191						
Total number of evaluable subjects in feeder (extension) trials by dose group[b]		**211**	**201**	**1361 (558)**	**(99)**	**191**	**95**	**382 (147)**	**217 (216)**	**112**	**(41)**	**304**

Source: 041022 CTR Table 9, 041021 CTR Table 9, 041023 CTR Table 9, 25517 CTR Table 15, 041512 Table 5, 25520 CTR Table 15, 041513 CTR Table 5, 25543 CTR Table 6, 25544 CTR Table 5, and A7501012 CTR Table 6.

a Decreases only during DB

b Numbers and totals (in parentheses) include subjects who completed a short-term trial and were enrolled and treated in an extension trial.

AC = active control; BID = twice daily; d = day; DB = double blind; FD = fixed dose; Flex D = flexible dose; OL = open label, PC = placebo control; QD = once daily; SB = single blind; wk = week.

Table 3 Overview of ongoing trials in the schizophrenia clinical development program (as of the 01 December 2008 data cut-off date)

Trial No.	Description
A7501013	6-month double-blind trial in the treatment of schizophrenia subjects with predominant persistent negative symptoms asenapine 5-10 mg BID, olanzapine 5-20 mg QD; Number of subjects treated as of data cut-off = 335
A7501014	6-month double-blind extension Number of subjects treated as of data cut-off = 104
A7501021	6-week open-label safety in elderly subjects with psychosis (≥65 yrs); blinded to dose. Number of subjects treated as of data cut-off = 29

BID = twice daily; QD = once daily; yrs = years

2.4.5.1. Dose response studies

The three main phase II dose ranging studies were performed and designed as short-term 6-week, randomized, double-blind placebo controlled trials (**041002, 041013, 041004**). In all 3 studies, the primary endpoint was the mean change from baseline on the PANSS total score.

In study 041002, six groups of twice daily doses of asepanine (0.2 mg, 0.4 mg, 0.8 mg, 1.6 mg, 2.4 mg, 5 mg) were studied versus twice daily doses of risperidone 3 mg and placebo. All dose groups of asenapine failed to demonstrate superiority over placebo. In contrast, the risperidone group showed statistically significant difference over placebo in the mean change from baseline score on the Total PANSS at weeks 4, 5, and 6 suggesting that the study was sensitive and the tested doses of asenapine were not effective. In the extension study 041500, a total of 51 subjects were enrolled and 49 continued treatment with the same treatment previously received in study 041002. No statistical significant differences were observed in measured efficacy outcomes between placebo and any of the active treatment groups.

In study 041013, higher twice daily doses of asenapine (1.6 mg and 2 mg) were compared to placebo. Mean changes from baseline were -3.68 (placebo), -8.67 (asenapine 1.6 mg) and – 5.81 (asenapine 1.6 mg) showing favourable trends. However, both tested doses failed to reach statistical significance. In addition, no dose-response could be established in this study.
In study 041004, twice daily dose of asenapine 5 mg was studied versus twice daily doses of risperidone 3 mg and placebo. The tested dose demonstrated statistical significant difference over placebo. Main patients characteristics and results of this study are presented in Tables 4-7.

Table 4 Patient disposition – study 004

	Placebo	5mg asenapine	Risperidone
Randomised	62	60	60
Treated	62	59	59
ITT population	60 (97%)	58 (98%)	56 (95%)
Completed study	21 (34%)	27 (46%)	25 (42%)
Discontinued treatment early	41	32	34
Adverse Event	7	7	4
Lack of Efficacy	18	9	16
Other	16	16	14

Table 5 Patients providing data at each visit

	Placebo	5mg asenapine	Risperidone
Day 7	57	56	56
Day 14	48	47	50
Day 21	43	42	44
Day 28	27	32	30
Day 36	25	29	28
Day 42	22	27	25

Results

Table 6 Change from baseline to week 6/endpoint in PANSS total score – ITT LOCF

	Placebo	5mg asenapine	Risperidone
Baseline	92.43	96.48	92.43
Change from baseline (SE)	-5.27 (2.30)	-15.86 (2.62)	-10.93 (2.67)
p-value*		p=0.0024	p=0.1186

*From t-test, SE: standard error

In addition, a responder analysis for study 41004 has been performed and is shown in Table 7

Table 7 Responders (≥ 30 or 20 % reduction in PANSS)

	Placebo	5mg	Risperidone
≥ 30 % LOCF ITT	15/60 (25%)	22/58 (38%)	22/56 (39%)
≥ 20 % LOCF ITT	21/60 (35%)	31/58 (53%)	28/56 (50%)
≥ 30 % Missing=failure	10/62 (16%)	17/59 (29%)	14/59 (23%)
≥ 20 % Missing=failure	14/62 (23%)	20/59 (34%)	19/59 (32%)

In the extension study 041502, a total of 39 subjects were enrolled (asenapine: 15, risperidone: 17, placebo: 7), primary efficacy result was consistent with the previous finding from study 041004.

2.4.5.2. Short term studies

2.4.5.2.1. Methods

Study design

The three main phase III short-term studies were designed as follows:

- 041021: a 6-week , fixed-dose, randomised, double blind placebo- and active –controlled (4 treatment groups: asenapine 5 mg BID, asenapine 10 mg BID, olanzapine 15 mg QD, or placebo in 1:1:1:1 ratio) study in subjects with schizophrenia.

- 041023 : a 6-week , fixed-dose, randomised, double blind placebo- and active –controlled (4 treatment groups: asenapine 5 mg BID, asenapine 10 mg BID, haloperidol 4 mg BID, or placebo in 1:1:1:1 ratio) study in subjects with schizophrenia;

- 041022: a 6-week, flexible-dose, randomised, double blind placebo- and active –controlled (3 treatment groups: asenapine 5/10 mg BID, olanzapine 10-20 mg QD, or placebo in 1:1:1 ratio) study in subjects with schizophrenia.

Studies 041021 and 041022 were conducted outside EU (Russia; Ukraine and US) and study 041023 was conducted in Romania, Canada, India, Russia and US.

Patients who completed the above short term studies were eligible to enter 1- year, double blind, flexible dose, active controlled extension studies (041512 for 041021 and 041022 , 041513 for 041023).

In studies 041512 and 041513, the randomized subjects continued on their medication into the extension trial, and were maintained on the same dosage regimen for the first week. Placebo-treated subjects were randomized to asenapine 5 mg BID during the first week of the long-term extension. After 1 week all blinded asenapine-treated subjects were maintained or titrated in either direction from 5–10 mg BID.

Study participants

Main inclusion criteria
Male or female (females must have been non-lactating, non-pregnant, and using an acceptable method of birth control, or not of childbearing potential) of at least 18 years of age, and current DSM-IV-TR−defined diagnosis of schizophrenia of the paranoid type [295.30], disorganized type [295.10], catatonic type [295.20], or undifferentiated type [295.90].

Other key inclusion criteria included having a PANSS score of at least 60 at screening and baseline (the baseline PANSS score could not have been 20% or more lower than the screening PANSS score); a score of at least 4 on two or more of the five items of the positive subscale of the PANSS at screening and baseline; and a CGI-S score at least 4 ("moderately ill") at baseline.

Subjects were also required to have had a positive response to an antipsychotic medication other than clozapine, discontinued any depot neuroleptics prior to baseline, and provided written informed assent.

Main exclusion criteria
Potential participants were to be excluded from the trial if they met DSM-IV-TR diagnostic criteria for schizophrenia of residual subtype (295.60) or schizoaffective disorder (295.70), or had a concurrent Axis I psychiatric disorder other than schizophrenia or a primary diagnosis other than schizophrenia.

Other key exclusion criteria included the presence of an uncontrolled, unstable clinically significant medical condition that in the opinion of the investigator could interfere with the interpretation of safety and efficacy evaluations; a seizure disorder beyond childhood or the use of anticonvulsants to prevent seizures; any clinically significant abnormal laboratory, vital sign, physical examination, or ECG findings at screening that precluded trial participation; a requirement during the inpatient phase of the trial for concomitant treatment with a benzodiazepine at a dose greater than 6 mg/day of lorazepam (or the equivalent dose of another short-acting benzodiazepine); a history of substance abuse or dependence (excluding nicotine) according to DSM-IV criteria within 6 months before screening. Subjects previously treated in an asenapine trial, taking clozapine within the last 12 weeks and subjects at imminent risk of self-harm or harm to others were also excluded.

Treatments

Prior active treatment period (6 weeks), there were a screening and a 2-day taper period (eligible severely ill subjects were permitted to be randomized immediately at the discretion of the investigator). The active treatment period was initiated on Day 1 following randomization of subjects.

In study 041-022, subjects randomized to the asenapine treatment group received 5 mg asenapine BID and subjects randomized to the olanzapine treatment group received 10 mg olanzapine once daily during the first 7 days of the double-blind treatment period. At the Day 7 visit, the dose could be increased in an increment of 5 mg BID for asenapine or 5 mg QD for olanzapine, or the dose could remain the same. At each visit thereafter, doses could be increased in 5 mg increments (to a maximum of asenapine 10 mg BID or olanzapine 20 mg QD), decreased (to a minimum of asenapine 5 mg BID or olanzapine 10 mg QD), or remain the same. Decisions to change the dose were to be made by the investigator at the subject's visit, and were to be based on symptomatology and tolerability. Dose decreases could be made between visits only if intolerable adverse events prohibited a delay.

Outcomes/endpoints

The primary efficacy measure was the mean change from baseline to Week 6 on the total Positive and Negative Syndrome Scale (PANSS).

Main secondary efficacy measures were mean change from baseline to Week 6 on the Clinical Global Impressions of Severity of Illness (CGI-S) and Improvement (CGI-I) scales, Calgary Depression Scale for Schizophrenia (CDSS), Hamilton Anxiety Scale (HAM-A), InterSePT Scale for Suicidal Thinking (ISST-Modified), Readiness for Discharge Questionnaire (RDQ), Fleming/Potkin neurocognitive battery; and Cognitive Function scale (CogFu).

Health outcomes measures included functional outcomes, health-related quality of life, and treatment satisfaction using the Quality of Life Scale (QLS), Personal Evaluation of Transitions and Treatments (PETiT), Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).

Statistical Methods

All hypothesis testing was conducted using two-sided tests with alpha = 0.05 level of significance. The primary efficacy analysis was defined as a comparison of the least squares (LS) mean changes from baseline to endpoint in the PANSS total score in each asenapine treatment group versus placebo using the last observation carried forward (LOCF) and an analysis of covariance (ANCOVA) model with fixed effects for treatment and investigative site (or pooled site) and baseline as covariate included in the model. In the primary analysis only, a Hochberg adjustment method was used to adjust the two comparisons.

To assess the robustness of the results against potential bias caused by missing data due to drop outs, supportive analyses based on the intent-to-treat (ITT) group were conducted using two methods: the previously defined ANCOVA model using observed cases (OC) and a mixed model analysis using repeated measures (MMRM). Comparisons between each asenapine group and the placebo treatment group for all other efficacy endpoints were considered secondary and were used to support the findings of the primary analysis. An ANCOVA model was also used to compare between treatments changes from baseline in the PANSS subscale and Marder factor scores, CGI-S scores, CDSS scores, HAM-A total and subscale scores, ISST-Modified scores, Fleming/Potkin neurocognitive scores, CogFu scores, QLS total and subscale scores, PETiT total and subscale scores, and Q-LES-Q subscale scores. RDQ

data were analyzed using Kaplan-Meier survival methods. The number and proportion of PANSS responders (a 30% or more decrease from baseline in the PANSS total score) and CGI-I responders (at least "much improved" from baseline) were analyzed using the Cochran-Mantel- Haentzel test with adjustment for site.

The olanzapine (studies 041021 and 041022) and haloperidol (study 041023) group versus placebo group comparison were made for assessing assay sensitivity only.

2.4.5.2.2. Results

Study 041021

Participant flow

A total of 417 subjects were randomized in the trial: placebo, 106 subjects; asenapine 5mg BID, 106 subjects; asenapine 10 mg BID, 102 subjects; olanzapine 15 mg QD, 103 subjects. Of these subjects, 408 subjects received treatment: placebo, 100 subjects; asenapine 5mg BID, 104 subjects; asenapine 10 mg BID, 102; olanzapine 15 mg QD, 102 subjects. This set of subjects was defined as the all-subjects-treated group. A total of 386 subjects (92.6% of those randomly assigned to treatment) were included in the intent-to-treat group, including 93, 102, 96, and 95 subjects subjects in the placebo, asenapine 5 mg BID, asenapine 10 mg BID, and olanzapine 15 QD treatment groups, respectively.

Baseline data

The proportions of subjects in the placebo, asenapine 5 mg BID, asenapine 10 mg BID, and olanzapine 15 mg QD treatment groups who withdrew from the trial during the double-blind treatment phase of the trial were 50.0%, 42.3%, 50.0%, and 43.1%, respectively.

Insufficient therapeutic effect (defined as lack of efficacy or an adverse event considered to be a worsening of schizophrenia) led 26 (26.0%) subjects treated with placebo, 15 (14.4%) subjects treated with asenapine 5 mg BID, 15 (14.7%) subjects treated with asenapine 10 mg BID, and 12 (11.8%) subjects treated with olanzapine to withdraw from the trial.

The four treatment groups were well balanced with respect to most demographic characteristics. Within the all-subjects-treated group, Most subjects were either Caucasian (46.3%) or Black (44.9%). Subjects ranged in age from 18 to 70 years, with an overall mean (SD) age of 40.2 (10.9) years. Subjects' BMI (Body Mass Index) ranged from 18 to 56 kg/m2; the mean BMI (SD) was 28.0 (5.5) kg/m2. The proportion of males was smaller in the placebo treatment group (58.0%) than in the asenapine 5 mg BID (74.0%), asenapine 10 mg BID (70.6%) and olanzapine (78.4%) treatment groups.

The duration of the present episode of schizophrenia (less than 1 month in 60.8% of olanzapine-treated subjects versus 50.0-52.9% of subjects in the other groups, and more than 1 year in 16.7% of subjects in the asenapine 10 mg BID treatment group versus 6.9-12.0% of subjects in the other treatment groups) and the number of years since the onset of schizophrenia (20 or more years prior to the start of the trial in greater than 40% of subjects treated with asenapine 10 mg BID and olanzapine compared with 28.0% of subjects treated with placebo).

Mean scores at baseline on all efficacy parameters were similar across treatment groups. The baseline PANSS total score means for placebo, asenapine and olanzapine groups were: 92.43, 96.48, and 92.43, respectively.

Outcomes

No statistically significant differences in the mean changes from baseline to endpoint in the PANSS total score were observed between placebo (-11.1) and asenapine 5 mg (-14.5) or asenapine 10 mg BID (-13.4). Mean change from baseline to week 6 on PANSS total score for placebo, asenapine 5 mg BID, asenapine 10 mg BID and olanzapine 15 mg QD were -11.1, -14.5, -13.4, -16.5, respectively. Compared with placebo, olanzapine treatment resulted in a statistically significantly greater mean change from baseline in the PANSS total score (-16.5, p=0.0168).

With respect to secondary outcome measures, asenapine 5 mg BID and olanzapine treatments resulted in statistically significantly greater decreases from baseline to endpoint in the PANSS positive subscale score, Marder positive symptoms factor score, and PANSS Marder hostility/excitement factor score at endpoint. Asenapine 10 mg BID was no different from placebo on these measures at endpoint. Statistically significant differences between placebo and olanzapine (but not asenapine at either dose level) were achieved in PANSS general psychopathology subscale and PANSS Marder disorganized thought factor scores at endpoint. None of the active treatments had a significant effect on PANSS negative subscale scores, or on PANSS Marder negative symptom or anxiety/depression factor scores.

No statistically significant differences in the mean changes from baseline in the CGI-S scores were observed between asenapine 5 mg BID or asenapine 10 mg BID and placebo at endpoint or any trial visit. No statistically significant differences between any active treatment and placebo were observed in the proportions of CGI-I responders at endpoint.
No statistically significant differences between any active treatment group and placebo were observed in the mean changes from baseline in the CDSS score, the ISST-modified, the RDQ, QLS total or subscale scores or PETiT total or subscale scores at endpoint .

Compared with placebo, treatment with asenapine 10 mg BID resulted in statistically significantly greater mean increases from baseline to endpoint in the Q-LES-Q leisure time activities and social relations subscale scores. Statistically significant differences between olanzapine and placebo were also observed on the Q-LES-Q leisure time activities subscale at endpoint. No statistically significant placebo corrected mean changes from baseline were observed at endpoint in the Intent-to- Treat group on any of the tests of neuropsychological function that comprise the Potkin's Fleming battery, the CogFu, for any active treatment group.

The proportion of PANSS responders was statistically significantly greater in the asenapine 5 mg BID and olanzapine treatment groups at endpoint (LOCF). No statistically significant differences in the proportions of PANSS responders were observed between asenapine 10 mg BID and placebo at endpoint.

Study 041023

Participant flow

A total of 458 subjects were randomized in the trial: placebo, 123 subjects; asenapine 5mg BID, 114 subjects; asenapine 10 mg BID, 106 subjects; haloperidol, 115 subjects. Of these subjects, 455 subjects received treatment and were included in the all-subjects treated group: placebo, 123 subjects; asenapine 5mg BID, 111 subjects; asenapine 10 mg BID, 106; haloperidol, 115 subjects. Of these subjects, 448 subjects had at least one post-baseline PANSS assessment and were included in the

intent-to-treat group: placebo, 122 subjects; asenapine 5 mg BID, 109 subjects; asenapine 10 mg BID,105 subjects; haloperidol, 112 subjects.

Baseline data

The proportions of subjects in the placebo, asenapine 5 mg BID, asenapine 10 mg BID, and haloperidol treatment groups who withdrew from the trial during the double-blind treatment period were 43.1%, 36.9%, 33.0%, and 40.9%, respectively.

Adverse events led 10.6%, 4.5%, 9.4%, and 10.4% of subjects in the placebo, asenapine 5 mg BID, asenapine 10 mg BID, and haloperidol treatment groups to withdraw from the trial. Insufficient therapeutic effect led 25.2%, 12.6%, 16.0%, and 8.7% of subjects in the placebo, asenapine 5 mg BID, asenapine 10 mg BID, and haloperidol treatment groups to withdraw from the trial.

The asenapine 5 mg BID and 10 mg BID treatment groups included a higher proportion of males (67.6% and 63.2%, respectively) than the placebo (52.0%) and haloperidol (54.8%) treatment groups. The four treatment groups were well balanced with respect to demographic characteristics at baseline. Most subjects were either Caucasian (62.0%) or Black (25.7%). Subjects ranged from 18 to 70 years, and the overall mean age was 38.6 years. Subjects' BMI ranged from 17 to 51 kg/m2; the mean BMI was 26.3 kg/m2.

The mean age of subjects at the onset of schizophrenia was 26.0 years, and for 56.7% of the subjects, the onset of their schizophrenia occurred more than 10 years before trial entry. Approximately 53.8% of subjects had previously experienced 4 or more episodes of schizophrenia that resulted in hospitalization.

Mean scores at baseline on all efficacy parameters were similar across treatment groups. The total PANSS mean scores at baseline were 89.0 for placebo treated subjects (n=122), 88.9 for (109) asenapine 5 mg BID treated subjects (n=109), 89.4 for asenapine 10 mg BID treated subjects (n=105) and 88.5 for haloperidol 4 mg BID treated subjects (n=112), respectively.

Outcomes

Treatment with asenapine 5 mg BID resulted in a statistically significantly greater mean change from baseline to endpoint (LOCF) in the PANSS total score compared with that in the placebo treatment group (placebo [-10.7] versus asenapine 5 mg BID [-16.2], adjusted p=0.0290). Statistically significant differences in favor of asenapine 5 mg BID relative to placebo were consistently apparent starting on day 21.

Statistical analysis of the mean change from baseline in the PANSS total scores using the observed-case (OC) method and the results of a MMRM were consistent with the findings of the LOCF analysis for asenapine 5 mg BID.

The mean change from baseline to endpoint (LOCF) in the PANSS total score was statistically significantly greater in the haloperidol treatment group compared with the placebo treatment group (placebo [-10.7] versus haloperidol [-15.4], unadjusted p=0.0342).

No statistically significant difference between asenapine 10 mg BID and placebo was observed in the mean change from baseline to endpoint (LOCF) in the PANSS total score (placebo [-10.7] versus asenapine 10 mg BID [-14.9], adjusted p=0.0680). In the OC and MMRM analyses of the primary endpoint starting on day 35, a statistically significant difference in favor of asenapine 10 mg BID [-18.5] compared with placebo [-14.0] was observed (p=0.0167).

With respect to secondary outcome measures, treatment with asenapine 5 mg BID resulted in statistically significant changes from baseline, compared with placebo, the PANSS positive and general psychopathology subscales and the PANSS Marder positive symptoms and disorganized thoughts factors; PANSS responders (defined as at least 30% change from the baseline total PANSS score) and CGI-I responder rates; as well as the CGI-S and CDSS. Improvements on cognition (OC), quality of life (QoL) were observed with statistical significant difference over placebo on scores in the composite memory and processing speed domains of the CNS Vital Signs neurocognitive battery, QLS total score. No differences between asenapine 5 mg BID and placebo were observed on measures of negative symptoms, the ISST, RDQ, PETiT, or Q-LES-Q.

Asenapine 10 mg BID showed statistically significant difference over placebo on changes from baseline to endpoint on both the PANSS positive subscale and Marder positive symptoms factor. The higher dose also resulted in a statistically significantly greater proportion of total PANSS 30% responder score change from baseline to endpoint, compared with placebo treatment. No further significant treatment effects were apparent for asenapine 10 mg BID on any other efficacy or health outcomes measures.

There was no statistically significant difference for PANSS 30% responder rate changes from baseline to endpoint between haloperidol 4 mg BID and placebo treatment.

Study 041022

Participant flow

A total of 277 subjects were randomized in the trial: placebo, 93 subjects; asenapine 5mg/10 mg BID, 91 subjects; olanzapine 10-20mg QD, 93 subjects. A total of 275 subjects (99.3% of those randomly assigned to treatment) received at least 1 dose of double-blind trial medication, including 93, 90, and 92 subjects who received placebo, asenapine, and olanzapine, respectively. This set of subjects was defined as the all-subjects-treated group. A total of 259 subjects (93.5% of those randomly assigned to treatment), including 89, 85, and 85 subjects in the placebo, asenapine; and olanzapine treatment groups, respectively, were included in the ITT group.

Baseline data

The proportions of subjects in the placebo, asenapine, and olanzapine treatment groups who withdrew from the trial during the double-blind treatmentperiod were 48.4%, 53.3%, and 53.3%, respectively.

Adverse events led 5.4% of placebo-treated subjects, 6.7% of asenapine-treated subjects, and 12.0% of olanzapine-treated subjects to discontinue during the double-blind treatment phase of the trial. Insufficient therapeutic response, led 17.2%, 7.8%, and 22.8% subjects in the placebo, asenapine, and olanzapine treatment groups, respectively, to withdraw from the trial.

Within the all-subjects-treated group, the three treatment groups were well balanced with respect to demographic characteristics at baseline. The trial population was predominantly male (77.5%), and most subjects were either Caucasian (46.5%) or Black (45.1%). The subjects ranged from 20 to 67 years, and the mean age was 42.5 years. Subjects' BMI ranged from 17 to 50 kg/m2, and the mean BMI was 28.1 kg/m2.

Within the all-subjects-treated group, the mean age of subjects at the onset of schizophrenia was 25.8 years. The duration of the present episode was greater than 6 months for 14.6% of subjects. The

proportion of subjects who had previously experienced 4 or more episodes of schizophrenia that resulted in hospitalization was 70.5%.

Mean scores at baseline on all efficacy parameters were similar across treatment groups. The baseline PANSS total score means for placebo, asenapine and olanzapine groups were: 84.7 ,86.8 , and 86.5, respectively.

Outcomes

No statistically significant differences ($p>0.05$) in the mean changes from baseline to endpoint in the PANSS total score were observed between asenapine (-9.4) and placebo (-9.9) or between olanzapine (-11.5) and placebo (-9.9).

No statistically significant ($p>0.05$) differences between asenapine and placebo or between olanzapine and placebo were observed in the mean changes from baseline to endpoint in any secondary efficacy or health outcomes measures.

Extension studies

- Study 041512

A total of 205 subjects were randomized and treated, comprising the all-subjects-treated group (57 subjects, placebo/asenapine; 86 subjects, asenapine 5-10 mg BID and 62 subjects, olanzapine 5-20 mg QD). The ITT group consisted of 192 subjects (52, placebo/asenapine; 81, asenapine 5-10 mg BID and 59, olanzapine 5-20 mg QD).

Based on the estimation of the time to loss of effect, the median survival times were 29 days in both asenapine and olanzapine groups. The number of subjects with a loss of effect in the asenapine 5-10 mg BID treatment group was 42/46 (91.3%) and in the olanzapine 5-20 mg QD treatment group was 32/36 (88.5%). In the OC analysis (ITT group), mean changes from baseline to week 52 and endpoint on PANSS total score, PANSS subscale scores, (positive, negative, and general psychopathology, PANSS Marder factor symptom scores, (positive, negative, disorganized thought, hostility/excitement and anxiety/depression), CGI-Severity (CGI-S) were comparable between the two groups. At Week 52 and at endpoint, the asenapine group had a lower proportion of responders (72.2% and 46.9%) compared to the olanzapine 5-20 mg QD treatment group (91.3% and 72.9%). In the placebo/asenapine treatment group, 71.2% of subjects were responders at endpoint. At endpoint, 35.8% of subjects in the asenapine group were responders compared to 54.2% in the olanzapine group and 71.2% in the placebo/asenapine group.

- Study 041513:

A total of 187 subjects were randomized, with 185 subjects treated, comprising 50 subjects in the placebo/asenapine treatment group; 92 subjects in the asenapine 5-10 mg BID treatment group and 43 subjects in the haloperidol 2-8 mg BID treatment group. The Intent-to-Treat group consisted of 176 subjects (47 subjects, placebo/asenapine; 88 subjects, asenapine 5-10 mg BID and 41 subjects, haloperidol 2-8 mg BID).

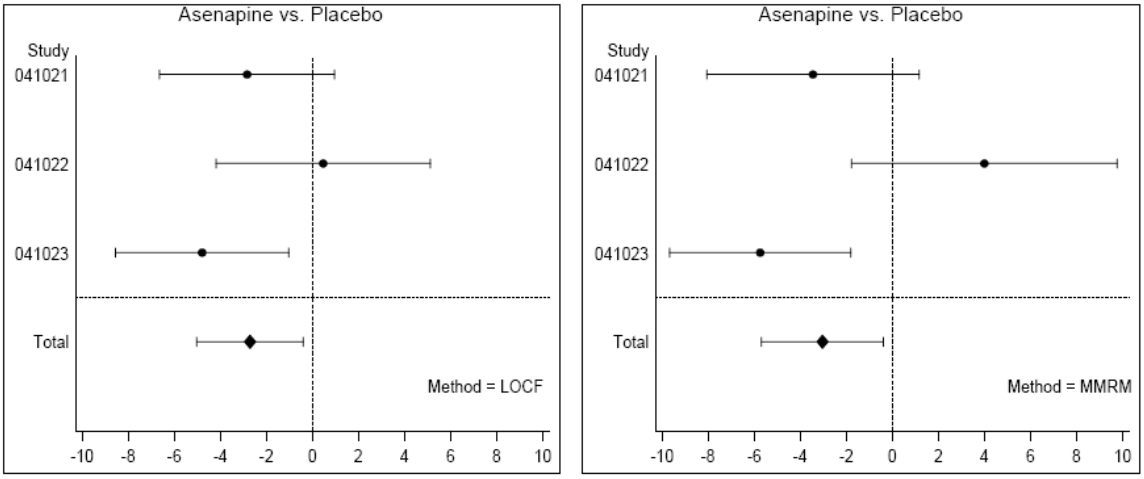
The number of subjects with loss of effect included 55/65 (84.6%) subjects in the asenapine 5-10 mg BID treatment group and 26/29 (89.7%) subjects in the haloperidol group.

In the OC analysis (ITT group), mean changes from baseline to week 52 and endpoint on PANSS total score, PANSS subscale scores, (positive, negative, and general psychopathology, PANSS Marder factor symptom scores, (positive, negative, disorganized thought, hostility/excitement and anxiety/depression), CGI-Severity (CGI-S) were comparable between the two groups. At Week 52 and at endpoint, the asenapine group had a lower proportion of PANSS total score responders (84.6% and 62.5%) compared to the haloperidol group (100.0% and 78.0%). In the placebo/asenapine treatment group 66.0% of subjects were responders at endpoint.

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

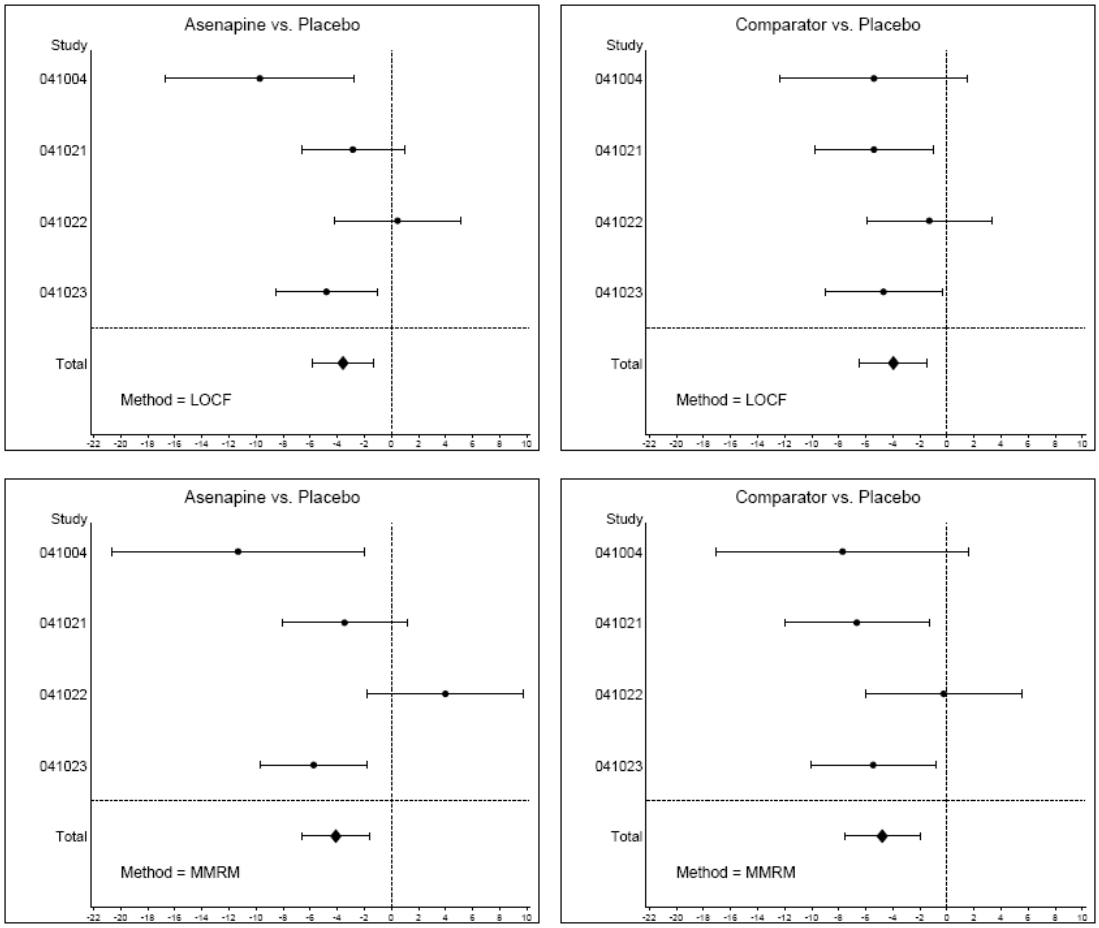
Several meta analyses on short term efficacy results were conducted by the applicant and are presented in Figures 1-2.

Figure 1 **Results of meta-analysis asenapine vs. placebo on PANSS – Total score. Studies 041021, 041022, 041023; Intent-to-treat population**



Using LOCF to impute missing data, the treatment effect was -2.7 points greater for asenapine versus placebo (p=0.021; 95% CI -5.0 to -0.4). Similarly, using MMRM to account for missing data the treatment effect was 3.0 points greater for asenapine versus placebo (p=0.024; 95% CI -5.7 to -0.4).

Figure 2 **Results of meta-analysis asenapine and comparator vs. placebo on PANSS – Total score. Trials in 5-10 mg BID dose range – Intent-to-treat population.**



Using LOCF to impute missing data, the treatment effect was -3.7 points greater for asenapine versus placebo (p=0.011; 95% CI -5.9 to -1.5). Similarly, using a mixed model for repeated measurements (MMRM) to account for missing data the treatment effect was 3.9 points greater for asenapine versus placebo (p=0.021; 95% CI -6.3 to -1.4).

The applicant also presented several sensitivity analyses to investigate the robustness of the estimate of the treatment effect for asenapine versus placebo. These are summarised in Table 8.

Table 8

Table 1 **Summary of sensitivity analyses on PANSS Total Score (LOCF). Short term placebo-controlled trials – Intent-to-Treat population.**

Analysis	Studies	Estimate (95% CI)		p-value
Primary	**041004, 041021, 041022, 041023**	**-3.7**	**(-5.9, -1.5)**	**0.0011**
Excl. failed	041021, 041023, 041004	-4.9	(-7.4, -2.4)	0.0001
Phase III	041021, 041022, 041023	-2.7	(-5.0, -0.4)	0.0210
Phase III/ excl. failed	041021, 041023	-4.0	(-6.6, -1.3)	0.0037

A summary of the responders meta analyses is presented in Table 9.

Table 9

Table 4 Summary of PANSS (30%) responder meta-analyses. Intent-to-Treat population.

Data set	Definition	Comparison[1]	Odds ratio[2]		Difference[3]	
			OR (95% CI)	p-value	Diff % (95% CI)	NNT
All data	Pre-specified	Asenapine	1.9 (1.4, 2.6)	<0.001	9.8 (2.9, 16.8)	10.2
		Comparator	1.7 (1.2, 2.4)	0.002	8.3 (0.6, 16.0)	12.0
	Missing=failure	Asenapine	1.6 (1.2, 2.3)	0.003	7.1 (0.1, 14.1)	14.1
		Comparator	1.5 (1.1, 2.2)	0.019	5.8 (-2.0, 13.6)	17.3
Phase III data	Pre-specified	Asenapine	1.9 (1.3, 2.6)	<0.001	9.6 (2.1, 17.0)	10.5
		Comparator	1.7 (1.2, 2.5)	0.005	7.9 (-0.5, 16.4)	12.6
	Missing=failure	Asenapine	1.6 (1.1, 2.2)	0.011	6.5 (-1.0, 14.0)	15.4
		Comparator	1.5 (1.0, 2.2)	0.032	5.8 (-2.7, 14.2)	17.4

[1] Comparison versus placebo; comparator indicates the combined active comparators (risperidone, olanzapine and haloperidol)
[2] As based on a logistic regression analysis using protocol, treatment (pooled) center nested in protocol and baseline PANSS Total score severity as fixed factors.
[3] As based on binomial regression analysis to obtain multivariate-adjusted risk differences, using protocol, treatment pooled center nested in protocol and baseline PANSS Total score severity as fixed factors. The Number Needed to Treat (NNT) is the inverse of the estimated difference.

Considering the phase III data, positive treatment effect of asenapine versus placebo (OR=1.9, 95% CI 1.3 to 2.6; p<0.001) was observed, meaning that for every 10 patients treated with asenapine instead of placebo one additional responder would be observed.

The actual response rates (and their 95% CIs) for asenapine, active control and placebo are presented in Table 10.

Table 10

Table 2 PANSS (30%) responder rates and difference versus placebo. Asenapine short term schizophrenia studies – Intent-to-Treat population.

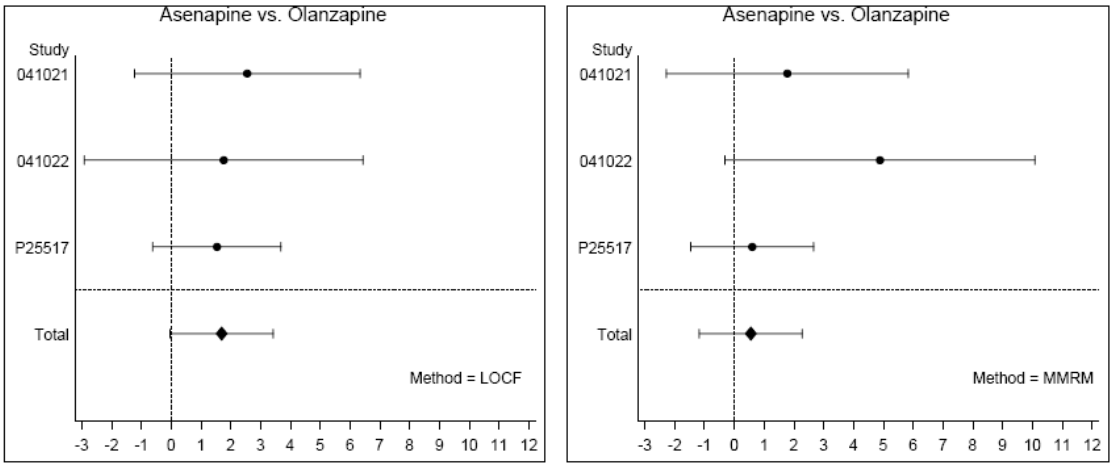
Study	Treatment	N	Responder rate (95% CI)			Difference vs. placebo			Odds ratio[4]	
			n	%	(95% CI)[1]	% (95% CI)[2]		p-val[3]	OR	(95% CI)
041004	Placebo	60	15	25.0	(14.7 - 37.9)					
	Asenapine 5 mg	58	22	37.9	(25.5 - 51.6)	12.9	(-3.9, 29.2)	0.13	2.0	(0.9, 4.7)
	Risperidone 3 mg	56	22	39.3	(26.5 - 53.2)	14.3	(-2.8, 30.8)	0.10	2.0	(0.8, 4.5)
041021	Placebo	93	22	23.7	(15.5 - 33.6)					
	Asenapine 5 mg	102	39	38.2	(28.8 - 48.4)	14.6	(1.5, 27.1)	0.029	2.2	(1.1, 4.4)
	Asenapine 10 mg	96	33	34.4	(25.0 - 44.8)	10.7	(-2.3, 23.4)	0.11	1.9	(0.9, 3.8)
	Asenapine	198	72	36.4	(29.7 - 43.5)	12.7	(1.2, 23.1)	0.031	2.0	(1.1, 3.8)
	Olanzapine 15 mg	95	39	41.1	(31.1 - 51.6)	17.4	(4.0, 30.2)	0.011	2.9	(1.4, 5.8)
041022	Placebo	89	35	39.3	(29.1 - 50.3)					
	Asenapine 5-10 mg	85	32	37.6	(27.4 - 48.8)	-1.7	(-16.0, 12.8)	0.82	1.1	(0.5, 2.1)
	Olanza. 10-20 mg	85	33	38.8	(28.4 - 50.0)	-0.5	(-14.9, 13.9)	0.95	1.2	(0.6, 2.3)
041023	Placebo	122	40	32.8	(24.6 - 41.9)					
	Asenapine 5 mg	109	60	55.0	(45.2 - 64.6)	22.3	(9.5, 34.4)	<0.01	3.0	(1.7, 5.5)
	Asenapine 10 mg	105	51	48.6	(38.7 - 58.5)	15.8	(3.0, 28.2)	0.016	2.2	(1.2, 4.0)
	Asenapine	214	111	51.9	(45.0 - 58.7)	19.1	(8.1, 29.4)	<0.01	2.6	(1.6, 4.4)
	Haloperidol 4 mg	112	48	42.9	(33.5 - 52.6)	10.1	(-2.4, 22.3)	0.11	1.6	(0.9, 3.0)

[1] Based on the method of Clopper-Pearson (1934).
[2] Based on the method of Miettinen and Nurminen (1985). Positive % indicates improvement versus placebo.
[3] It should be noted that in the trials statistical significance of responders rates was tested using the Cochran-Mantel-Haenszel method stratifying for pooled center which led to identical conclusions (041021 CTR Section 8.5.2.2; 041022 CTR Table 11.5.1.10.1; 041023 CTR Section 8.5.2.2). For study 041004, no inferential statistics were pre-specified (CTR Section 8.6.1.1).
[4] As based on a logistic regression analysis using treatment (pooled) center and baseline PANSS Total score severity as fixed factors.

In addition, the applicant presented a meta-analysis on the change from baseline in PANSS Total score of asenapine versus olanzapine, based on the available randomized trials 041022, 041023 and 25517. Results are summarised in Figure 3.

Figure 3

Figure 6 Meta-analysis of asenapine versus olanzapine PANSS Total score after six weeks. Based on trials 041022, 041023 and P25517. Intent-to-Treat population.

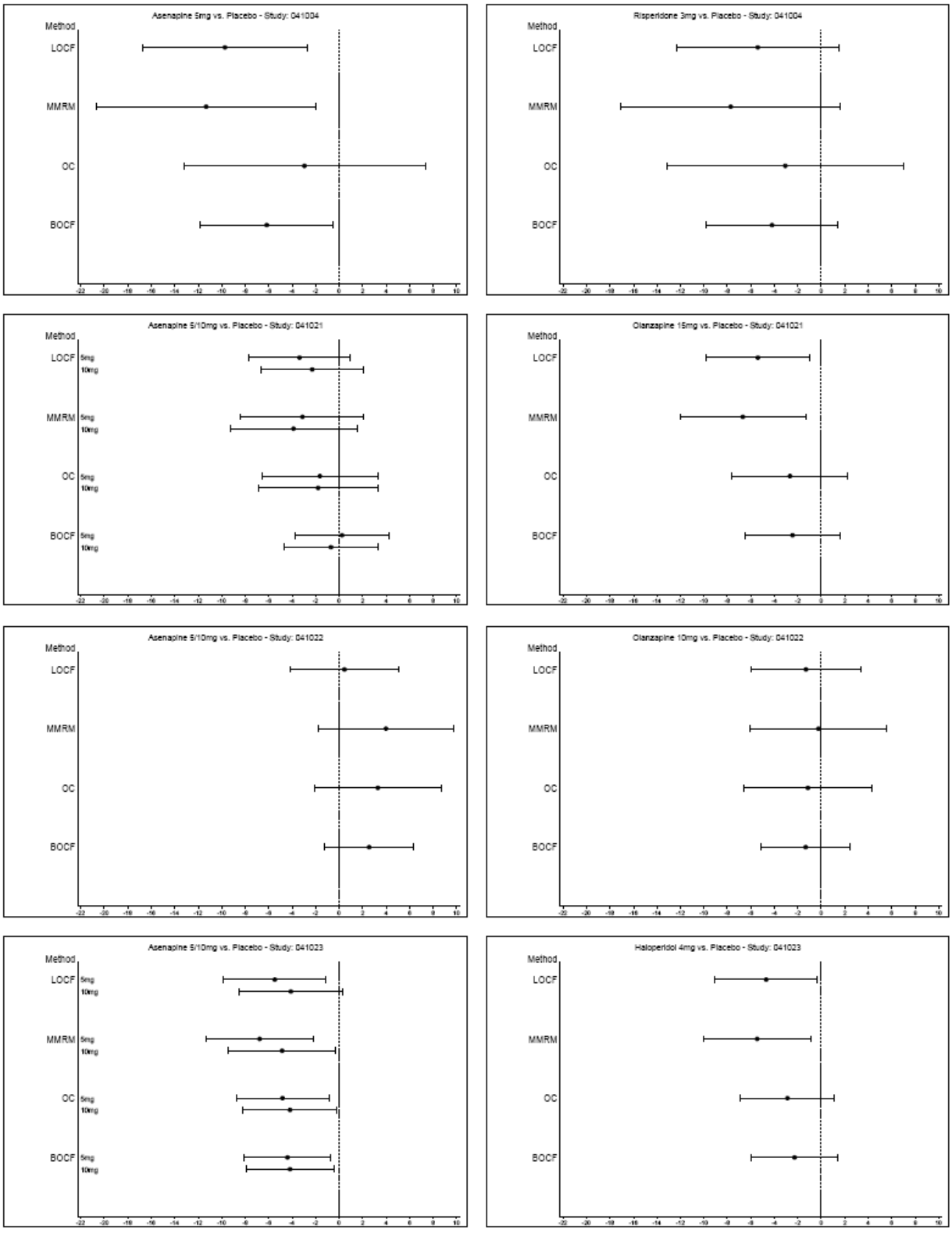


Based on the LOCF method, the difference was 1.7 points with a 95% confidence interval of -0.04 to 3.4 (p=0.055). Based on MMRM method, a treatment difference of 0.55 points is observed on the PANSS total scale with a 95% confidence interval of -1.17 to 2.28 (p=0.529).

2.4.5.2.4. Additional statistical analyses

Comparative statistical analyses on primary endpoints for studies 004, 021, 022 and 023 were performed using LOCF, MMRM, OC and BOCF analyses and are presented in Figure 4.

Figure 4 **Efficacy results (CFB PANSS Total score) comparing asenapine and active comparators to placebo by treatment arm. Short term efficacy trials in schizophrenia with asenapine 5 -10 mg BID.**
Intent-to-Treat population.



For each trial the efficacy results using different methods of handling missing data yielded similar results.

2.4.5.3. Long term studies

The main long-term studies were designed as follows:

- 25517: a 52-week, flexible-dose, randomised, double-blind, active-controlled (2 treatment groups: asenapine 5mg or 10 mg BID or olanzapine 10 mg to 20 mg QD, in 3:1 ratio) study in subjects with schizophrenia and schizoaffective disorder;
- A7501012: a 52 week, flexible-dose, randomised, placebo-controlled (2 treatment groups: asenapine 5mg or 10 mg BID or placebo in a 1:1 ratio) in subjects with schizophrenia. This trial had 3 phases (Periods 1,2 and 3)
- 22543: a 26 week, flexible-dose, randomised, double-blind, active controlled (2 treatment groups: asenapine 5mg-10 mg BID or olanzapine 10-20mg QD in 1:1 ratio) study in subjects with schizophrenia associated with predominant and persistent negative symptoms;

Study A7501012 was conducted in Latvia and outside EU (Croatia, India, Ukraine, US).Studies 25517 and 25543 were conducted in the EU and Australia. Study 25543 was also conducted in Russia and South Africa.

Patients who completed study 22517 were eligible to enter an extension study 25520 primarily aimed to provide additional long term safety data (see 3.4.6 Clinical Safety).

Patients who completed study 25543 were eligible to enter 6 month 26 weeks extension study 25544.

2.4.5.3.1. Study A25517

2.4.5.3.1.1. Methods

Study participants

Main inclusion criteria

Male or female (females had to be non-lactating and non-pregnant, or not of childbearing potential) of at least 18 years of age and a current DSM-IV-TR−defined diagnosis according to the diagnostic criteria for schizophrenia or schizoaffective disorder. Subjects were to have a PANSS score of at least 60 at screening and baseline; a score of ≥ 4 on two or more of the 5 items of the positive subscale of the PANSS at screening and baseline; a CGI-S score ≥ 4 ("moderately ill") at baseline; responded positively to an antipsychotic medication other than clozapine, if they had received neuroleptic medications previously; discontinued the use of all psychotropic medication 3 days prior to baseline except for antipsychotics (which had to be discontinued at least 12 hours prior to the first intake of trial medication), depot neuroleptics of which the next scheduled dosing cycle must be due on or prior to baseline, and zolpidem, zaleplon, zopiclone, chloral hydrate, or benzodiazepines; subjects discontinued anticholinergic agents 12 hours prior to the baseline assessments.

Main exclusion criteria

Potential participants were to be excluded from further consideration if they responded well to current antipsychotic treatment and there was no clinical need to stop this treatment; had taken an investigational drug within 30 days prior to baseline; had an uncontrolled, unstable clinically significant renal, endocrine, hepatic, respiratory, cardiovascular, hematological, immunologic, or cerebrovascular disorder, or malignancy; had a seizure disorder beyond childhood or were taking anticonvulsants to prevent seizures; had any clinically significant abnormal laboratory, vital sign, physical examination, or ECG findings prior to randomization that precluded trial participation; showed a positive result for hepatitis; had a diagnosis of schizophrenia of the residual type (DSM-IV, 295.60) required concomitant treatment at baseline with psychotropic drugs other than zolpidem, zaleplon, zopiclone, chloral hydrate, or benzodiazepines; had a score greater than "mild" (i.e. Score > 2) on any item of the Abnormal Involuntary Movement Scale (AIMS) at baseline; showed continued use of illicit drugs and/or alcohol within 30 days before the screening visit or showed positive findings in the alcohol/drug screen, unless the investigator felt that the subject would be compliant with the study medication and would be a suitable candidate for the study; had a concurrent psychiatric disorder other than schizophrenia or schizoaffective disorder coded on Axis I DSM-IV; were a risk of self-harm or harm to others at screening, during the run-in period, or baseline; were previously exposed to asenapine; or did not tolerate, or did not respond well to previous treatment with olanzapine at 'adequate' dosage (≥20 mg/day, ≥ 6 consecutive weeks).

Treatments

Prior active treatment period (52 weeks), there were a screening and a 3 to 9 days run-in period. The active treatment period was initiated on Day 1 following randomization of subjects to either asenapine 5 or 10 mg BID or olanzapine 10 to 20 mg QD in a 3:1 ratio.

Outcomes/endpoints

The primary efficacy measure was the mean change from baseline to Week 52 on the total Positive and Negative Syndrome Scale (PANSS).

Main secondary efficacy measures were mean change from baseline to Week 52 on the three PANSS subscales (Positive, Negative, General Psychopathology) and on the five PANSS Marder factors (Positive symptom, Negative symptom, Disorganized thought symptom, Hostility/Excitement symptom and Anxiety/Depression symptom), on Clinical Global Impressions of Severity of Illness (CGI-S) and Improvement (CGI-I) scales.

Health outcomes measures included Quality of life using the Subjective Well-being under Neuroleptics (SWN) short form, the norm-based Physical Component Scale (PCS) and the Mental Component Scale (MCS) of the Short Form health survey (SF-12). Satisfaction with treatment was measured through patient's and investigator's opinions, and depression with the Calgary Depression Scale for Schizophrenia (CDSS).

Statistical Methods

All hypothesis testing was conducted using two-sided tests with alpha = 0.05 level of significance. The primary efficacy analysis was defined as a comparison of the change from baseline in the total PANSS score at Endpoint in the asenapine and olanzapine treatment groups using an analysis of covariance (ANCOVA) with treatment as fixed effect, center as random effect and baseline as covariate included in the model.

ANCOVA was also used to compare between treatments the changes from baseline in the total PANSS score over time (repeated measures model), the PANSS subscales and the PANSS Marder factors.

2.4.5.3.1.2. Results

Participant flow

A total of 1225 subjects were randomized in the trial: asenapine 5-10 mg BID, 913 subjects; olanzapine 10-20 mg QD, 312 subjects. Of these subjects, 1219 subjects received treatment: asenapine 5-10 mg BID, 908 subjects; olanzapine 10-20mg QD, 311 subjects.

Baseline data

The majority of subjects (77.8%) suffered from schizophrenia of the paranoid type, while 13.1% of the subjects were diagnosed with schizoaffective disorder. For almost half of the subjects (43.9%), the duration of the present episode was 1 to 6 months. Most of the subjects (93.2%) had experienced one or more earlier episodes of schizophrenia or schizo-affective disorder. The longitudinal course was classified as 'Episodic with interepisodic residual symptoms' for 49.7% of the subjects. A total of 691 treated subjects (56.7%) discontinued the trial prematurely. The proportion of discontinued subjects was higher in the asenapine group (61.5%) compared to the olanzapine group (42.8%). Subjects in the asenapine group were more likely to withdraw due to adverse events related to worsening of the disease, lack of efficacy and withdrawal of consent. The discontinuation rate caused by adverse events not related to worsening of the disease was similar in both treatment groups (6.3% for the asenapine group versus 6.8% for the olanzapine group). The total number of subjects who dropped out due to insufficient therapeutic effect (i.e. the combination of the subjects discontinued due to lack of efficacy and the subjects discontinued due to AEs related to worsening of the disease) was 25.1% and 14.5% for the asenapine group and olanzapine group, respectively. In the asenapine group, 59.5% of the subjects had their dose increased to the high dose at some point in time during their treatment. In the olanzapine group, 54.3% of the subjects had their dose increased to the high dose.

Outcomes

Statistically significant difference ($p<0.001$) in the mean change from baseline to endpoint in the PANSS total score was observed in favour of olanzapine. At baseline, the PANSS total scores were 92.1 for both asenapine and olanzapine groups. At week 52, the PANSS total scores were 71.0 and 64.6 for asenapine and olanzapine groups, respectively (difference: 6.54, 95% CI: 3,87-9,21). Results of main secondary efficacy measures were consistent with those of the total PANSS score.

2.4.5.3.2. Study A7501012

2.4.5.3.2.1. Methods

Study participants

Main inclusion criteria

Male or female of at least 18 years of age and a primary diagnosis of schizophrenia (DSM-IV-295) with documented history of at least one prior episode of acute schizophrenia in the three years preceding the screening assessment and requiring continuous antipsychotic treatment for at least one year preceding screening. Subjects were clinically stable at the time of being recruited into the trial defined by at least a 4-week period of stable symptoms (Period 1) Subjects were eligible for the double-blind

treatment phase (Period 3) if they had continued stable presentation of symptoms during the open-label phase (Periods 1 and 2). Loss of stability was defined as an increase from open-label baseline in PANSS of 20% or 12 points (whichever was higher) a PANSS total score >75or if any of the other PANSS/ISST screening thresholds were failed.

Main exclusion criteria
Subjects were excluded if PANSS was > 80 at screening, CGI-S was >4 at screening or if any of PANSS "unusual thought content", "conceptual disorganisation", "hallucinatory behaviour", "hostility" or "uncooperativeness" were ≥4 at screening and InterSePT Scale for Suicidal Thinking-Modified (ISST-Modified) item score of 2 on item #7 "control over suicidal action," #10 "method: specificity/planning," or #11 "expectancy/ anticipation."

Treatments

Period 1: up to 4 weeks of open-label cross-titration from prior medication to sublingually administered asenapine 5 or 10 mg BID

Period 2: at least 22 weeks of open label monotherapy treatment during which subjects were maintained on sublingually administered asenapine 5 or 10 mg BID.

Period 3: A randomised double-blind of treatment of up to 26 weeks , during which subjects stabilised on asenapine were randomised in a 1:1 ratio to received asenapine 5 or 10 mg BID or placebo sublingually administered.

The starting dose of asenapine was 5 mg BID; after the first week of treatment, all subjects were titrated up to a dose of 10 mg BID. The dose could be reduced to 5 mg BID for individual subjects if undesirable effects occurred at the 10 mg BID dose; after the effects subsided the dose of asenapine could be increased back to 10 mg. Subjects who could not tolerate the 10 mg BID dose after rechallenge were allowed to continue at a 5 mg BID dose.

Outcomes/endpoints
The primary endpoint was defined as time to relapse or an impending relapse. A relapse or impending relapse was declared if any of the criteria 1, 2, 3 and 4 (1-3 are referred to as "symptomatic relapse criteria" were met:

Criteria 1: a) PANSS total score increase of ≥20% from baseline of the double-blind treatment phase and b) Clinical Global Impression (Severity of Illness) (CGI-S) ≥4 (moderately ill), on at least 2 days within a 1 week period (Subjects with a PANSS total score <50 at baseline must have had an increase from baseline of at least 10 points on the PANSS total score).

OR

Criteria 2: a) PANSS score of ≥5 (moderately severe) on items of "hostility" (Item 7), or "uncooperativeness" (Item 22) and b) CGI-S ≥4 (moderately ill), on at least 2 days within a 1-week period.

OR

Criteria 3 a) PANSS score of ≥5 (moderately severe) on 2 items of "unusual thought content" (Item 23), "conceptual disorganization" (Item 2), or "hallucinatory behavior" (Item 3) and b) CGI-S ≥4 (moderately ill), on at least 2 days within a 1-week period

OR

Criteria 4: 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 (eg, supervised living, day hospital care);
- Hospitalization or increase in the level of hospitalization;
- An arrest or imprisonment for objectionable behavior;
- Electroconvulsive therapy;
- Other.

Secondary endpoint was defined as time to early discontinuation for any reason. Main secondary efficacy measures included:proportion of subjects in each treatment arm having experienced a relapse or impending relapse; having discontinued the study prematurely; change from baseline to the double-blind treatment phase (Period 3) on the PANSS total score, the PANSS Marder factor scores (positive, negative, disorganized thought, hostility/excitement, anxiety/depression), CGI-S, Clinical Global Impression of Improvement (CGI-I), the Calgary Depression Scale in Schizophrenia (CDS), the modified InterSePT Scale for Suicidal Thinking (ISST Modified), the Global Cognitive Function Scale (CogFu), and cognitive function as assessed with a computerized cognitive battery (CNS Vital Signs), change during open-label treatment (Periods 1 and 2) in Personal Evaluation of Transitions in Treatment (PETiT) total and subscale scores was evaluated.

Statistical Methods

Descriptive statistics using Kaplan-Meier survival curves were performed to estimate the probability of remaining free of relapse or impending relapse on asenapine compared with placebo. The log-rank test was used to test the hypothesis that there was no difference in relapse rates between asenapine and placebo. The same methods, Kaplan-Meier estimation and log-rank testing, were used to assess time to early discontinuation for any reason.

The Type I error was controlled at 0.05 for the study.

2.4.5.3.2.2. Results

Participant flow

A total of 700 subjects received at least one dose of trial medication in the open-label phase of the trial. Of these, 386 subjects were randomized into the double-blind phase of the trial, 194 to asenapine and 192 to placebo, and 314 were not randomized and did not participate in the double-blind phase of the trial.

Baseline data

A total of 207 subjects completed the double-blind phase of the trial. The percentage of subjects completing the double-blind phase was 69.6% in the asenapine group (69.6%) compared with the placebo group (37.5%). A total of 114 subjects relapsed with a lower percentage of subjects relapsing

in the asenapine group (12.4%) compared with the placebo group (46.9%). Most of the relapsed subjects in both groups (21/24 relapsed asenapine subjects and 64/90 relapsed placebo subjects) were considered relapsed because their symptoms deteriorated and/or intervention was necessary.

Overall, within the all-subjects-Treated group, most subjects were Caucasian (67.3%). Subjects ranged in age from 18 to 78 years with an overall mean (SD) age of 39.4 (12.07) years. A majority (59.4%) of subjects were male. Subjects' BMI ranged from 17 to 65 kg/m2, with a mean (SD) BMI of 27.0 (6.38) kg/m2. The percentage of Caucasian subjects was higher among randomized subjects (72.8%) compared with non-randomized subjects (60.5%) and the percentage of Black subjects was lower among randomized subjects (10.4%) compared with non-randomized subjects (19.1%).

Additionally, within the group of subjects who were randomized to double-blind treatment, with the exception of gender, there were no notable differences between the asenapine and placebo groups with respect to demographic characteristics. The percentage of female subjects was higher in the asenapine group (45.9%) than in the placebo group (39.6%).

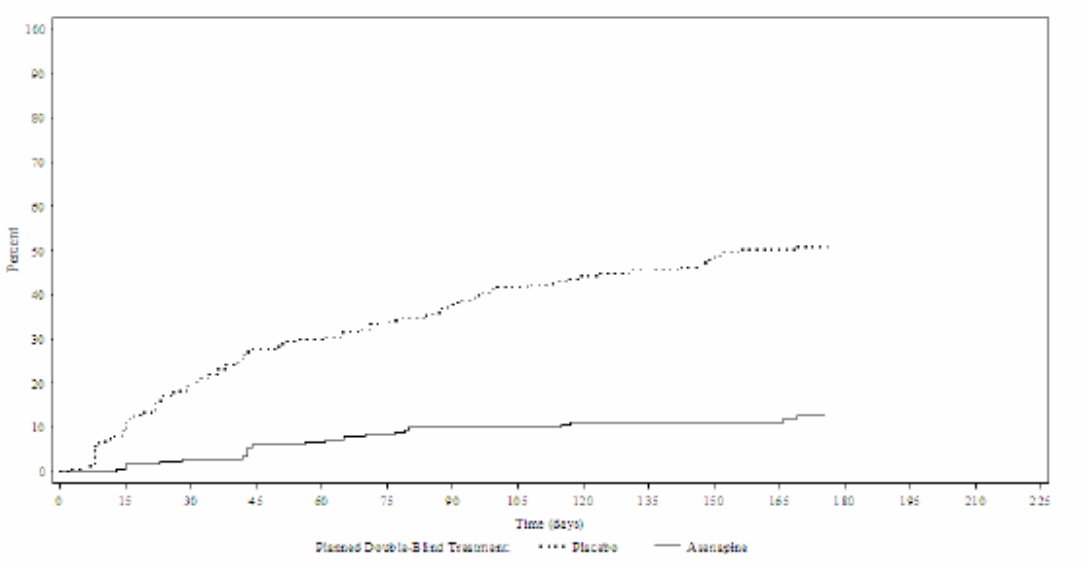
The mean daily dose of asenapine was 16.7 mg during the open-label period and 17.6 mg during the double-blind period. The daily modal dose of asenapine during both the open-label period and the double-blind period was 20 mg.

Outcomes

Based on a log-rank test, there was a statistically significant difference in favor of asenapine between the treatment groups with respect to the time to relapse or impending relapse ($p<0.0001$). The time to relapse was longer in the asenapine group compared with the placebo group (see figure 5).

Figure 5

Figure 2 Kaplan-Meier estimation of percent relapse/impending relapse as determined by the investigator (Intent-to-treat)



Asenapine was also shown to be more effective than placebo in prolonging the time to early termination for any reason and the time to relapse or impending relapse.

2.4.5.3.3. Studies 25543 and 25544

2.4.5.3.3.1. Methods

Study participants

Main inclusion criteria

In study 25543, male or female (females had to be non-lactating and non-pregnant, or not of childbearing potential) of at least 18 years of age and a current diagnosis of schizophrenia of paranoid (295.30), disorganized (295.10), catatonic (295.20), residual (295.60), or undifferentiated (295.90) subtype (the MINI International Neuropsychiatric Interview [MINI] will be used). Subjects were to have a minimum PANSS negative subscale score of 20 at screening and baseline, with a minimum score of 4 (moderate) on at least 3 of the Marder factors for negative symptoms (blunted affect [N1], emotional withdrawal [N2], poor rapport [N3], passive social withdrawal [N4], lack of spontaneity [N6], motor retardation [G7], active social avoidance [G16]), a PANSS positive subscale (Marder factor) score <the PANSS negative subscale (Marder factor) score at screening and baseline; and demonstrated clinical stability for the past 5 months at time of screening (defined as: no significant changes in schizophrenia symptomatology, no hospitalizations/ increase level of care/jailing or imprisonment due to worsening of the symptoms of schizophrenia during the past 5 months).

In study 25544, subjects who completed study 25543 and received double-blind therapy.

Treatments

In study 25543, subjects received the initial dose of either 5 mg BID asenapine or 10 mg once daily (QD) olanzapine as the active dose matched with the comparator placebo for 1 week. After 1 week, doses could be increased, decreased, or held constant at the discretion of the investigator only.

Decisions to change the dose were to be made at the subject's visit, and based on the subject's symptomotology and tolerability. Dose changes could only be made between visits if intolerable adverse events (AEs) prohibit a delay.

In study 25544, subjects continued in their original treatment group—asenapine (5- 10 mg BID) or olanzapine (5-20 mg QD)—at the dose received at the end of the treatment visit in study 25543 for the first week. After the first week, decisions to change doses were made at subject visits based on symptomatology and tolerability. (If intolerable adverse events prohibited a delay, dose changes could be made between visits.) The 26-week extension trial continued until all subjects completed treatment or discontinued early.

Outcomes/endpoints

The primary efficacy measures were the mean changes from baseline to day 182 (study 25543) and day 365 (study 25544) on Negative Symptoms Assessment (NSA) score, a 16 item clinician rating scale on negative symptomatology of schizophrenia.

The key secondary endpoints were the mean changes from baseline to day 182 (study 25543) and day 365 (study 25544) on QLS total score, a 21-item, clinician rating scale on psychosocial functioning. Other secondary efficacy measures were : PANSS, CDSS, CNS vital signs, PETiT, LOF, and Q-LES-Q as well as CGI-S, CGI-I, CGI-I responders (defined as "very much improved" and "much improved") and time to first CGI-I response.

Statistical Methods

Primary and key secondary endpoints were analysed using MMRM method. All statistical tests were two-sided with a = 0.05 significance level.

Additionally, two separate sensitivity analyses were performed using analysis of covariance (ANCOVA) on the changes from baseline in NSA total score, in QLS score at each visit with baseline NSA total score, QLS score and duration of predominant, persistent negative symptoms as covariates. In the first analysis, the missing data were imputed by LOCF method. In the second analysis, only the OC method was used.

The differences between asenapine with olanzapine on PANSS, CDSS, and CGI-S were analyzed using a MMRM analysis, and were further examined with LOCF and OC approaches. The other secondary endpoints, CNS vital signs, PETiT, LOF, and Q-LES-Q, were analyzed using LOCF and OC. Descriptive statistics were produced for CGI. The treatment groups were compared with respect to CGI responder rates using Cochran Mantel-Haentzel test. Both treatment groups were compared with respect to time to first CGI response using Kaplan-Meier product limit method and the Cox's proportional hazard model. Analyses were stratified by duration of persistent negative symptoms (2 year duration strata).

2.4.5.3.3.2. Results

Participant flow

In study 25543, a total of 481 subjects were randomly assigned to treatment (241 subjects were assigned to asenapine and 240 subjects were assigned to olanzapine) and received at least 1 dose of double-blind trial medication. A total of 433 subjects (90.0% of those randomly assigned to treatment) received at least 1 dose of double-blind trial medication and had a least 1 post-baseline NSA evaluation (216 and 217 subjects in the asenapine and olanzapine groups, respectively).

In study 25544, a total of 306 subjects received at least 1 dose of double-blind trial medication in 25544, including 134 subjects in the asenapine group and 172 subjects in the olanzapine group. A total of 279 subjects received at least 1 dose of double-blind trial medication and had a least 1 post-baseline NSA evaluation in 25544, including 122 and 157 subjects in the asenapine and olanzapine groups, respectively. A total of 266 (86.9%) subjects completed the trial (113 asenapine [84.3%]; 153 olanzapine [89.0%]).

Baseline data

In study 25543, the most common reason for withdrawal was due to adverse events/SAEs in the asenapine treatment group (36 asenapine [14.9%] subjects versus 18 olanzapine [7.5%] subjects). The 481 subjects participating in the trial had a mean age of 40.5 years (range 18 to 73 years). Most subjects in both treatment groups were in the 18-64 years age category; there were 10 (4.1%) subjects in the asenapine group and 5 (2.1%) subject in the olanzapine group who were ≥65 years old. Overall, there were 153 (31.8%) females and 328 (68.2%) males. Mean weight was 79.8 kg (range 43 to 140 kg) and mean BMI was 26.7 kg/m2 (range 16 to 44 kg/m2). Over the course of the entire trial, the median total daily asenapine dose was 15 mg, and the modal total daily asenapine dose was 20mg. The median total daily olanzapine dose was 11 mg, and the modal total daily olanzapine dose was 10 mg.

In study 25544, the asenapine treatment group, the most common reason for discontinuation was due to adverse events in the asenapine treatment group (10 asenapine [7.5%] subjects versus 7 olanzapine [4.1%] subjects).The 306 subjects participating in the extension trial 25544 had a mean age of 40.4 years (range 18 to 71 years). Most subjects in both treatment groups were in the 18- 64 years age category; there were 3 (2.2%) subjects in the asenapine group and 4 (2.3%) subjects in the olanzapine group who were ≥65 years old. Overall, there were 96 (31.4%) females and 210 (68.6%) males. Mean weight was 81.0 kg (range 45.4 to 137.5 kg) and mean BMI was 27.2 kg/m2 (range 16.5 to 44.6 kg/m2). Over the course of the entire trial, the median total daily asenapine dose was 20 mg, and the modal total daily asenapine dose was 20 mg. The median total daily olanzapine dose was 10 mg, and the modal total daily olanzapine dose was 10 mg.

Outcome

In study 25543, asenapine (5 mg-10 mg BID) was not significantly different from olanzapine (5mg-20mg QD) on the primary efficacy and key secondary endpoints, changes from baseline to Day 182 in NSA total score ($p = 0.7869$) and in QLS total score ($p = 0.9298$).

In study 25544, asenapine (5 mg-10 mg BID) was not significantly different from olanzapine (5mg-20mg QD) on the primary efficacy and key secondary endpoints, changes from baseline to Day 365 in NSA total score ($p = 0.2344$) and in QLS total score ($p=0.2838$).

In both studies, mean change from baseline over time on the NSA total score was comparable between the two groups. The results of the primary analysis, using MMRM, were corroborated by the LOCF and OC analyses. Secondary analyses, such as the NSA global scores, QLS total score, PANSS total score, CGI-S scores and CGI-I response rates showed no differences between asenapine and olanzapine.

2.4.5.4. Discussion on clinical efficacy

2.4.5.4.1. Short term studies

With respect to phase II short-term trials (041002, 041013 and 041004), no dose response could be established. Six doses were tested across the three trials. In trials 041002 and 041013, the trend favoured 0.4mg over 0.8mg, and 1.6mg over 2.4mg, respectively. Only 1 out of 6 comparisons achieved statistical significance (asenapine 5 mg BID in trial 041004) but no other doses were tested in this trial to allow the dose response to be assessed.

The concern over dose response extended into phase III as trials (041023 and 041021) did not provide any evidence that the 10mg dose provided additional benefit compared to 5mg, with the trend in both studies favouring 5mg, and the 10mg dose never achieving statistically significant superiority over placebo. A major concern over the proposed posology (using 10 mg dose in addition to 5mg) and lack of evidence of efficacy of asenapine 10 mg BID was raised by the CHMP.

After the positive finding for the 5mg dose in study 041004, three confirmatory phase III short-term trials (041021, 041022 and 041023) were conducted. The CHMP considered that there was insufficient evidence of efficacy as only 1 out of 5 comparisons to placebo achieved statistical significance (the 5 mg arm in study 041023) and the size of the effect of the estimated benefit was considered not to be of clinical significance . The CHMP was also concerned whether the analysis was robust to the method used to impute missing data (LOCF and MMRM), in view of the high proportion of withdrawal before week 6.

To address the major concern over insufficient evidence of efficacy, the applicant claimed that study 041004 also provided primary data in support of the efficacy of asenapine in the acute treatment of schizophrenia on the basis of the following reasons:

- This study met the criteria for quality of design and conduct of a well-designed proof of efficacy study as per EMA guidance[1], and as such provided robust evidence of the efficacy of asenapine in the treatment of schizophrenia, in the effective dose range of 5-10 mg BID.
- The strength of the positive primary endpoint analysis results for the 041004 and 041023 trials is supported by tests of robustness for the primary analysis.
- The efficacy of asenapine in the treatment of schizophrenia is also supported by numerous results of the short term trials, when analyzing secondary efficacy endpoints, as specified in the respective study protocols.
- A meta-analysis of the short-term trials (041004,041021,041022 and 041023) clearly showed that asenapine was superior to placebo and had a comparable effect size to the active controls in the studies.
- The overall success rate of the program with respect to the number of positive trials versus negative/failed trials is consistent with the results of the initial development program of some of the more recently approved antipsychotics.
- The phase III relapse prevention trial A7501012 provided robust evidence of the efficacy of asenapine 5-10 mg BID in the long term treatment of schizophrenia.
- An additional analysis using baseline observation carried forward (BOCF) provided generally similar results to those seen before and provided reassurance that the study conclusions were robust to the method used for handling missing data.

[1] Note for Guidance on General Considerations for Clinical Trials (CPMP/ICH/291/95, 1998).

In the CHMP view, the above claims were not addressing the major concern over the insufficient evidence of efficacy observed in the phase III studies (041021,041022 and 041023) in the acute treatment of schizophrenia. Particularly, the CHMP was of the opinion that:

- Study 041004 could not be regarded as pivotal study, although it was supportive of the efficacy of asenapine. This study generated the hypothesis that the 5mg dose was efficacious, and the phase III studies alone needed to be convincing in confirming that hypothesis. Furthermore, the sample size of this study was modest (n=58 for asenapine) and there were considerable drop outs (n= 32 for asenapine). A new meta analysis (excluding study 041004) should therefore be provided to further substantiate the short term efficacy of asenapine.
- In the absence of a demonstration of a benefit of short-term treatment, the long-term randomised withdrawal trial cannot be considered to provide evidence of efficacy.
- The clinical significance of difference from placebo in mean total PANSS score and of the difference from placebo in the response rates should be further substantiated.

As requested by the CHMP, the applicant performed a new meta-analysis (excluding study 041004). Also at the CHMP request, the responder analysis was conducted using missing= failure. Results from this retrospective meta-analysis was suggestive of efficacy (for PANSS total score: 2.7 points greater for asenapine versus placebo (p=0.021; 95% CI -5.0 to -0.4); for responder rates (missing=failure): OR=1.6, 95% CI 1.1 to 2.1; p=0.011). However, the pooled 95% CI was very close to zero and this finding raised some concern over the level of evidence from this meta-analysis, taking into account the CPMP point to consider on application with 1. Meta analyses 2. One pivotal study (CPMP/EWP/2330/99).

To support the significance of difference from placebo in mean total PANSS score, the applicant claimed the following:

- treatment effect as measured by the primary efficacy endpoint in the asenapine clinical program was very similar for asenapine compared with the pooled data for the active controls used i.e risperidone, olanzapine and haloperidol used at approved dosages (comparators: -4.1 PANSS Total score points on the primary endpoint; 95% CI -6.5 to -1.7; p=0.0010; asenapine: -3.7 points 95% CI -5.9 to -1.5, p=0.0011).
- a literature review (Leucht et al., 2009[1]) on 53 randomised clinical trials (a total 117 relevant treatment arms and 14,861 patients) showed that the effect of asenapine is comparable to that of the broad class of second generation antipsychotics.
- Results from responder analysis (clinically relevant response as defined as 30% reduction of the individual baseline PANSS total score) are supportive of the observed point estimate of PANSS Total Score change from baseline in the pooled phase III studies

The CHMP noted the comparative data presented by the applicant to support the clinical relevance of the efficacy results for asenapine. Based on the available published data on aripiprazole and paliperidone, the CHMP noted that difference from placebo could range from 7 to 19 points on the PANSS score. These results appeared substantially greater than the treatment effect observed with asenapine, further questioning the magnitude of the effect observed for asenapine and its clinical relevance. In conclusion, mean treatment difference from placebo of 2.7 (or 3.7 points if the phase 2 study 004 is included) from a baseline score of about 90 appeared to be very modest and its clinical significance is still questioned by the CHMP.

[1] Leucht et al, 2009. A Meta-Analysis of Head-to-Head Comparisons of Second-Generation Antipsychotics in the Treatment of Schizophrenia. Am. J. Psychiatry 166(2),152-163.

2.4.5.4.2. Long term studies

In study A7501012 , which used a randomised responder design, there was a statistically significant difference in favor of asenapine between the treatment groups with respect to the time to relapse or impending relapse ($p<0.0001$). The time to relapse was longer in the asenapine group compared with the placebo group. Asenapine was also shown to be more effective than placebo in prolonging the time to early termination for any reason and the time to relapse or impending relapse. However in the absence of adequate evidence of efficacy from short-term trials, a randomised-responder relapse prevention trial cannot provide meaningful evidence of efficacy.

In study 25517, statistically significant difference (6.5 points, 95% CI 3.9, 9.2, $p<0.0001$) in the mean change from baseline to endpoint (LOCF) in the PANSS total score was observed in favour of olanzapine. The CHMP raised a major concern in this regard. The applicant argued that the difference across groups was driven primarily by a difference in rates of discontinuation, similarly to what has been observed in the CATIE trial[1]. Overall, the CHMP was not reassured. In fact the differences in the withdrawal rate presented a concern (as the withdrawals were mainly due to lack of efficacy). As this study showed inferiority to olanzapine, and did not contain any other comparison to provide positive evidence, it was concluded that this study did not provide evidence of efficacy for asenapine.

2.4.5.5. Conclusions on the clinical efficacy

The CHMP concluded the following:
- There is insufficient evidence of efficacy from short term trials.
- The magnitude of the claimed efficacy is of doubtful clinical significance.
- In the absence of adequate evidence of efficacy from short term trials, the randomised responder relapse prevention trial cannot provide meaningful evidence of efficacy.
- The long term comparison to olanzapine did not provide evidence of efficacy.

[1] Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK (2005) Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N. Engl. J. Med. 353(12):1209-1223.

BIPOLAR I DISORDER

The clinical development program comprised a total of 6 trials, as summarised in Table 11.

Table 11

Table 1 Overview of Clinical Trials in Bipolar Disorder

Trial & Design	Trial Dates	Treatments [a]	Dosing Regimen	Number of Subjects Evaluable for Efficacy [b]		
				placebo	asenapine	olanzapine
Efficacy trials						
A7501004 [1] DB, PC, AC 21-day treatment	30 Nov 2004 – 29 April 2006 (last Day 30 follow up)	asenapine olanzapine placebo	10 mg SL BID on Day 1, then 5-10 mg SL BID Days 2-21 15 mg PO QD on Day 1, then 5-20 mg PO QD Days 2-21 SL BID, PO QD	94	183	203
A7501005 [2] DB, PC, AC 21-day treatment	14 Dec 2004 – 28 April 2006 (last Day 30 follow up)	asenapine olanzapine placebo	10 mg SL BID on Day 1, then 5-10 mg SL BID Days 2-21 15 mg PO QD on Day 1, then 5-20 mg PO QD Days 2-21 SL BID, PO QD	103	189	188
A7501006 [3] [c] DB, AC 63-day treatment	07 Jan 2005 – 28 June 2006	asenapine [d] asenapine olanzapine	10 mg SL BID on Day 1, then 5-10 mg SL BID Days 2-63 5-10 mg SL BID 5-20 mg PO QD	--	173	221
A7501008 [4] DB, PC 84-day treatment	30 May 2005 - 28 Feb. 2007	asenapine placebo	5-10 mg SL BID on Day 1, then 5-10 mg SL BID Days 2-84 [e] SL BID	166	158	--
Safety continuation trials						
A7501007 [5] DB, AC 40-week treatment A7501006 continuation	13 July 2005 - 05 April 2007	asenapine olanzapine	5-10 mg SL BID 5-20 mg PO QD	--	79	107
A7501009 [6] DB, PC 40-week treatment A7501008 continuation	June 2005 - November 2007	asenapine placebo	5 mg SL BID on Day 1, then 5-10 mg SL BID Days 2-84 [e] SL BID	36	41	--

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

[b] For protocols A7501004, A7501005, A7501007, A7501008 and A7501009, represents the intent-to-treat group (ITT, full analysis set), defined as all randomized subjects who took at least one dose of double-blind trial medication and had at least one post-baseline Young-Mania Rating Scale (Y-MRS)assessment.

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

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

[e] In protocols A7501008 and A7501009 asenapine was studied in comparison to placebo in subjects who had not completely responded to continuing treatment of lithium or valproic acid (valproate)

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

2.4.5.6. Dose response studies

No studies were conducted.

2.4.5.7. Short term studies

2.4.5.7.1. Methods

Study design

The two main phase III short-term studies were designed as follows:

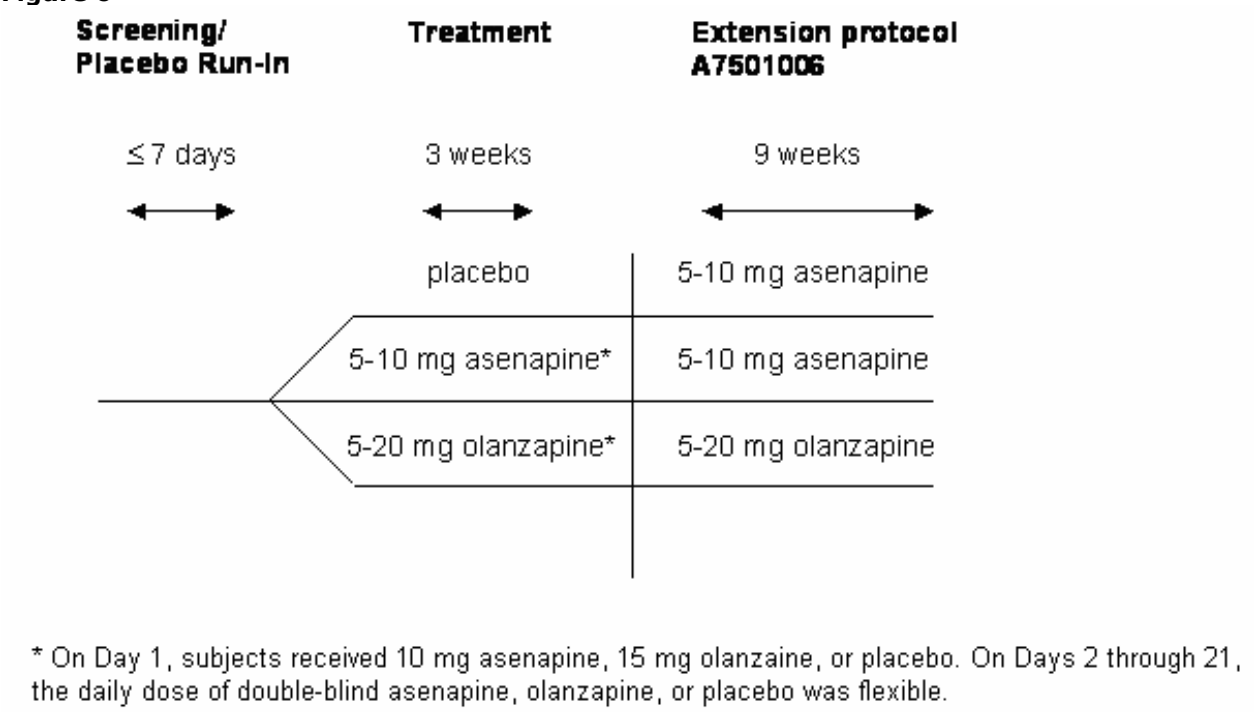
- A7501004 and A7501005: 3-week randomised, double blind placebo–controlled and active – controlled (3 treatment groups: asenapine 5-10mg BID, olanzapine 5-20 mg QD, or placebo in 2:2:1 ratio) studies in subjects with manic or mixed episodes associated with bipolar I disorder;

These studies were conducted in Bulgaria and Romania and outside EU (US, India, Asia, Russia, Ukraine and Turkey).

Patients who completed studies A7501004 and A7501005 were eligible to enter 9 week extension study A7501006 (see 3.4.9.3. Long term studies).

The design of these studies and their extension study A7501006 is presented in Figure 6.

Figure 6



* On Day 1, subjects received 10 mg asenapine, 15 mg olanzaine, or placebo. On Days 2 through 21, the daily dose of double-blind asenapine, olanzapine, or placebo was flexible.

Study participants

Main inclusion criteria

Subjects had a primary diagnosis of bipolar I disorder, current episode manic (DSM-IV 296.4x) or mixed (DSM-IV 296.6x). Subjects were men or women of at least 18 years of age with documented history of at least one previous moderate-to-severe mood episode with or without psychotic features (manic or mixed). Subjects were to have a Young-Mania Rating Scale (Y-MRS) score ≥20 at screening

and at baseline, and have a current manic or mixed bipolar I episode that must have begun no more than 3 months prior to the screening visit.

Main exclusion criteria

Main exclusion criteria included the presence of an uncontrolled, unstable clinically significant medical condition that in the opinion of the investigator could interfere with the interpretation of safety and efficacy evaluations; a seizure disorder beyond childhood or the use of anticonvulsants to prevent seizures; any clinically significant abnormal laboratory, vital sign, physical examination, or ECG findings at screening that precluded trial participation; subjects unable to reduce his/her daily benzodiazepine intake to a maximum of 4 mg per day of lorazepam (or the equivalent dose of another short-acting benzodiazepine); subjects having 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; a history of substance abuse or dependence (excluding nicotine) according to DSM-IV criteria within 6 months before screening; subjects having narrow angle glaucoma; subjects having seizure disorder or taking anticonvulsivants; a history of rapid cycling. Subjects previously treated in an asenapine trial, taking clozapine within the last 12 weeks and subjects at imminent risk of self-harm or harm to others were also excluded.

Treatments
There was a single-blind placebo washout period up to 7 days followed by double-blind, randomized period of 21 days.

After week 3, patients were given the option to continue into the extension study (A7501006).

Outcomes/endpoints
The primary efficacy measure was the mean change from baseline to Day 21 on the Y-MRS total score.

Main secondary efficacy measures were the mean change from baseline in Y-MRS total score (all time points); Y-MRS responders (defined as a 50% decrease from baseline in Y-MRS score at any given visit); Y-MRS remitters (defined as a Y-MRS total score of 12 or lower at any given visit); change from baseline in CGI-BP severity in mania.

Statistical Methods
The primary efficacy endpoint was analyzed by a fixed-effects analysis of covariance (ANCOVA). The primary model used the baseline score as a covariate. Comparisons between treatment groups were made using the difference in the model based least square means. No adjustment was made for multiple comparisons since the olanzapine versus placebo comparison was made for assessing sensitivity only. The robustness of the results against potential bias caused by missing data was checked by 2 methods: 1) an OC analysis, and 2) a MMRM analysis.

2.4.5.7.1.1. Results

Participant flow
In study A7501004, a total of 611 subjects were enrolled in the trial, of whom 488 subjects were randomized and took at least 1 dose of trial medication: 98 subjects (placebo),185 subjects (asenapine 5-10 mg BID) and 205 subjects (olanzapine 5-20 mg once daily QD). A total of 342 subjects completed the trial (124 asenapine [67.0%]; 161 olanzapine [78.5%]; and 57 placebo [58.2%]). There were 17 (9.2%) asenapine-treated subjects, 7 (3.4%) olanzapine-treated subjects, and 4 (4.1%)

placebo-treated subjects who withdrew due to an adverse event/SAE. Of these 6 (3.2%) asenapine-treated subjects, 2 (1.0%) olanzapine-treated subjects, and 4 (4.1%) placebo-treated subjects who withdrew due to an adverse event/SAE related to bipolar I disorder.
A total of 76 subjects, including 30 from the asenapine group, 12 from the placebo group, and 34 from the olanzapine group, who completed the trial, did not continue into the extension trial (A7501006). The most frequent reason for not continuing into the extension trial was withdrawal of consent (23 of the 30 subjects from the asenapine group, 11 of the 12 subjects from the placebo group, and 29 of the 34 subjects in the olanzapine group). There were 14 (7.6%) asenapine-treated subjects, 13 (6.3%) olanzapine-treated subjects, and 14 (14.3%) placebo-treated subjects who withdrew due to lack of efficacy. There were 25 (13.5%) asenapine-treated subjects, 15 (7.3%) olanzapine-treated subjects, and 13 (13.3%) placebo-treated subjects for whom the reason for withdrawal was withdrawn consent.

In study A7501005, a total of 654 subjects were enrolled in the trial, of whom 489 subjects were randomized and 488 took at least 1 dose of trial medication: 104 subjects (placebo), 194 subjects (asenapine 5-10 mg BID) and 190 subjects (olanzapine 5-20 mg once daily QD).A total of 338 subjects completed the trial (122 asenapine [62.9%]; 152 olanzapine [79.6%]; and 64 placebo [61.5%]). There were 20 (10.3%) asenapine-treated subjects, 8 (4.2%) olanzapine-treated subjects, and 7 (6.7%) placebo-treated subjects who withdrew due to an adverse event/SAE. Of these, 11 (5.7%) asenapine-treated subjects, 2 (1.0%) olanzapine-treated subjects, and 5 (4.8%) placebo-treated subjects who withdrew due to an adverse event/SAE related to bipolar I disorder.
A total of 100 subjects, including 35 from the asenapine group, 15 from the placebo group, and 50 from the olanzapine group, who completed the trial, did not continue into the extension trial (A7501006). The most frequent reason for not continuing into the extension trial was withdrawal of consent (25 of the 35 subjects from the asenapine group, 13 of the 15 subjects from the placebo group, and 38 of the 50 subjects in the olanzapine group). There were 16 (8.2%) asenapine-treated subjects, 11 (5.8%) olanzapine-treated subjects, and 17 (16.3%) placebo-treated subjects who withdrew due to lack of efficacy. There were 28 (14.4%) asenapine-treated subjects, 16 (8.4%) olanzapine-treated subjects, and 13 (12.5%) placebo-treated subjects for whom the reason for withdrawal was withdrawn consent.

Baseline data
In study A7501004, subjects had a mean age of 38.6 years. Overall, there were 231 (47.3%) females and 257 (52.7%) males. Mean weight was 77.2 kg and mean BMI was 26.9 kg/m2. The proportion of male subjects was higher in the olanzapine group (57.1%) than in the asenapine (49.7%) or placebo (49.0%) groups. Overall, 68.9% of subjects had a diagnosis of a manic episode and 31.1% had a diagnosis of a mixed episode. The mean total daily dose for asenapine was 18.2 mg/day for asenapine and 15.9 mg/day for olanzapine. The most commonly used concomitant medications in all 3 treatment groups were psycholeptics (65.4%asenapine, 67.3% olanzapine, and 70.4% placebo).

In study A7501005, subjects had a mean age of 39.4 years. Overall, there were 42.6% (208) women and 57.4% (280) men. Mean weight was 78.6 kg and mean BMI was 27.0 kg/m2.The proportion of male subjects was higher in the olanzapine (60.0%) and asenapine groups (58.8%) than in the placebo (50.0%) groups. Overall, 69.3% of had a diagnosis of a manic episode and 30.7% had a diagnosis of a mixed episode. The mean total daily dose for asenapine was 18.2 mg/day for asenapine and 15.8 mg/day for olanzapine. Overall, 84.5% of asenapine subjects, 77.9% of olanzapine subjects, and 83.7% of placebo subjects reported the use of concomitant medications during the trial. The most commonly used concomitant medications in all 3 treatment groups were psycholeptics (67.0% asenapine, 60.5% olanzapine, and 69.2% placebo).

Outcome

In study A7501004, Y-MRS total scores were statistically significantly improved in the asenapine and olanzapine treatment groups compared with the placebo treatment group (p=0.0065 for asenapine versus placebo and p<0.0001 for olanzapine versus placebo). The mean change from baseline to Day 21 was -11.5, -7.8, and -14.6 for the asenapine, placebo, and olanzapine treatment groups, respectively. Mean changes from baseline in the CGI-BP, severity of mania also showed statistically significant improvements in the asenapine group over placebo at Day 21.

At Day 21, 42.6% of subjects in the asenapine group were responders compared with 34.0% in the placebo group. However, this treatment difference was not statistically significant (p=0.1951). A statistically significant greater percentage of subjects in the olanzapine group were responders compared with the placebo group (p=0.0011) at day 21.

At Day 21, 35.5% of subjects in the asenapine group were remitters compared with 30.9% in the placebo group. However, this treatment difference was not statistically significant (p=0.5033).A statistically significant greater percentage of subjects in the olanzapine group were remitters compared with the placebo group at Day 21 (p=0.0159).

In study A7501005, Y-MRS total scores were statistically significantly improved in the asenapine and olanzapine treatment groups compared with the placebo treatment group (p<0.0001 for both comparisons with placebo). The mean change from baseline to Day 21 was -10.8, -5.5, and -12.6 for the asenapine, placebo, and olanzapine treatment groups, respectively. Mean changes from baseline in the CGI-BP, severity of mania also showed statistically significant improvements in the asenapine group over placebo at Day 21.

At Day 21, 42.3% of subjects in the asenapine group were responders compared with 25.2% in the placebo group. This treatment difference was statistically significant (p=0.0049). A statistically significant greater percentage of subjects in the olanzapine group were responders compared with the placebo at day 21(p<0.0001).

At Day 21, 40.2% of subjects in the asenapine group were remitters compared with 22.3%in the placebo group. This treatment difference was statistically significant (p=0.0020). A statistically significant greater percentage of subjects in the olanzapine group were remitters compared with the placebo group at Day 21 (p=0.0041).

2.4.5.8. Long term studies

The main long-term studies were designed as follows:

- A7501006: a 9-week, randomised, double-blind, placebo and active-controlled (3 treatment groups: asenapine 5-10 mg BID or olanzapine 5-20 mg QD, placebo/asenapine in 3:1 ratio) study in subjects with manic or mixed episodes associated with bipolar I disorder;
- A7501008 (add on therapy): a 12-week,randomised, double-blind, placebo-controlled (2 treatment groups: asenapine 5-10 mg BID or placebo in 3:1 ratio) study in subjects with manic or mixed episodes associated with bipolar I disorder;

Study A7501006 was conducted in Bulgaria and Romania and outside EU (US, India, Asia, Russia, Ukraine and Turkey). Study A751008 was performed in Czech Republic and outside EU (US, Australia, India, Asia and Russia).

Patients who completed studies A7501006 and A7501008 were eligible to enter a 40 week extension studies A7501007 A7501009, respectively and primarily aimed to provide additional long term safety data (see 3.4.6. Clinical Safety).

2.4.5.8.1. Study A7501006

2.4.5.8.1.1. Methods

Study design

This was a 9-week, olanzapine-controlled, double-blind, double-dummy, multicenter, parallel group, continuation trial.

Study participants

Main inclusion criteria
Subjects had a primary diagnosis of bipolar I disorder. Subjects were to have completed studies A7501004 or A7501005 (so called "feeder study") without major protocol violations. Subjects were men or women of at least 18 years of age. Subjects were to be willing to discontinue all psychotropic medication during the treatment period except of those specified in the protocol.

Treatments
Those subjects treated with active, double-blind therapy were to continue in their original treatment group (asenapine 5-10 mg twice daily [BID] or olanzapine 5-20 mg once daily [QD]). Subjects previously receiving placebo were blindly allocated to receive asenapine (5-10 mg BID), and these subjects were only included in the safety analyses (see Figure 6).

Outcomes/endpoints

The primary efficacy endpoint was the change from baseline to Week 12 on the Young-Mania Rating Scale (Y-MRS).

Main secondary efficacy measures were the mean change from baseline in Y-MRS total score (all time points); Y-MRS responders (defined as a 50% decrease from baseline in Y-MRS score at any given visit); Y-MRS remitters (defined as a Y-MRS total score of 12 or lower at any given visit); change from baseline in CGI-BP severity in mania.

Statistical Method

For the primary analysis, non-inferiority limit was set at four points on the Y-MRS scale. An ANCOVA with fixed effects for treatment and investigative site (or pooled site) and baseline Y-MRS scores as a covariate was used to test the hypothesis of non-inferiority using a one-sided $\alpha = 0.025$ significance level. Comparison between asenapine and olanzapine was based on the difference in the model based least square means . The robustness of the results against potential bias caused by missing data was checked by 2 methods: 1) an OC analysis, and 2) a MMRM analysis.

2.4.5.8.1.2. Results

Participant flow

A total of 504 subjects, 94 who had received placebo in the feeder study, 181 who had received asenapine in the feeder study, and 229 who had received olanzapine in the feeder study, received at least 1 dose of trial medication in this extension study. A total of 308 subjects completed the trial (112 asenapine [61.9%]; 146 olanzapine [63.8%]; and 50 placebo/asenapine [53.2%]). There were 18 (19.1%) placebo/asenapine-treated subjects, 24 (13.3%) asenapine-treated subjects, 22(9.6%) olanzapine-treated subjects who withdrew due to an adverse event/SAE. Of these 9 (9.6%) placebo/asenapine-treated subjects, 16 (8.8%) asenapine-treated subjects, and 11 (4.8%) olanzapine-treated subjects who withdrew due to an adverse event/SAE related to bipolar I disorder.

Baseline data

Subjects had a mean age of 39.5 years. Mean weight was 76.3 kg and mean BMI was 26.7 kg/m2. Overall, the proportion of men participating in the study (55.0%) was slightly higher than the proportion of women (45.0%).

For asenapine group, 72.4% of subjects had manic episode versus 72.5% for olanzapine group and 27.6% had mixed episode for asenapine group versus 27.5% for olanzapine group. In the placebo/asenapine group, 60.6% of subjects had a manic episode and 39.4% had a mixed episode. The mean total daily dose of asenapine was 16.1 mg/day in the placebo/asenapine group, 17.6 mg/day in the asenapine group and 16.1mg/day in the olanzapine group. Psycholeptics were the most commonly used concomitant medications in the asenapine and olanzapine groups (63.5% asenapine and 59.8% olanzapine)

Outcome

The mean change from baseline to Day 84 for the asenapine treatment group was -27.3 while the mean change from baseline to Day 84 was -23.7 for the olanzapine treatment group.

At Day 21, 60.7% and 68.7% of subjects in the asenapine and olanzapine groups were responders, respectively. At Day 84, 89.5% and 92.2% of subjects in the asenapine and olanzapine groups were responders, respectively. No statistically significant differences were observed between the percentage of Y-MRS responders in the asenapine treatment group and the olanzapine treatment group, at any time point.

At Day 21, 54.8% and 55.3% of subjects in the asenapine and olanzapine groups were remitters, respectively. At Day 84, 88.4% and 90.6% of subjects in the asenapine and olanzapine groups were remitters, respectively. No statistically significant differences were observed between the percentage of Y-MRS remitters in the asenapine treatment group and those in the olanzapine treatment group, at any time point.

Both the asenapine and olanzapine groups demonstrated improvement on the CGI-BP severity of mania, with scores in the asenapine group decreasing from a mean of 4.7 (moderately to markedly ill) at baseline to 1.7 (normal to borderline mentally ill) at Day 84 and scores in the olanzapine group decreasing from a mean of 4.6 at baseline to 1.8 at Day 84. The mean changes from baseline to Day 84 were -2.9 for the asenapine treatment group and -2.8 for the olanzapine treatment group. The mean change from baseline to Day 21 was -1.9 for both the asenapine and olanzapine treatment groups. No statistically significant differences were observed between the asenapine treatment group and the olanzapine treatment group for CGI-BP severity of mania.

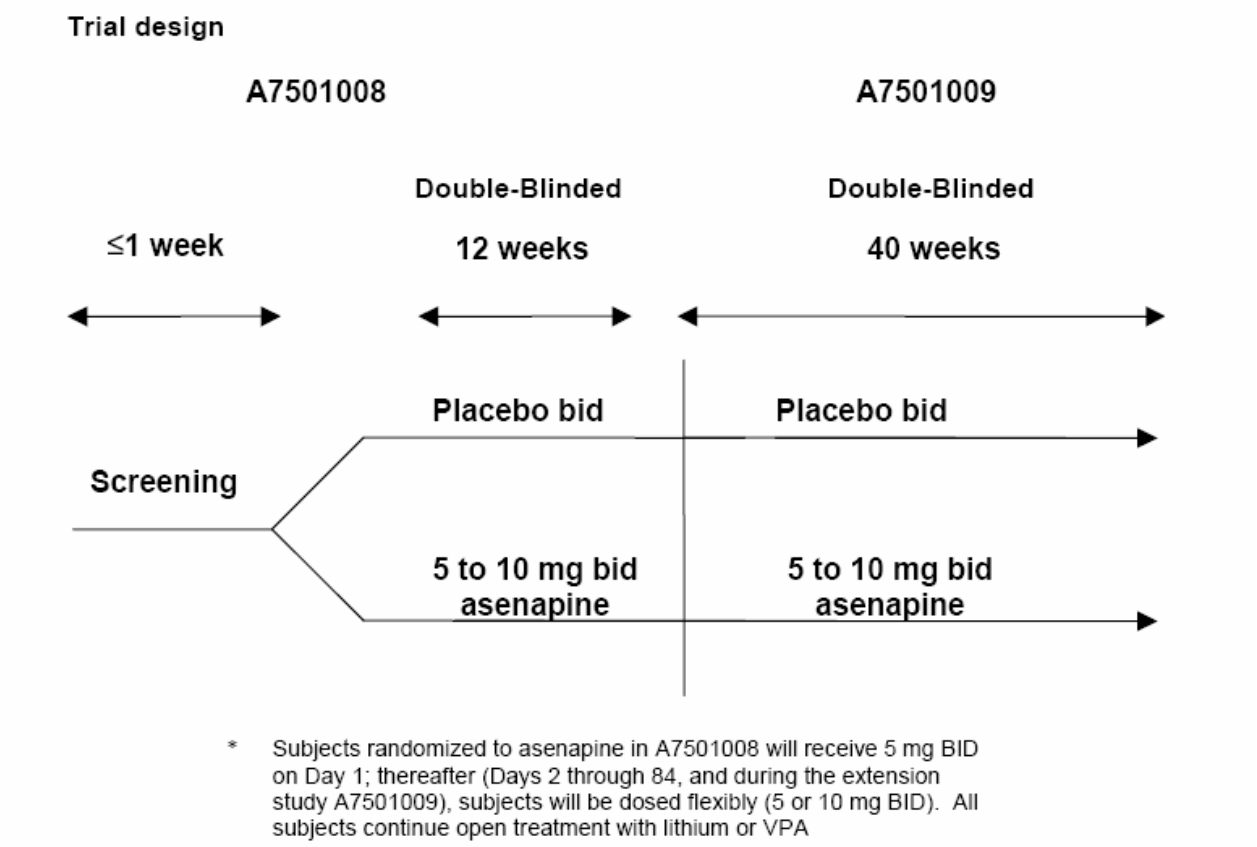
2.4.5.8.2. Study A7501008

2.4.5.8.2.1. Methods

Study design

This was a randomized, placebo-controlled, double-blind, multicenter trial. The design of this study and its extension study A7501009 is presented in Figure 7.

Figure 7



Study participants

Main inclusion criteria

Subjects had a primary diagnosis of bipolar I disorder, current episode manic (DSM-IV 296.4x) or mixed (DSM-IV 296.6x). Subjects were men or women of at least 18 years of age with documented history of at least one previous moderate-to-severe mood episode with or without psychotic features (manic or mixed). Subjects were to have a Young-Mania Rating Scale (Y-MRS) score ≥20 at screening and at baseline, have a current manic or mixed bipolar I episode that must have begun no more than 3 months prior to the screening visit, and been continuously treated with lithium or valproate (VPA) for at least 2 weeks immediately prior to screening. Subjects completing the trial were eligible for enrollment in a 40-week, double-blinded extension trial, A7501009, regardless of the degree to which they had responded to study medication in study A7501008, provided they met the inclusion and exclusion criteria for the study A7501009.

Treatments
On Day 1, subjects received 5 mg asenapine BID or placebo BID. On Days 2 through 84, double-blinded asenapine (or placebo) was dosed flexibly (5 or 10 mg BID), based on efficacy, safety, and tolerability. All subjects continued open treatment with lithium or VPA for the duration of the trial.

Treatment with lithium or VPA was continued throughout the course of the trial; that is, 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 mcg/mL]) obtained at the discretion of the investigator. An exception to this scenario was that dose reductions were permitted in the event of adverse events that in the investigator's opinion were due to the mood stabilizer. That is, the mood stabilizer dose was reduced because of related adverse events even if the corresponding plasma level was in the therapeutic range and the resulting new mood stabilizer plasma concentration fell into the sub-therapeutic range, so long as the adverse event attributed to the mood stabilizer resolved after this reduction was made.

Outcomes/endpoints
The primary efficacy endpoint was the change from baseline, LOCF, to Week 3 on the Y-MRS total score.
Main secondary efficacy measures were the mean change from baseline in Y-MRS total score (all time points); Y-MRS responders (defined as a 50% decrease from baseline in Y-MRS score at any given visit); Y-MRS remitters (defined as a Y-MRS total score of 12 or lower at any given visit); change from baseline in CGI-BP severity in mania.

Statistical methods

The primary endpoint was the change from baseline to Week 3 in the Y-MRS LOCF score, for which the primary analysis was based upon the ITT data set: all subjects who were randomly assigned to therapy, who had at least 1 post-baseline Y MRS score, and who took at least 1 dose of study medication. This primary analysis compared asenapine with placebo using a fixed effects analysis of covariance (ANCOVA) with baseline Y-MRS scores and site as covariates.

All hypothesis tests comparing the treatment groups were performed using a 2-tailed 0.05 level of significance. The robustness of the results against potential bias caused by missing data was checked by 2 methods: 1) an OC analysis, and 2) a MMRM analysis.

2.4.5.8.2.2. Results

Participant flow
A total of 438 subjects were screened for participation in the trial. Of these, 112 subjects withdrew during screening, with the most common reason for withdrawal during screening being not meeting entry criteria (81/112, 72.3%). A total of 326 subjects were randomized to study medication: 159 subjects to asenapine, and 167 subjects to placebo. Of these, 324 subjects (158 asenapine; 166 placebo) received at least 1 dose of study medication.

A total of 116 subjects completed the trial (61 asenapine [38.4%] and 55 placebo [32.9%]). A slightly higher percentage of asenapine-treated subjects (15.7%) withdrew due to an adverse event compared with placebo-treated subjects (11.4%). Similarly, a slightly higher percentage of asenapine-treated subjects (11.3%) withdrew due to an adverse event related to the disease under study (bipolar I

disorder) compared with placebo- treated subjects (9.6%). The percentage of subjects who withdrew due to lack of efficacy was higher in the placebo group (16.2%) than in the asenapine group (8.2%).

Baseline data

The 324 adult subjects participating in the trial had a mean age of 39.3 years. Most subjects in all treatment groups were in the 18-64 years age category; there was 1 (0.6%) subject in the asenapine group and 2 (1.2%) subjects in the placebo group who were ≥65 years old. Overall, there were 42.3% (137) females and 57.7% (187) males. Mean weight was 80.5 kg and mean BMI was 27.5 kg/m2 (range 17 to 46 kg/m2).

Overall, 61.1% of had a diagnosis of a manic episode and 38.9% had a diagnosis of a mixed episode; this was a consistent finding across treatment groups. The mean total daily dose of asenapine was 11.8 mg/day.

A similar percentage of subjects in the asenapine group (80.4%) and the placebo group (81.9%) took concomitant medications, excluding lithium and VPA, during the study. Excluding lithium and VPA, the most common concomitant medications used in both treatment groups were lorazepam (asenapine 50.0%, placebo 50.6%), zolpidem (asenapine 29.7%, placebo 28.3%), paracetamol (asenapine 20.9%, placebo 19.9%), ibuprofen (asenapine 19.0%, placebo 10.8%), and temazepam (asenapine 9.5%, placebo 10.8%).

Outcome

Using LOCF method, Y-MRS total scores were statistically significantly improved in the asenapine treatment group compared with the placebo treatment group ($p = 0.0257$). The mean change from baseline to Day 21 was -10.3 and -7.9 for the asenapine and placebo treatment groups, respectively.

Using OC method, statistical analysis of the mean changes from baseline in the Y-MRS total scores did not demonstrate a statistically significant difference between the asenapine and placebo groups ($p = 0.2279$). The mean change from baseline to Day 21 was -13.0 and -11.6 for the asenapine and placebo treatment groups, respectively. In addition, using MMRM analysis, change from baseline to Day 21 in Y-MRS total score was not statistically significantly different between the asenapine and placebo group ($p = 0.0991$).

At week 12, there was a mean change from baseline of -12.7 YMRS points for asenapine and -9.3 Y-MRS points for placebo which was statistically significant ($p =0.0073$).

Using LOCF method, the percentage of Y-MRS responders in the asenapine treatment was statistically significantly higher than in the placebo treatment group at Day 42 ($p = 0.0370$), Day 63 ($p = 0.0488$), and Day 84 ($p = 0.0152$), but not at Day 21 ($p = 0.1634$). Using the OC method, the percentage of responders was not statistically significantly different between the asenapine and placebo treatment groups at any time point from Day 3 to Day 84.

Using LOCF method, the percentage of Y-MRS remitters in the asenapine treatment group was statistically significantly higher at Day 21 ($p = 0.0158$), Day 42 ($p = 0.0143$), Day 63 ($p = 0.0196$), and Day 84 ($p = 0.0148$). Using the OC method, the percentage of remitters was statistically significantly different between the asenapine and placebo treatment groups only at Day 21 ($p = 0.0227$)

Using the LOCF method, improvements in CGI-BP severity of mania were statistically significantly greater in the asenapine treatment group compared with the placebo treatment group at all time points. The mean changes from baseline to Day 21 were - 1.1 in the asenapine group compared with -0.8 in the placebo group and the mean changes from baseline to Day 84 were -1.5 in the asenapine group compared with -1.0 in the placebo group. Using OC method, CGI-BP severity of mania results also revealed statistically significant improvements in the asenapine group compared with the placebo group at day 21 ($p = 0.0009$). The difference between the placebo and asenapine groups at Day 84 was not statistically significant ($p = 0.0772$).

2.4.5.8.3. Additional statistical analyses

Additional analysis on primary endpoint for studies A7501006 and A7501008 were performed taking into account all randomised patients for study A7501006 (i.e including patients from studies A7501004 and A7501005) and using BOCF analysis for study A7501008.

Study A7501006

Descriptive statistics for the change from baseline of the Y-MRS Total scores are presented for the combined dataset in Table 12 by treatment and assessment.

Table 12

Table 2 Descriptive statistics of the change from baseline of Y-MRS Total score by treatment and assessment. Intent-to-treat population. Combined data of trials A7501004, A7501005 and A7501006

Visit	Statistic	Observed cases (OC)			Last observation carried forward (LOCF)		
		Asenapine (N=372)	Olanzapine (N=391)	Placebo (N=197)	Asenapine (N=372)	Olanzapine (N=391)	Placebo (N=197)
Day 2	N	358	382	194	358	382	194
	Mean (SD)	-3.2 (5.3)	-4.0 (6.1)	-1.6 (4.5)	-3.2 (5.3)	-4.0 (6.1)	-1.6 (4.5)
	Median	-2.0	-2.0	-1.0	-2.0	-2.0	-1.0
	(Range)	(-30 - 10)	(-38 - 8)	(-19 - 17)	(-30 - 10)	(-38 - 8)	(-19 - 17)
Day 4	n	348	359	181	372	391	197
	Mean (SD)	-5.9 (6.5)	-7.2 (6.8)	-3.6 (6.0)	-5.6 (6.5)	-7.1 (6.8)	-3.3 (6.3)
	Median	-5.0	-6.0	-2.0	-4.0	-6.0	-2.0
	(Range)	(-35 - 11)	(-35 - 14)	(-29 - 21)	(-35 - 11)	(-35 - 14)	(-29 - 21)
Day 7	n	324	361	171	372	391	197
	Mean (SD)	-8.0 (8.4)	-9.7 (8.1)	-5.4 (8.6)	-7.7 (8.3)	-9.6 (8.1)	-4.6 (8.8)
	Median	-7.0	-9.0	-5.0	-7.0	-9.0	-4.0
	(Range)	(-43 - 17)	(-35 - 24)	(-30 - 27)	(-43 - 17)	(-35 - 24)	(-30 - 27)
Day 14	n	284	327	148	372	391	197
	Mean (SD)	-12.2 (9.7)	-12.7 (8.6)	-8.4 (8.9)	-9.9 (10.5)	-11.9 (9.1)	-6.0 (10.2)
	Median	-11.0	-13.0	-8.0	-9.5	-12.0	-6.0
	(Range)	(-44 - 15)	(-39 - 14)	(-34 - 19)	(-44 - 18)	(-39 - 24)	(-34 - 27)
Day 21	n	240	303	116	372	391	197
	Mean (SD)	-14.9 (9.7)	-15.9 (9.0)	-10.7 (9.7)	-11.1 (11.2)	-13.7 (10.1)	-6.7 (11.1)
	Median	-15.0	-16.0	-10.5	-11.0	-14.0	-7.0
	(Range)	(-38 - 15)	(-45 - 11)	(-36 - 22)	(-44 - 18)	(-45 - 24)	(-36 - 27)
Week 4	n	167	213		372	391	
	Mean (SD)	-17.9 (9.7)	-18.5 (8.8)		-11.8 (11.5)	-14.6 (10.7)	
	Median	-19.0	-18.0		-12.0	-16.0	
	(Range)	(-42 - 10)	(-49 - 6)		(-42 - 18)	(-49 - 24)	
Week 6	n	143	180		372	391	
	Mean (SD)	-20.4 (8.6)	-21.1 (8.1)		-12.5 (11.9)	-15.3 (11.0)	
	Median	-21.0	-20.5		-13.0	-16.0	
	(Range)	(-45 - 3)	(-51 - 0)		(-45 - 18)	(-51 - 24)	
Week 9	n	107	151		372	391	
	Mean (SD)	-22.8 (8.8)	-22.8 (8.0)		-12.7 (12.3)	-15.8 (11.4)	
	Median	-23.0	-23.0		-13.0	-17.0	
	(Range)	(-46 - 3)	(-49 - -4)		(-46 - 18)	(-51 - 24)	
Week 12	n	87	128		372	391	
	Mean (SD)	-24.6 (8.8)	-23.9 (7.9)		-12.9 (12.5)	-16.2 (11.7)	
	Median	-25.0	-24.0		-13.0	-17.0	
	(Range)	(-48 - 4)	(-49 - 2)		(-48 - 18)	(-51 - 24)	

Note that data for the patients randomized to placebo have been removed after Day 21 when the patients were switched to asenapine treatment. These data were not considered in inferential analysis.

Post-hoc analyses using MMRM, MI and OC are presented in Table 13.

Table 13

Table 3 Estimates of treatment difference of Asenapine vs. Olanzapine (Y-MRS Total score) at Week 12.
Intent to Treat population – combined data of trials A7501004, A7501005 and A7501006

Assumption	Method	Missing data handling	Role	Estimated Difference	95% CI
MAR	**MMRM**	**Likelihood based**	**Primary**	**0.6**	**(-1.3, 2.5)**
MAR	MI	Multiple inputation	Sensitivity	1.0	(-0.5, 2.5)
MCAR	LOCF	Single imputation	Sensitivity	3.1	(1.6, 4.7)
NA	OC	No imputation	Sensitivity	0.6	(-0.9, 2.2)

MMRM: mixed model for repeated measures; LOCF: Last Observation Carried Forward; MI: Multiple Imputation; OC: Observed Case; NA: Not applicable. Positive numbers favor Olanzapine. Post-hoc analyses as based on models as defined in the protocols. Throughout pooled centers as defined in trials A7501004 and A7501005 have been used. The window of the day 7 assessment includes Day 8 to prevent many missing observations (180 cases) to reduce number of missing data for multiple imputation models.

Analysis of the observed change from baseline in the Y-MRS data at Day 21 as an indicator for drop-out at Week 12 indicated that decreased response on Y-MRS at Day 21 is highly predictive of discontinuing treatment: for each one point increase in Y-MRS point at Day 21, the odds of discontinuing treatment before Week 12 increased by 12.8% (see Table 14).

Table 14

Table 4 Logistic regression of Week 3 Y-MRS change from baseline on drop-out until Week 12 using data collected up to Week 3

Estimated Odds ratio*	(95% Wald Confidence Limit)	Significance (p-value)
1.128	(1.123 1.132)	<.0001

*The logistic regression model on treatment discontinuation before Week 12 (Yes/No) included treatment, baseline Y-MRS score, pooled center and the change from baseline to Day 21 Y-MRS total score (using LOCF).

Study A7501008

In the BOCF analysis there was a mean change from baseline of -9.1 YMRS points for asenapine and -7.2 Y-MRS points for placebo (based on means). The difference between asenapine and placebo using the BOCF method to handle missing data approached statistical significance (p=0.053), whereas the primary analysis was statistically significant (p=0.026).

The observed responder rate was 32% for asenapine versus 23% on placebo applying the missing equals failure approach. Adjusting for (pooled) center this leads to an odds ratio of 1.8 in favor of asenapine, which was statistically significant (p=0.03).

For asenapine the remitter rate was 31%, versus 18% on placebo (p=0.002). This leads to an OR of 2.4 (95% CI 1.4 – 4.1), indicating that as add-on therapy the odds of being in remission at Week 3 with asenapine treatment was more than twice as likely as when treated with placebo.

3.4.6 Discussion on clinical efficacy

Short term studies

With respect to phase III short terms trials (A7501004 and A7501005), the CHMP considered that the efficacy of asenapine has been demonstrated with both studies showing superiority of asenapine over placebo at week 3 on the primary endpoint. However, the CHMP was concerned over the clinical significance of the treatment effect seen with asenapine, especially in study A7501004. In this study, treatment differences were not statistically significant at day 21 for the responder (p=0.1951) and remitter analyses (p=0.5033). In contrast, a statistically significant greater percentage of subjects in the olanzapine group were responders and remitters compared with the placebo group (p=0.0011 and p=0.0159, respectively) at day 21. The applicant further justified the clinical significance of the treatment effect seen in short-term trials, presenting meta-analyses on published randomised placebo-controlled short term studies using second generation antipsychotics. An estimate of a treatment effect was calculated based on a meta-analysis combining all compounds was performed, leading to a pooled treatment effect of -4.9 points on the YMRS scale (95% CI: 6.0 to -3.8). The average treatment effect obtained for asenapine of -4.7 YMRS points (with a 95% CI of -6.6 to -2.7 YMRS points) was considered clinically relevant.

Long term studies

With respect to phase III long term trials, the CHMP considered that the results for study A7501006, as presented by the applicant, required further statistical analysis (taking into account all patients randomised into studies A7501004 and A7501005) and justification on the choice of non-inferiority margin in this study prior concluding on the maintenance of the effect during the episode. The additional statistical analyses showed estimates of treatment difference between asenapine and olanzapine within the pre-specified non-inferiority margin of 3 of the methods used (MMRM, MI and OC). However, the upper bound of the 95% confidence interval limit exceeded this pre-specified non-inferiority margin using LOCF method, considered by the CHMP as a more appropriate method account for the early drop outs observed in the study, in this case. The CHMP concluded that non-inferiority of asenapine versus olanzapine was not shown. Further argumentations were provided by the applicant to support the maintenance of the effect of asenapine at week 12. These were related to the chosen non-inferiority margin and observed effect size with other antipsychotics at week 12. Furthermore, two studies (including quetiapine as active treatment) were identified as suitable for comparison of effect sizes over placebo at week 12[1]. Based on these data, the applicant considered that there was some evidence of superiority of asenapine versus putative placebo using a worst case scenario (95%-95% rule).

There were some limitations in the presented analysis (e.g indirect trials comparison). Nevertheless, the CHMP was of the opinion that given the demonstrated short term efficacy of asenapine at week 3 and positive trend of the YRMS score over time (using both LOCF and OC methods), although non-inferiority to olanzapine could not be concluded, the overall data were supportive of the maintenance of the effect of asenapine during the episode.

[1] McIntyre RS, Brecher M, Paulsson B, Huizar K, Mullen J (2005) Quetiapine or haloperidol as monotherapy for bipolar mania--a 12-week, double-blind, randomised, parallel-group, placebocontrolled trial. Neuropsychopharmacol. 15(5),573-585; Bowden CL, Grunze H, Mullen J, Brecher M, Paulsson B, Jones M, Vagero M, Svensson K (2005) A Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Quetiapine or Lithium as Monotherapy for Mania in Bipolar Disorder. J. Clin. Psychiatry 66(1),111-121.

With respect to the phase III long term trial investigating add-on therapy (A7501008), the CHMP questioned the clinical relevance of the treatment difference seen over placebo, particularly, given the lack of an active comparator in this study. As for the monotherapy indication the applicant provided justification that the magnitude of the difference between asenapine and placebo on the Y-MRS was in line with that seen for other atypical antipsychotics approved for the mania indication and was clinically relevant. An additional statistical analysis was conducted using BOCF method. Results showed a mean change from baseline of -9.1 YMRS points for asenapine and -7.2 Y-MRS points for placebo approaching statistical significance (p =0.053), consistent with the primary LOCF analysis which was statistically significant with a mean change from baseline of -10.3 YMRS point for asenapine and -7.9 Y-MRS points for placebo (p=0.026). At week 12, there was a mean change from baseline of -12.7 YMRS points for asenapine and -9.3 Y-MRS points for placebo which was statistically significant (p =0.0073). The observed responder rate was 32% for asenapine versus 23% on placebo (OR=1.8) and remitter rate was 31%, versus 18% on placebo (OR=2.4; 95% CI: 1.4 – 4.1). In the CHMP view, the overall analysis on the add-on therapy results was supportive of the use of asenapine in combination with a mood-stabilizer.

Dose-response studies

No dose response studies were conducted. The CHMP was concerned that the optimal dosing regimen had not been established for the bipolar I disorder indication applied for, particularly considering that the phase II data from the schizophrenia clinical program could not be extrapolated. The applicant argued that data on dopamine D2 receptor occupancy and PK/PD modelling using doses of 5 and 10 mg BID were supportive of the proposed dosing regimen. Furthermore, more than 90% of patients in studies A7501004 and A7501005 remained on the starting dose of 10 mg BID, providing reassurance on the tolerability of this proposed regimen. In view of the applicant's argumentation and the demonstrated benefit of asenapine using flexible 5-10 BID regimen, the CHMP considered overall the proposed dosing regimen acceptable, provided that further supportive data are generated via a proper dose finding study as part of a post-approval commitment. The company submitted an outline protocol for a dose-response study. The overall design and size of the trial was considered satisfactory. The choice of two doses - 5 and 10 mg - plus placebo was considered to represent the minimum requirement, 2.5mg dose (which produced a high level of D2 occupancy) in order to explore the minimum effective dose could have also been considered in this study. However, as the dose for mania tends to be higher than for schizophrenia the applicant's proposal could be accepted.

3.4.7 Conclusions on clinical efficacy

The CHMP concluded the following:
- The efficacy in reducing manic symptoms over 3 weeks was demonstrated.
- Maintenance of the effect during the manic episode after 12 weeks was demonstrated.
- Superior efficacy over lithium or valproate monotherapy was also shown and maintained for up to 12 weeks.
- The proposed dosing regimen is acceptable provided that further supportive data are generated via a proper dose finding study as part of a post-approval commitment.

3.4.8 Clinical safety

The safety database presented in the dossier included the following cohorts: combined population Phase 2/3 efficacy and safety trials (**cohort E1**), 6 week short term schizophrenia trials (**cohort A1:** 041002, 041013; 041004), long term schizophrenia trials (**cohort B1:** 25517; 25520 , 041512; 041513; 25543; 25544; A7501012**),** 3 week short term bipolar mania trial (**cohort C1:** A7501004; A7501005), long term bipolar mania trials (**cohort D1**: A7501006 ; A7501007; A7501008; A7501009), clinical pharmacology trials in healthy volunteers (cohort F1), clinical pharmacology trials in subjects with psychosis (cohort G1) and ongoing trials (cohort NC1).

Patient exposure

Overall 4565 subjects had received sublingual asenapine including 3457 subjects in the Phase 2/3 clinical program. Of these 3159 (91.4%) received the proposed therapeutic dose of 5 to 10 mg BID. as either fixed or flexible doses, while 298 (8.6%) received doses less than 5 mg BID, 2826 (298 received < 5 mg BID) of these subjects had schizophrenia and 631 subjects had bipolar I disorder.

One thousand and three hundred and fourteen subjects had received asenapine for at least 6 months and 785 for at least 12 months. Almost all of these subjects received doses of 5-10 mg BID.

Adverse events

Combined safety data from short term placebo controlled trials are presented in Table 15.

Tables 15

Table 38 Adverse events by preferred term with an incidence ≥ 2.0% (short-term placebo-controlled trials, cohorts A1 and C1)

Adverse Event (Preferred Term) n (%)	Placebo (N=706)	Asenapine					Risperidone 3 mg BID (N=120)	Haloperidol 4 mg BID (N=115)	Olanzapine 5-20 mg QD (N=588)
		< 5 mg BID (N=298)	5 mg BID Fixed Dose (N=274)	10 mg BID Fixed Dose (N=208)	All 5-10 mg BID[a] (N=951)	All <5-10 mg BID[a] (N=1249)			
Any adverse event	481 (68.1)	240 (80.5)	196 (71.5)	155 (74.5)	696 (73.2)	936 (74.9)	104 (86.7)	87 (75.7)	402 (68.4)
Headache	107 (15.2)	75 (25.2)	32 (11.7)	20 (9.6)	114 (12.0)	189 (15.1)	25 (20.8)	5 (4.3)	71 (12.1)
Insomnia	77 (10.9)	47 (15.8)	43 (15.7)	31 (14.9)	107 (11.3)	154 (12.3)	25 (20.8)	16 (13.9)	47 (8.0)
Agitation	65 (9.2)	41 (13.8)	26 (9.5)	16 (7.7)	66 (6.9)	107 (8.6)	15 (12.5)	9 (7.8)	31 (5.3)
Dizziness	31 (4.4)	28 (9.4)	18 (6.6)	7 (3.4)	68 (7.2)	96 (7.7)	14 (11.7)	2 (1.7)	40 (6.8)
Somnolence	16 (2.3)	15 (5.0)	25 (9.1)	13 (6.3)	80 (8.4)	95 (7.6)	5 (4.2)	2 (1.7)	48 (8.2)
Sedation	31 (4.4)	6 (2.0)	17 (6.2)	13 (6.3)	87 (9.1)	93 (7.4)	8 (6.7)	4 (3.5)	89 (15.1)
Anxiety	49 (6.9)	31 (10.4)	19 (6.9)	11 (5.3)	56 (5.9)	87 (7.0)	16 (13.3)	7 (6.1)	15 (2.6)
Nausea	58 (8.2)	22 (7.4)	18 (6.6)	12 (5.8)	56 (5.9)	78 (6.2)	10 (8.3)	3 (2.6)	19 (3.2)
Constipation	40 (5.7)	19 (6.4)	18 (6.6)	8 (3.8)	58 (5.0)	67 (5.4)	7 (5.8)	3 (2.6)	33 (5.6)
Dyspepsia	30 (4.2)	26 (8.7)	12 (4.4)	8 (3.8)	41 (4.3)	67 (5.4)	13 (10.8)	4 (3.5)	24 (4.1)
Vomiting	33 (4.7)	15 (5.0)	10 (3.6)	15 (7.2)	45 (4.7)	60 (4.8)	8 (6.7)	2 (1.7)	12 (2.0)
Hypoesthesia oral	5 (0.7)	6 (2.0)	16 (5.8)	14 (6.7)	48 (5.0)	54 (4.3)	0 (0.0)	0 (0.0)	2 (0.3)
Akathisia	17 (2.4)	2 (0.7)	11 (4.0)	22 (10.6)	51 (5.4)	53 (4.2)	5 (4.2)	17 (14.8)	30 (5.1)
Schizophrenia	28 (4.0)	29 (9.7)	6 (2.2)	13 (6.3)	22 (2.3)	51 (4.1)	5 (4.2)	8 (7.0)	2 (0.3)
Fatigue	17 (2.4)	9 (3.0)	12 (4.4)	6 (2.9)	34 (3.6)	43 (3.4)	10 (8.3)	0 (0.0)	23 (3.9)
Weight increased	3 (0.4)	0 (0.0)	6 (2.2)	4 (1.9)	33 (3.5)	33 (2.6)	4 (3.3)	1 (0.9)	45 (7.7)
Cough	15 (2.1)	13 (4.4)	6 (2.2)	4 (1.9)	19 (2.0)	32 (2.6)	4 (3.3)	1 (0.9)	6 (1.0)

Table 38 Adverse events by preferred term with an incidence ≥ 2.0% (short-term placebo-controlled trials, cohorts A1 and C1) (continued)

Adverse Event (Preferred Term) n (%)	Placebo (N=706)	Asenapine					Risperidone 3 mg BID (N=120)	Haloperidol 4 mg BID (N=115)	Olanzapine 5-20 mg QD (N=115)
		< 5 mg BID (N=298)	5 mg BID Fixed Dose (N=274)	10 mg BID Fixed Dose (N=208)	All 5-10 mg BID[a] (N=951)	All <5-10 mg BID[a] (N=1249)			
Increased appetite	5 (0.7)	5 (1.7)	7 (2.6)	0	24 (2.5)	29 (2.3)	0	0	26 (4.4)
Tremor	10 (1.4)	5 (1.7)	5 (1.8)	9 (4.3)	24 (2.5)	29 (2.3)	0	5 (4.3)	17 (2.9)
Dry mouth	11 (1.6)	4 (1.3)	8 (2.9)	3 (1.4)	25 (2.6)	29 (2.3)	5 (4.2)	2 (1.7)	47 (8.0)
Toothache	15 (2.1)	7 (2.3)	5 (1.8)	1 (0.5)	20 (2.1)	27 (2.2)	5 (4.2)	1 (0.9)	11 (1.9)
Back pain	20 (2.8)	10 (3.4)	5 (1.8)	2 (1.0)	17 (1.8)	27 (2.2)	6 (5.0)	3 (2.6)	11 (1.9)
Psychotic disorder	12 (1.7)	11 (3.7)	8 (2.9)	5 (2.4)	15 (1.6)	26 (2.1)	5 (4.2)	1 (0.9)	7 (1.2)
Dystonia	4 (0.6)	1 (0.3)	6 (2.2)	4 (1.9)	24 (2.5)	25 (2.0)	1 (0.8)	11 (9.6)	4 (0.7)
Pain in extremity	11 (1.6)	5 (1.7)	5 (1.8)	2 (1.0)	20 (2.1)	25 (2.0)	4 (3.3)	0	10 (1.7)
Hypertension	8 (1.1)	4 (1.3)	6 (2.2)	7 (3.4)	20 (2.1)	24 (1.9)	1 (0.8)	2 (1.7)	7 (1.2)
Parkinsonism	8 (1.1)	0	9 (3.3)	7 (3.4)	23 (2.4)	23 (1.8)	0	16 (13.9)	4 (0.7)
Mania	13 (1.8)	0	0	0	19 (2.0)	19 (1.5)	0	0	8 (1.4)

[a] fixed and flexible doses
Incidence of 2.0% or greater in the asenapine 5-10 mg BID group or all asenapine group
Risp=risperidone, Halo=haloperidol, Olan=olanzapine
Source: 2.7.4 Appendix Table 2.10.4.E.1

Safety data from long term placebo trials are presented in Tables 16 and 17.

Table 16

Table 48 Adverse events by preferred term with an incidence greater than or equal to 5.0% (long-term schizophrenia trials, cohort B1)

Adverse Event (Preferred Term) n (%)	Placebo (N=192)	Asenapine flexible dose 5-10 mg BID (N=2134)	Olanzapine flexible dose 5-20 mg QD (N=613)	Haloperidol flexible dose 2-8 mg BID (N=43)
Any adverse event	106 (55.2)	1695 (79.4)	498 (81.2)	37 (86.0)
Insomnia	26 (13.5)	407 (19.1)	94 (15.3)	9 (20.9)
Schizophrenia	31 (16.1)	279 (13.1)	71 (11.6)	6 (14.0)
Somnolence	2 (1.0)	267 (12.5)	68 (11.1)	2 (4.7)
Anxiety	21 (10.9)	259 (12.1)	64 (10.4)	2 (4.7)
Headache	2 (1.0)	232 (10.9)	74 (12.1)	8 (18.6)
Weight increased	7 (3.6)	216 (10.1)	170 (27.7)	3 (7.0)
Akathisia	3 (1.6)	174 (8.2)	23 (3.8)	12 (27.9)
Depression	5 (2.6)	171 (8.0)	45 (7.3)	3 (7.0)
Agitation	11 (5.7)	143 (6.7)	19 (3.1)	6 (14.0)
Sedation	2 (1.0)	133 (6.2)	55 (9.0)	2 (4.7)
Nausea	3 (1.6)	106 (5.0)	28 (4.6)	7 (16.3)
Parkinsonism	3 (1.6)	96 (4.5)	12 (2.0)	12 (27.9)
Nasopharyngitis	4 (2.1)	88 (4.1)	28 (4.6)	4 (9.3)
Fatigue	4 (2.1)	87 (4.1)	41 (6.7)	2 (4.7)
Influenza	3 (1.6)	78 (3.7)	28 (4.6)	4 (9.3)
Weight decreased	16 (8.3)	71 (3.3)	15 (2.4)	0
Asthenia	1 (0.5)	66 (3.1)	16 (2.6)	6 (14.0)
Vomiting	3 (1.6)	65 (3.0)	19 (3.1)	4 (9.3)
Constipation	1 (0.5)	63 (3.0)	17 (2.8)	3 (7.0)
Tremor	1 (0.5)	52 (2.4)	4 (0.7)	5 (11.6)
Delusion	11 (5.7)	36 (1.7)	8 (1.3)	0
Salivary hypersecretion	0	34 (1.6)	2 (0.3)	4 (9.3)
Dystonia	0	25 (1.2)	3 (0.5)	3 (7.0)
Pyrexia	1 (0.5)	24 (1.1)	5 (0.8)	3 (7.0)
Hallucination	13 (6.8)	18 (0.8)	4 (0.7)	0

Table 17

Table 54 Adverse events by preferred term with an incidence greater than or equal to 3.0% (long-term bipolar mania, cohort D1)

Adverse Event Category n (%)	Placebo (N=166)	Asenapine 5-10 mg BID flexible dose (N=433)	Olanzapine 5-20 mg QD flexible dose (N=229)
Any adverse event	119 (71.7)	337 (77.8)	189 (82.5)
Sedation	10 (6.0)	58 (13.4)	42 (18.3)
Insomnia	18 (10.8)	57 (13.2)	27 (11.8)
Headache	23 (13.9)	53 (12.2)	36 (15.7)
Somnolence	8 (4.8)	53 (12.2)	36 (15.7)
Dizziness	6 (3.6)	40 (9.2)	17 (7.4)
Depression	7 (4.2)	37 (8.5)	19 (8.3)
Weight increased	1 (0.6)	31 (7.2)	39 (17.0)
Mania	19 (11.4)	30 (6.9)	11 (4.8)
Nausea	11 (6.6)	28 (6.5)	8 (3.5)
Akathisia	9 (5.4)	25 (5.8)	21 (9.2)
Tremor	9 (5.4)	24 (5.5)	8 (3.5)
Anxiety	10 (6.0)	22 (5.1)	8 (3.5)
Constipation	7 (4.2)	21 (4.8)	11 (4.8)
Increased appetite	0	20 (4.6)	17 (7.4)
Agitation	10 (6.0)	20 (4.6)	9 (3.9)
Hypoaesthesia oral	1 (0.6)	20 (4.6)	3 (1.3)
Vomiting	3 (1.8)	19 (4.4)	1 (0.4)
Parkinsonism	3 (1.8)	18 (4.2)	5 (2.2)
Dyspepsia	4 (2.4)	18 (4.2)	9 (3.9)
Fatigue	5 (3.0)	17 (3.9)	19 (8.3)
Diarrhoea	15 (9.0)	16 (3.7)	9 (3.9)
Suicidal ideation	3 (1.8)	14 (3.2)	4 (1.7)
Arthralgia	0	14 (3.2)	4 (1.7)
Upper respiratory tract infection	1 (0.6)	13 (3.0)	3 (1.3)
Dry mouth	6 (3.6)	13 (3.0)	25 (10.9)
Toothache	3 (1.8)	13 (3.0)	5 (2.2)
Nasopharyngitis	2 (1.2)	12 (2.8)	12 (5.2)
Cough	6 (3.6)	12 (2.8)	4 (1.7)
Back pain	6 (3.6)	10 (2.3)	7 (3.1)
Vision blurred	1 (0.6)	7 (1.6)	8 (3.5)

In the combined phase II/III safety data (cohort E1), the most commonly reported adverse events with an incidence greater than or equal to 2.0% were insomnia (17%), headache (13%) somnolence (11%) and anxiety (10.4%) in the pooled asenapine group (<5 mg and 5-10 mg BID).

Serious adverse event/deaths/other significant events

In the combined phase II/III safety data (cohort E1), serious adverse events were reported in 16% of asenapine treated subjects as compared to 10 % in the placebo group and 12 % in the olanzapine

group. Four % of asenapine treated subjects experienced an SAE related to treatment, as judged by the investigator, most commonly psychiatric related AEs.
The rate of serious adverse events was consistently higher compared to olanzapine. Of the 6 comparisons with olanzapine (3 for each indication) all favoured olanzapine (lower rates). The differences in the schizophrenia studies reached statistical significance.

In cohort E1, there were 19 deaths (0.5%) in the pooled asenapine group. Four deaths (0.1%) were considered related to study medication, as judged by the investigator: a neonatal death that occurred in a 37 year old female who became pregnant during the trial (A7501005) and three subjects who completed suicide (25543, A7501004 and A7501008/A7501009) including one subject with intentional overdose not related to asenapine (A7501008/A7501009).

Laboratory findings

Few subjects (<0.5%) reported haematogical related AEs. In all asenapine groups, the most commonly reported AEs (0.2-0.3%) was anaemia. None of these reports were considered treatment related and none led to discontinuation. Some cases of white blood cells decreased (n=4, 0.1%) leukopenia (n=4, 0.1%); neutropenia (n=2, 0.1%) and granulocytopenia (n=1, 0.1%) were also reported. None of these reports were considered treatment related, one subject discontinued due to these related AEs.

The incidence of blood CPK increased reported as an adverse event was 1.2% for the asenapine BID 5-10 mg group versus 1.2% for olanzapine.

The incidence of adverse events related to electrolyte abnormalities for asenapine was less than or equal to 0.3% with hypokalaemia having an incidence of 0.3% for the asenapine 5-10 mg BID group. One subject discontinued due to this AE. The incidence of adverse events related to renal function was 0.1% for asenapine group with one subject experiencing acute renal failure that led to discontinuation.

The incidence of transaminases (ALT increased) for asenapine 5-10 mg BID group was 1.7% versus 3.3% for olanzapine group. These AEs were transient.

The occurrence of adverse events related to lipid metabolism disorders (HLGT) was 0.8% for asenapine 5-10 mg BID group versus 1.4% for olanzapine group. These AEs led to discontinuation for one subject in the asenapine group (n=1, increased triglycerides) versus 3 subjects in the olanzapine group (n=1, elevated cholesterol; n=2, hyperlipidaemia).

The incidence of blood glucose increased was 1.1% for asenapine 5-10 mg BID group versus 1.6% for olanzapine group.

There were some reported adverse events related to prolactin abnormalities (<1% of all menstrual cycle and uterine bleeding disorders), the incidences were comparable among the treatment groups. One subject on asenapine discontinued due to amenorrhea. In the combined Phase II/III study population (cohort E1), the proportions of asenapine subjects in the 5-10 mg BID group with shifted to elevated prolactin levels (37%) was 37% for asenapine group versus 46% for olanzapine group. In the short-term trials (cohorts A1 and C1), the haloperidol and risperidone groups had a proportion of subjects with elevations in prolactin levels above the reference range of 50% and 85%, respectively at endpoint.

A positive effect for asenapine was observed on the QTc interval with no dose-response relationship at 5, 10, 15, and 20 mg of asenapine(study A7501001). The difference from placebo in time-matched change from baseline in QTc at tmax was statistically significant for both 10 mg BID dose regimen of asenapine and quetiapine on Day 16. Exposure-response modeling showed a mild positive effect on the QTc interval. The point estimates of QTcF prolongation associated with mean steady state plasma asenapine Cmax values were less than 5 msec for all doses studied versus 7-8 msec for quetiapine. The upper bound of both the 90% CI and 95% CI of the asenapine effect was less than 8 msec for all asenapine dose groups. In the combined phase II/III safety data (cohort E1), incidences of ECG QT prolongation and syncope were 0.7 % and 0.4%, respectively, for both asenapine and olanzapine groups.

Mean sitting heart rate was increased by 1.0 beats/min for asenapine group versus 1.9 beats/min for olanzapine group. The haloperidol group had a mean decrease in sitting heart rate (-1.9 beats/min). No relevant changes in sitting systolic or diastolic BP were observed in the asenapine group.

Other safety findings

Extrapyramidal symptoms (EPS)

In short term schizophrenia trials (cohort A1), 13.6% of the asenapine 5-10 mg BID group had at least one extrapyramidal symptom and a dose-response relationship was apparent. The incidence at < 5 mg BID. (6.4%) was comparable to placebo (7.8%) while at the therapeutic doses the incidence was greater (10.9% at 5 mg BID and 18.3% at 10 mg BID). An excess for asenapine 5-10 mg BID over placebo was seen for most of the EPS categories i.e. akathisia (6.3% versus 2.6%), dystonia (2.6% versus 0.8%), and parkinsonism (5.6% versus 2.8%).

The incidence of akathisia showed a potential dose relationship: placebo 2.6%, asenapine < 5 mg BID fixed dose 0.7%, asenapine 5 mg BID fixed dose 4.0%, and asenapine 10 mg BID. fixed dose 10.6%. There was also an increasing trend with the higher dose regimens of asenapine for events in the category of parkinsonism: placebo 2.8%, asenapine < 5 mg BID. fixed dose 2.0%, asenapine 5 mg BID fixed dose 5.1%, and asenapine 10 mg BID fixed dose 7.7%. There was no dose relationship for the EPS categories of dyskinesia, dystonia, or "unspecified".

Highest percentage of subjects with extrapyramidal symptoms was reported in the haloperidol group (39.1%). For risperidone and olanzapine, the percentages were 7.5% and 8.8%, respectively.

The asenapine 10 mg BID group did show a greater percentage of subjects with Barnes Akathisia Rating Scale (BARS) score ≥2 (15.5%) compared to placebo (9.0%).

The proportion of subjects prescribed EPS medication in the asenapine 5-10 mg BID group was 11.2% versus 8.2%, 9.3%, and 10.0% for placebo, olanzapine and risperidone groups, respectively. The proportion of subjects prescribed EPS medication was 41.7% for the haloperidol group.

In long term schizophrenia trials (cohort B1), incidence of EPS adverse events in the asenapine group was 16% versus 5% and 8% for the placebo and olanzapine groups. This incidence was 60% for the haloperidol group. Main symptoms were akathisia, parkinsonism, dystonia and dyskinesia.

In short term bipolar mania trials (cohort C1), the percentage of asenapine treated subjects with at least one extrapyramidal symptom was 10.0% versus 4.4% and 9.4% for placebo and olanzapine groups, respectively. The incidence of discontinuations due to EPS was 0.5% for placebo, 1.3% for asenapine, and 0.3% for olanzapine. In the EPS Rating Scales, the incidence of subjects meeting the

SARS (Simpson-Angus Rating Scale) threshold was greater for asenapine as compared to both placebo and olanzapine groups. A greater proportion of subjects randomized to asenapine received medications for EPS (8.7%) compared to placebo and olanzapine (5.4% and 5.8%, respectively).

In long term bipolar mania trials (cohort D1), the incidence of EPS adverse events for asenapine was 15.7% versus 12.7 % and 16.2% for placebo and olanzapine groups, respectively. A greater proportion of asenapine subjects received medications for EPS (10.4%) compared to olanzapine (8.3%).

In the combined phase II/III safety data (cohort E1), there were 14 cases reported cases of tardive dyskinesia in subjects treated with asenapine, resulting in an incidence of 0.4% (incidence 1.0 per 100 patient-years). Ten of the 14 were considered at least possibly related to study drug by the investigators. One case in the asenapine 5-10 mg BID group led to permanent discontinuation and 6 of the 14 cases were not resolved at the end of the trial.Two cases occurred in the placebo group (0.2%, incidence 1.4 per 100 patient-years), one in the haloperidol group (0.9%, incidence per 100 exposure years = 2.9) and none in the risperidone or olanzapine groups.

Neuroleptic malignant syndrome (NMS)

In total there were three NMS cases as judged by the investigators. All three subjects had received asenapine 5-10 mg BID and all were considered SAEs related to study treatment. One was assessed as mild and two as severe. All three subjects fully recovered. There were no cases of NMS reported in either of the active comparator groups.

Suicidality

An analysis of the InterSePT Scale for Suicidal Thinking (ISST) was conducted in a number of cohorts. Overall, no or small decreases were observed in the mean total ISST score across all treatment groups at endpoint.

Seizures

There were 13 reported cases of seizures in total, one in the asenapine < 5 mg BID group (0.3%), seven in the asenapine 5-10 mg BID (0.2%), one in the haloperidol group (0.9%), and four in the olanzapine group (0.4%). Ten cases were considered SAEs. Eight of the 13 seizures led to discontinuation, four in the asenapine 5-10 mg BID group (0.1%) and four in the olanzapine group (0.4%). The incidence of seizures for the pooled asenapine group per 100 patient exposure years was 0.58, versus 0.7 for olanzapine and 2.89 for haloperidol.

Cerebrovascular adverse events

The incidence of cerebrovascular accidents (excluding Transient Ischaemic Attacks= TIA) during asenapine treatment in patients included in phase II/III trials was 0.068 per 100 patient exposure years. Two subjects treated with asenapine experienced a serious cerebrovascular event (haemorrhagic stroke and TIA, respectively) both had known risk factors for developing these conditions.

Weight gain

Weight increase was reported as an adverse event in 8.4% of subjects in the asenapine 5-10mg BID dose group compared to 1.0% for placebo, 2.6% for haloperidol, 5% for risperidone and 19.5% for olanzapine. Mean body weight change was +0.8 kg in the asenapine 5-10 mg BID group compared with a minimal change for placebo and +3.5 kg for olanzapine. The proportion of subjects with clinically significant weight gain (≥ 7 % weight gain from baseline at endpoint) in the short-term schizophrenia trials was 5.3 % for asenapine compared to 2.3 % for placebo. The proportion of

subjects with clinically significant weight gain (≥ 7 % weight gain from baseline at endpoint) in the short-term bipolar mania trials was 6.5 % for asenapine compared to 0.6 % for placebo.

Orthostatic hypotension
In the pooled asenapine group, the incidence of dizziness and postural dizziness was relatively high (18.8% and 8.1%, respectively). Pre-syncope, syncope, and vasovagal syncope occurred with an incidence of 3.5%, 1.5% and 1.1%, respectively. No dose-relationship was observed for these events.

In the combined Phase II/III study population, the AE with the highest incidence in the asenapine 5-10 mg BID group was dizziness (5.5%) versus 5.4% for olanzapine group. Dizziness was reported with an incidence 18.8% in healthy volunteers studies.

The incidences for orthostatic hypotension and syncope in both the asenapine 5-10 mg BID and olanzapine groups were 0.4% each. In elderly subjects, the incidence of orthostatic hypotension was 4.1% compared to 0.3% in the combined Phase II/III study population.

Rhabdomyolysis
Three cases were reported in the asenapine treated subjects. All were reported as SAEs and two cases led to discontinuations.

Safety in special populations

The population pharmacokinetic analysis of Phase II/III data showed moderately decreasing clearance of asenapine with increasing age. There was a 26% increase in AUC between 20 and 60 year old patients. Subgroup analyses of the impact of age on the safety of asenapine for the combined population all Phase 2/3 data were performed but the number of subjects aged 65 years and older was insufficient for a meaningful comparison. Patients under 18 years of age were not studied in the clinical trial programme.

Patients with hepatic and renal impairment were not studied in the Phase II / III studies.

No marked differences were observed with respect to race in the adverse events that are potentially associated with asenapine at the recommended doses of 5-10 mg BID. With respect to gender, a slightly greater proportion of females had elevated prolactin levels, in both active treatment comparator groups.

Safety related to drug-drug interactions and other interactions

There are no reports of AEs relating to drug interactions in the phase II/III clinical trials.

Discontinuation due to adverse events

In the combined phase II/III safety data (cohort E1), discontinuation due to AEs (with an incidence equal or greater than 1%) was reported in 17% of asenapine subjects. These AEs were related to psychiatric disorders, most commonly schizophrenia (3.4%) and depression (1.5%).

Post marketing experience

Not applicable

3.4.9 Discussion on clinical safety

The majority of the safety database included patients with schizophrenia.

The most common adverse events associated with asenapine 5-10 mg BID were sedation, somnolence, extrapyramidal effects, oral hypoaesthesia, increased appetite and weight gain. All these effects except oral hypoaesthesia are well known AEs of the antipsychotic drug class. The applicant has provided a satisfactory justification that the incidence of oral hypoaesthesia is due to the local anaesthetic activity. This seemed unlikely to be of major clinical concern although there is probably some risk of oral injury e.g. by inadvertent biting. The amount of local anaesthetic is insufficient to cause concerns relating to impairment of protective airway reflexes.

There were also reports of other important AEs known for this class of drug including Neuroleptic Malignant Syndrome, seizures, orthostatic hypotension, dysphagia, body temperature regulation. Warnings related to these AEs are reflected in the SPC. Particularly, if a patient develops signs and symptoms indicative of NMS, asenapine must be discontinued.

The incidence of psychiatric serious adverse events was higher in the asenapine groups as compared to both placebo and olanzapine groups. Particularly, the incidence of "schizophrenia" as an SAE in the asenapine group was 4.8%versus 2.3% and 2.4% for the placebo and olanzapine groups, respectively. The incidence of depression (1.2%) was also greater than for placebo (0.5%), although comparable to olanzapine (1.1%) whereas mania was more commonly reported in the placebo group (2.3 versus 1.0%).

Dry mouth was reported for asenapine (2.6%) but less frequently than for olanzapine (8%).

There were some reported adverse events related to prolactin abnormalities (<1% of all menstrual cycle and uterine bleeding disorders), the incidences were comparable among the treatment groups.

Overall there is no clear signal of a causal relationship of asenapine to suicidality. However, a warning related to this AE is reflected in SPC as a suicide attempt is inherent in psychotic illnesses including bipolar I disorder and close supervision of high-risk patients is required.

Asenapine induced extrapyramidal symptoms in a proportion of patients with schizophrenia in the short-term and long term studies. The overall incidence of EPS in subjects treated with asenapine was slightly higher than in the risperidone or olanzapine groups, but significantly lower than in the haloperidol group. The excess incidence over olanzapine was not apparent in the bipolar I disorder studies. A warning related to tardive dyskinesia has been reflected in the SPC.

Asenapine may lead to substantial weight gain, particularly in subjects who are not overweight at baseline. Close monitoring of this AE was recommended by the CHMP.

Asenapine has a mild effect on QTc at the intended therapeutic doses of 5 to 10 mg BID. A warning for patients with known cardiovascular disease or family history of QT prolongation or using medicinal products thought to prolong QT interval has been reflected in the SPC.

A number of cerebrovascular events have been reported in patients treated with asenapine. There was no signal of an excess of cerebrovascular risk associated with asenapine. However, in line with other antipsychotic drugs of the class, a warning related to elderly patients with dementia-related psychosis has been reflected in the SPC.

3.4.10 Conclusions on the clinical safety

Based on data collected to date, the safety profile of asenapine appeared favourable. From the safety database all the adverse reactions reported in clinical trials have been included in the SPC.

2.5. Pharmacovigilance

2.5.1. Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.5.2. Risk management plan

The MAA submitted a risk management plan (Table 18).

Table 18 Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimization activities
Important identified risks		
EPS, inclusing tardive dyskinesia	Routine pharmacovigilance practice	• Warning in section 4.4 of the SPC on tardive dyskinesia that the onset of extrapyramidal symptoms is a risk factor for tardive dyskinesia and that discontinuation should be considered when symptoms of tardive dyskinesia appear in a patient • Akathisia, dyskinesia, dystonia, parkinsonism and extrapyramidal disorder are included in section 4.8 of the SPC
Somnolence and sedation	Routine pharmacovigilance practice	• Warning in section 4.7 of the SPC that patients should be cautioned about operating machinery, including motor vehicles • Sedation and somnolence are included in section 4.8 of the

		SPC
Weight gain	Routine pharmacovigilance practice	• Weight gain and increased appetite are included in section 4.8 of the SPC
Increased exposure in patients with severe hepatic impairment	Routine pharmacovigilance practice	• Statement in section 4.2 of the SPC that caution is advised in patients with moderate hepatic impairment and that asenapine is not recommended in patients with severe hepatic impairment • Warning in section 4.4 of the SPC that asenapine is not recommended in patients with severe hepatic impairment • Statement in section 5.2 of the SPC that the pharmacokinetics of asenapine were similar among subjects with mild, moderate or no hepatic impairment. In subjects with severe hepatic impairment, a 7-fold increase in asenapine exposure was observed.
Oral hypoaesthesia	Routine pharmacovigilance practice	• Oral hypoaesthesia is included in section 4.8 of the SPC
Swelling of tongue and throat	Routine pharmacovigilance practice	• Swollen tongue is included in section 4.8 of the SPC
Increased liver transaminases and GGT	Routine pharmacovigilance practice	• Alanine aminotransferase increased and Aspartate aminotransferase increased are included in section 4.8 of the SPC
Orthostatic hypotension in the elderly	Routine pharmacovigilance practice	• Warning in section 4.4 of the SPC that elderly patients are particularly at risk for orthostatic hypotension and that Sycrest should be used with caution in elderly patients • Orthostatic hypotension in the elderly is included in section 4.8 of the SPC
Important potential risks		
NMS	Routine pharmacovigilance practice	• Warning in section 4.4 of the SPC that if a patients develops signs and symptoms indicative of NMS, asenapine must be discontinued • NMS is included in section 4.8 of the SPC

Rhabdomyolysis	Routine pharmacovigilance practice	• Rhabdomyolysis is included in section 4.8 of the SPC
Seizures	Routine pharmacovigilance practice	• Warning in section 4.4 of the SPC that asenapine should be used with caution in patients who have a history of seizure disorder or have conditions associated with seizures. • Seizure is included in section 4.8 of the SPC
Hyperprolactinaemia	Routine pharmacovigilance practice	• Warning in section 4.4 of the SPC that increases in prolactin levels were observed in some patients with asenapine and that there were few adverse reactions reported in clinical trials related to abnormal prolactin levels reported • Sexual dysfunction, amenorrhoea, gynaecomastia and galactorrhoea are included in section 4.8 of the SPC
Cardiovascular effects (QT prolongation and orthostatic hypotension)	Routine pharmacovigilance practice	• Warning in section 4.4 of the SPC that caution should be exercised when asenapine is prescribed in elderly patients and in patients with known cardiovascular disease or family history of QT prolongation, and in concomitant use with other medicinal products thought to prolong the QT interval • Warning in section 4.4 of the SPC that asenapine should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions that predispose the patient to hypotension • Statement in section 4.5 of the SPC that Sycrest may enhance the effects of certain antihypertensive agents. • Orthostatic hypotension, hypotension, dizziness, syncope, sinus bradycardia, electrocardiogram QT prolonged are included in section 4.8 of the SPC
Neutropenia	Routine pharmacovigilance practice <u>Additional pharmacovigilance</u>	• Neutropenia is included in section 4.8 of the SPC

	activities: Active follow-up will be performed for reports indicative of neutropenia on a case by case basis by means of a targeted questionnaire. Detailed reporting will be included in each scheduled PSUR.	
Metabolic effects other than weight gain	Routine pharmacovigilance practice	• Warning in section 4.4. of the SPC that appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus • Hyperglycaemia is included in section 4.8 of the SPC
Overdose	Routine pharmacovigilance practice	• Information included in section 4.9 of the SPC about the possible signs and symptoms of overdose and recommendations for treatment
Non compliance with the 10-minute requirement for no food or fluids after sublingual administration	Routine pharmacovigilance practice	• Recommendation in sections 4.2, 4.5 and 5.2 of the SPC that eating and drinking should be avoided for 10 minutes after administration
Allergic reactions		• Contraindication in section 4.3 of the SPC for hypersensitivity to the active substance or to any of the excipients.
Important missing information		
Use during pregnancy and lactation	Routine pharmacovigilance practice	• Recommendation in section 4.6 of the SPC that asenapine should not be used during pregnancy unless clearly necessary and only if the potential benefit outweighs the potential risk to the foetus • Recommendation in section 4.6 of the SPC that women receiving asenapine should not breast feed

Misuse for illegal purposes	Routine pharmacovigilance practice	None
Off-label use	Routine pharmacovigilance practice	• Statement in section 4.1 of the SPC that Sycrest is indicated for the treatment of moderate to severe manic episodes associated with bipolar I disorder in adults
Off-label paediatric use	Routine pharmacovigilance practice Additional pharmacovigilance activities: Studies for the indications of Schizophrenia and Bipolar Mania in paediatric patients will be initiated as per Paediatric Investigation Plan.	• Section 4.2 of the SPC states that safety and efficacy in paediatric patients have not been established and that no recommendation on a posology can be made

To further investigate the safety profile of asenapine in clinical practice, the applicant has agreed to provide protocols for post-authorisation safety studies as a post-approval commitment.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*

2.5.3. Benefit-risk balance

2.5.3.1. Benefits

2.5.3.1.1. Beneficial effects

SCHIZOPHRENIA

In study 041004, twice daily dose of asenapine 5 mg was studied versus twice daily doses of risperidone 3 mg and placebo. The tested dose demonstrated statistically significant difference over placebo with a change from baseline to week 6 in PANSS total score of -15.86 for asenapine versus -5.27 for placebo (p=0.0024).

In study 041023, treatment with asenapine 5 mg BID resulted in a statistically significantly greater mean change from baseline to week 6 in the PANSS total score of -16.2 for asenapine versus -10.7 for placebo (p=0.0290).

In study A7501012, there was a statistically significant difference in favour of asenapine between the treatment groups with respect to the time to relapse or impending relapse (p<0.0001) based on a log-rank test. The time to relapse was longer in the asenapine group compared with the placebo group. Asenapine was also shown to be more effective than placebo in prolonging the time to early termination for any reason and the time to relapse or impending relapse.

BIPOLAR I DISORDER

In study A7501004, Y-MRS total scores were statistically significantly improved in the asenapine and olanzapine treatment groups compared with the placebo treatment group (p=0.0065 for asenapine versus placebo and p<0.0001 for olanzapine versus placebo). The mean change from baseline to Day 21 was -11.5, -7.8, and -14.6 for the asenapine, placebo, and olanzapine treatment groups, respectively. Mean changes from baseline in the CGI-BP, severity of mania also showed statistically significant improvements in the asenapine group over placebo at Day 21.

In study A7501005, Y-MRS total scores were statistically significantly improved in the asenapine and olanzapine treatment groups compared with the placebo treatment group (p<0.0001 for both comparisons with placebo). The mean change from baseline to Day 21 was -10.8, -5.5, and -12.6 for the asenapine, placebo, and olanzapine treatment groups, respectively. Mean changes from baseline in the CGI-BP, severity of mania also showed statistically significant improvements in the asenapine group over placebo at Day 21. At Day 21, 42.3% of subjects in the asenapine group were responders compared with 25.2% in the placebo group. This treatment difference was statistically significant (p=0.0049). A statistically significant greater percentage of subjects in the olanzapine group were responders compared with the placebo at day 21(p<0.0001). At Day 21, 40.2% of subjects in the asenapine group were remitters compared with 22.3%in the placebo group. This treatment difference was statistically significant (p=0.0020). A statistically significant greater percentage of subjects in the olanzapine group were remitters compared with the placebo group at Day 21 (p=0.0041).

In study A7501006, a 9-week, olanzapine-controlled, double-blind, double-dummy, multicentre, parallel group, continuation trial, both the asenapine and olanzapine groups showed improvement on the primary efficacy endpoint. The mean change from baseline to Week 12 on the Young-Mania Rating Scale (Y-MRS) was -27.3 for the asenapine treatment group and -23.7 for the olanzapine treatment group.

2.5.3.1.2. Uncertainty in the knowledge about the beneficial effects.

SCHIZOPHRENIA

With respect to phase II short-term trials (041002, 041013 and 041004), no dose response could be established.

In study 041021, no statistically significant differences in the mean changes from baseline to week 6 in the PANSS total score were observed between placebo (-11.1) and asenapine 5 mg (-14.5) or asenapine 10 mg BID (-13.4). Mean change from baseline to week 6 on PANSS total score for placebo, asenapine 5 mg BID, asenapine 10 mg BID and olanzapine 15 mg QD were -11.1 (1.64), -14.5 (1.59), -13.4 (1.63), -16.5 (1.64), respectively. Compared with placebo, olanzapine treatment resulted in a statistically significantly greater mean change from baseline in the PANSS total score (-16.5, p=0.0168).

In study 041023, no statistically significant difference between asenapine 10 mg BID and placebo was observed in the mean change from baseline to week 6 in the PANSS total score (placebo [-10.7] versus asenapine 10 mg BID [-14.9], adjusted p=0.0680) using the LOCF method. Analyses of the primary endpoint using OC and MMRM analyses showed a statistically significant difference in favor of asenapine 10 mg BID [-18.5] compared with placebo [-14.0] was observed (p=0.0167).

In study 041022, no statistically significant differences (p>0.05) in the mean changes from baseline to week 6 in the PANSS total score were observed between asenapine (-9.4) and placebo (-9.9) or

between olanzapine (-11.5) and placebo (-9.9). Furthermore, no statistically significant (p>0.05) differences between asenapine and placebo or between olanzapine and placebo were observed in the mean changes from baseline to endpoint in any secondary efficacy or health outcomes measures.
Results from a retrospective meta-analysis (including short term phase III studies) was suggestive of efficacy (for PANSS total score: 2.7 points greater for asenapine versus placebo (p=0.021; 95% CI -5.0 to -0.4); for responder rates: OR=1.9, 95% CI 1.3 to 2.6; p<0.001). However, the pooled 95% CI was very close to zero. Adding in the data from the phase 2 study 041004 improved the result, with the lower bound improving to -1.5 and the p-value becoming p=0.0011. But as this combines the hypothesis generating and the pivotal data there is a higher hurdle to meet. Ideally the phase 3 data alone should provide compelling evidence of efficacy.

In the long term placebo-controlled, double-blind trial A7501012, asenapine was statistically significantly superior to placebo (p<0.001 on log-rank test). If short term benefit could be established this would provide support for long-term treatment. However, in the absence of short-term benefit having been demonstrated the study is of limited relevance.

In study A25517, statistically significant difference (p<0.001) in the mean change from baseline to week 52 in the PANSS total score was observed in favour of olanzapine. At baseline, the PANSS total scores were 92.1 for both asenapine and olanzapine groups. At week 52, the PANSS total scores were 71.0 and 64.6 for asenapine and olanzapine groups, respectively (difference: 6.54, 95% CI: 3.87-9.21).

BIPOLAR I DISORDER
No dose response studies were conducted.

In study A7501004, 42.6% of subjects in the asenapine group were responders compared with 34.0% in the placebo group at week 3. However, this treatment difference was not statistically significant (p=0.1951). A statistically significant greater percentage of subjects in the olanzapine group were responders compared with the placebo group (p=0.0011) at week 3. Additionally, 35.5% of subjects in the asenapine group were remitters compared with 30.9% in the placebo group and this treatment difference was also not statistically significant (p=0.5033).A statistically significant greater percentage of subjects in the olanzapine group were remitters compared with the placebo group at Day 21 (p=0.0159).

In study A7501008, analyses using several methods for handling missing data (LOCF, OC, MMRM) showed different results. Overall, the CHMP concluded that non-inferiority of asenapine versus olanzapine was not shown.

2.5.3.2. Risks

2.5.3.2.1. Unfavourable effects

The incidences of the most common AEs were generally comparable to those seen for olanzapine except for sedation (but not somnolence) which seemed to be more common with olanzapine (15.1%), and "hypoaesthesia oral". The applicant has provided a satisfactory justification that the incidence of oral hypoaesthesia is due to the local anaesthetic activity. This seemed unlikely to be of major clinical concern although there is probably some risk of oral injury e.g. by inadvertent biting. The amount of local anaesthetic is insufficient to cause concerns relating to impairment of protective airway reflexes.

The overall AE rates were not substantially different from olanzapine. However the rates of severe adverse events, serious adverse events and adverse events leading to discontinuation were consistently higher. There was no indication of a different safety profile in the two patient populations. The severe / serious / discontinuation AEs were predominantly in the psychiatric, nervous system and gastrointestinal (GI) system organ class (SOC). The excess over olanzapine is seen to lie almost entirely in the psychiatric SOC; there is a weak trend at best to an excess in the nervous system and none at all in the GI SOC.

Differences in psychiatric adverse event rates appear to become apparent in particular with long term treatment. This is of potential concern as treatment is often required in the long term especially in schizophrenia where treatment is often required life long. However it is agreed that a substantial proportion of reported serious psychiatric adverse events are likely to reflect hospitalizations and/or other events due to exacerbations of the illness being treated. As asenapine showed consistently less efficacy than olanzapine in the clinical trials it seemed plausible that the excess incidence in severe / serious / discontinuation AEs is attributable to those efficacy differences (e.g increased hospitalisations) rather than to a safety issue per se.

Asenapine shows clinically important advantages over olanzapine in terms of weight gain and effects on metabolic laboratory parameters. However, it may lead to substantial weight gain, particularly in subjects who are not overweight at baseline. Furthermore, olanzapine is recognised as being particularly problematic in this regard and most atypical antipsychotics are superior to it. The profile of asenapine in terms of weight gain appears broadly similar to risperidone.

The incidence of extrapyramidal symptoms (EPS) in subjects treated with asenapine at therapeutic doses (5-10mg BID) was slightly higher than in the risperidone or olanzapine groups. All of the atypical antipsychotics studied produced substantially less EPS than haloperidol which is to be expected.

Dry mouth was reported for asenapine (2.6%) but less frequently than for olanzapine (8%).

For prolactin there was no clear difference from olanzapine but asenapine caused significantly less elevation of prolactin levels than risperidone and haloperidol.

Asenapine seemed to be benign in terms of QT prolongation which is an advantage over sertindole and ziprasidone.

2.5.3.2.2. Uncertainty in the knowledge about the unfavourable effects

The safety profile is generally in line with that known for this class of drug. Further data are required from the risk management programme to characterise less common undesirable effects but no substantial issues are identified at the present time.

2.5.3.3. Benefit-risk balance

2.5.3.3.1. Importance of favourable and unfavourable effects

Atypical antipsychotics have an important role in treating very serious psychiatric illnesses but also have substantial potential to cause harm. The various products differ from each other to varying degrees in their safety and efficacy profiles. Certain products, including clozapine and probably olanzapine, are more efficacious than others but the additional efficacy comes at the cost of additional

safety problems. The choice of a particular atypical antipsychotic therefore needs to be tailored to the requirements of the individual patient. A new atypical antipsychotic may have a positive risk-benefit if it has safety and/or tolerability advantages over other available agents, even if there is a disadvantage in terms of efficacy. In this case the value of the safety advantage needs to be weighed against the cost in terms of lost efficacy.

2.5.3.3.2. Benefit-risk balance

SCHIZOPHRENIA

The evidence from the phase 3 short term studies is weak, with inconsistent results and questionable clinical relevance. Only 1 out of 5 comparisons to placebo achieved statistical significance. In the numerous comparisons between olanzapine and asenapine the efficacy of sublingual asenapine appeared consistently to be inferior to that of olanzapine although this is probably also true for most other antipsychotics (and olanzapine has important disadvantages in terms of safety and tolerability profiles). In a meta-analysis of the three pivotal phase 3 trials the overall treatment effect of -2.7 points difference from placebo was statistically significant, but at a level that falls short of compelling ($p=0.021$; 95% CI -5.0 to -0.4). The lower confidence limit was not far from zero. This level of evidence from the meta-analysis is considered not extreme enough to be convincing. Adding in the phase 2 data did improve the result, with the lower bound improving to -1.5 and the p-value becoming $p=0.0011$. But as this combined the hypothesis generating and the pivotal data there is a higher hurdle to meet. Ideally the phase 3 data alone should provide compelling evidence of efficacy.

The meta-analysis of PANSS 30% responders did not seem to greatly strengthen the equivocal findings on the primary endpoint. The confidence interval for the phase III meta-analysis for the difference between treatments did not exclude zero, though the trend favoured asenapine. Even if the phase II study 041004 is added in the lower bound is only 0.1%.

The clinical significance of the difference from placebo in mean PANSS score remains doubtful. The mean treatment effect seen for Sycrest of 2.7 points on the PANSS (3.7 if the phase 2 study 041004 is included) was substantially less than the comparable results from the phase 3 trials for currently approved products. The responder analyses for the combined Phase 3 population were also unconvincing.

There was a total absence of clinical evidence that the proposed upper dose of 10mg is superior to 5mg; indeed the trends tend to favour 5mg over 10mg.

Asenapine was shown to be inferior to Olanzapine in the long-term trial 25517. As the trial did not include a placebo group it cannot provide any evidence of efficacy.

In the relapse prevention trial A7501012 there was a statistically significant benefit for staying with asenapine compared to staying on placebo ($p<0.001$ on log-rank test). If short term benefit can be established this would provide support for long-term treatment, but as short-term benefit has not been

demonstrated the study is of limited relevance. The extensions to the phase III short-term trials lacked the power to draw any conclusions on the comparative efficacy of the two treatments and the lack of a placebo control in Negative Symptoms trial 25543 meant that it could not provide evidence of efficacy.

In conclusion there is insufficient evidence of short term efficacy to support the schizophrenia indication.

Given that the overall safety profile appeared comparable to other approved antipsychotics in this indication, the benefit-risk balance for asenapine is negative.

BIPOLAR I DISORDER

The efficacy in reducing manic symptoms over 3 weeks was demonstrated. However, the clinical significance of the treatment effect of Sycrest in the short term studies A7501004 and A7501005 appeared modest (especially in the former) and Sycrest appeared to have inferior efficacy to Olanzapine. In the company's responses the size of the treatment effect was shown to be in line with responses seen for other approved atypical antipsychotics, and the results were also comparable to those from the phase 3 pivotal trials supporting the marketing authorisation applications for other atypical antipsychotics. The fact that olanzapine seemed to show greater efficacy is not a barrier to approval as olanzapine probably has greater efficacy than a number of atypical antipsychotics approved for the treatment of bipolar I disorder but also has major safety and tolerability disadvantages.

Maintenance of effect during the episode has been demonstrated. The original analysis of A7501006 was inadequate as it did not represent a comparison of randomised groups. In the re-presentation of the 12-week data accounting for all randomised patients, non-inferiority to olanzapine was not formally shown. It is not considered a requirement to achieve this as olanzapine probably has superior efficacy to most other atypical antipsychotics. Superiority to a putative placebo was shown indirectly but reasonably convincingly and this is considered sufficient. Maintenance of effect is therefore considered to be adequately shown.

The benefit of combination treatment with a mood-stabiliser has been sufficiently established.

The efficacy for asenapine can be considered to be adequately demonstrated as a treatment for Bipolar I disorder.

The overall safety profile appeared comparable to other approved antipsychotics in this indication.

In conclusion, the benefit-risk balance for asenapine is positive.

However, the optimal dosing regimen has not been established as no dose finding studies have been conducted. The company has provided a commitment to perform a dose finding study as a post-approval commitment.

2.5.3.4. Discussion on the benefit-risk balance

SCHIZOPHRENIA

The CHMP considered the risk-benefit of asenapine in "the treatment of schizophrenia in adults" is negative for the following reasons:

- There is insufficient evidence of efficacy from short term trials.
- The magnitude of the claimed efficacy is of doubtful clinical significance.
- In the absence of adequate evidence of efficacy from short term trials, the long term trials cannot provide meaningful evidence of efficacy.
- The long term comparison to olanzapine did not provide evidence of efficacy.

BIPOLAR I DISORDER

The CHMP considered the risk-benefit of asenapine is positive, provided the indication is as follows: "treatment of moderate to severe manic episodes associated with bipolar I disorder in adults". A dose finding study will be carried out by the applicant as part of post-approval commitment.

2.5.3.5. Risk management plan

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.
- no additional risk minimisation activities were required beyond those included in the product information.

2.5.4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by majority decision that the risk-benefit balance of Sycrest in the treatment of moderate to severe manic episodes associated with bipolar I disorder in adults was favourable and therefore recommended the granting of the marketing authorisation.