EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 December 2012
EMA/91055/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Adasuve

International non-proprietary name: **loxapine**

Procedure No. **EMEA/H/C/002400**

Note

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

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List of abbreviations

ACES	Agitation-Calmness Evaluation Scale
AEs	Adverse events
ANCOVA	Analysis of covariance
API	Active pharmaceutical Ingredient
ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical
AUC	Last area under the concentration-time curve from Time 0 to last measurement
AUC0-2h	Area under the concentration-time curve from 0 to 2 hours post-dose, also known as PK-AUC0-2h
AUCinf	Area under the concentration-time curve from Time 0 to infinity
BPRS	Pediatric behavior rating scale
CABS	The Cerebrovascular Attitudes and Beliefs Scale
CAS	Chemical Abstracts Service
CGI-I	Clinical Global Impression - Improvement Scale
CGI-S	Clinical Global Impression – Severity Scale
CI	Confidence interval
Cmax	Maximum concentration (at Tmax)
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CYP	Cytochrome
DDC	Dopa decarboxylase
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
EC	European Commission
ECG	Electrocardiogram
EEG	Electroencephalogram
EMA	European Medicines Agency
EURD	European Union reference dates
FEV1	Forced expiratory volume in 1 second
FMOs	flavin-containing monooxygenases
FVC	Forced Vital Capacity
GC	Gas chromatography
GCP	Good clinical practice

GLP	Good laboratory practice
HCP	Health Care Professional
hERG	Human ether-a-go-go related gene
HPLC	High performance liquid chromatography
hrs	Hours
IC_{50}	Half maximal inhibitory concentration
i.m.	Intramuscular
i.p.	Intraperitoneal
i.v.	intravenous
INN	International Nonproprietary Name
IR	Infrared spectroscopy
ITT	Intent to treat
Iv	Intravenous
K_D	Affinity of radioligand for receptor
LC/MS/MS	Liquid chromatography tandem mass spectrometry
LDPE	Low-density polyethylene
µg	Microgram
mg	Milligram
LOCF	Last observation carried forward
mRNA	Messenger RNA
n/a	Non applicable
NOAEL	No-observed-adverse-effect level
NMRI	Nuclear Magnetic Resonance Imaging
PANSS	Positive and Negative Syndrome Scale
PASS	Post authorisation study
PBT	Persistent, Bioaccumulative, and Toxic Profiler
PCP	Phencyclidine
PD	Pharmacodynamic(s)
PEC	Positive and Negative Symptom Scale, Excited Component
pED50	Log value of concentration of 50% maximal response
PET	Positron Emission Tomography
P-gp	P-glycoprotein
PIP	Paediatric investigational plan

PK	Pharmacokinetic(s)
PRAC	Pharmacovigilance Risk Assessment Committee
Prn	Pro re nata
QT	Interval between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QTc	Interval corrected QT interval
QTcI	Interval individually corrected QT interval
RH	Relative Humidity
RMP	Risk management plan
SAG	Scientific Advisory Group
SD	Standard deviation
SmPC	Summary of product characteristics
Sp02	Oxygen saturation level
s.c.	subcutaneous
TH	Tyrosine hydroxylase
Tmax	Time to maximum concentration
UGT1A1	Uridine diphosphate glucuronosyltransferase 1-1
UGT1A3	Uridine diphosphate glucuronosyltransferase 1-3
VAS	Visual analog scale
YMRS	Young Mania Rating Scale

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Alexza UK Ltd. submitted on 26 October 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Adasuve, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 October 2010. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of significant technical innovation.

The applicant applied for the following indication: ADASUVE inhalation powder is indicated for the rapid control of agitation in adult patients with schizophrenia or bipolar disorder.

The legal basis for this application refers to:

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

The application submitted is

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).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/220/2011 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

A new application was filed in the United States.

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

1.2. Steps taken for the assessment of the product

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

Rapporteur: **Barbara van Zwieten-Boot** Co-Rapporteur: **Daniela Melchiorri**

- The application was received by the EMA on 26 October 2011.
- The procedure started on 16 November 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 3 February 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 3 February 2012.
- During the meeting on 15 March 2012, 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 16 March 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 July 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 12 September 2012.
- During the CHMP meeting on 20 September 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 15 October 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of outstanding issues to all CHMP members on 1 November 2012.
- During a meeting of SAG on 6 November 2012, experts were convened to address questions raised by the CHMP.
- During the CHMP meeting on 15 November 2012, the CHMP agreed on a second list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the second List of outstanding issues on 17 November 2012.
- Upon request of the CHMP, the PRAC provided an advice on questions related to the Risk Management Plan.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the second List of outstanding issues to all CHMP members on 29 November 2012.
- During the meeting on 10-13 December 2012, 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 Adasuve on 13 December 2012.

2. Scientific discussion

2.1. Introduction

This is a complete, Article 8(3) application for ADASUVE (loxapine) for a known active substance (loxapine) through the centralised procedure. The product is intended for prescription only.

Loxapine is an antipsychotic agent belonging to the dibenzoxazepine class. The antipsychotic effects of Loxapine may primarily be attributable to its antagonism of dopamine D2 receptors. Loxapine also has 5-HT2A antagonist activity and has anti-cholinergic, anti-histaminergic and anti-alpha-adrenergic properties. Loxapine has been approved as oral and/or injectable formulations in Member States of the European Union (EU) and other regions (e.g US, Canada) for the treatment of schizophrenia and/or the treatment of agitation associated with specified psychotic disorders. It was firstly approved for marketing in the EU in the 70's. Currently, Loxapine is available in France as film coated tablets, oral solution and intramuscular (i.m) injection.

The following indication and posology were initially applied for: ADASUVE is indicated for the rapid control of agitation in adult patients with schizophrenia or bipolar disorder. The recommended initial dose of ADASUVE is 10 mg. A lower dose of 5 mg may be given, on the basis of individual clinical status, which should also include consideration of medicinal products already administered either for maintenance or acute treatment. A second dose of ADASUVE, 5 or 10 mg, may be administered 2 hours after the first, on the basis of individual clinical status. ADASUVE is intended for short-term use only. The maximum daily dose of ADASUVE of 30 mg should not be exceeded and not more than three inhalation units should be given in any 24 hour period.

The final recommended indication and posology by the CHMP is: ADASUVE is indicated for the rapid control of mild-to-moderate agitation in adult patients with schizophrenia or bipolar disorder. Patients should receive regular treatment immediately after control of acute agitation symptoms. The recommended initial dose of ADASUVE is 9.1 mg. A second dose can be given after 2 hours, if necessary. No more than two doses should be administered. A lower dose of 4.5 mg may be given if the 9.1 mg dose was not previously tolerated by the patient or if the physician decides a lower dose is more appropriate. In this report, 10 mg and 5 mg dose correspond to the strengths of 9.1mg and 4.5 mg, respectively and that are expressed in delivered doses.

Agitation can be a complication of several mental illnesses, including schizophrenia, mania, delirium and dementia. Schizophrenia and bipolar disorder are common disorders with a worldwide lifetime morbidity risk of about 1% for schizophrenia and about 0.9% to 2.1% for bipolar disorder I and II.

Agitation can be defined as a state of motor restlessness accompanied by mental tension. Patients who experience agitation describe feeling an inner distress (nervous, restless, overwhelmed, out of control, anguish, panic) that may progress to an outwardly apparent dysfunctional state manifested by hostility, difficulty controlling impulses, uncooperative behaviour and increased potential for violence. The time course for agitation escalation can be minutes, hours or days, and patients may require prolonged treatment.

Currently, the standard of care in the treatment of acute agitation is tranquilisation with benzodiazepines, antipsychotics, or combination of both pharmacological classes. Antipsychotic drugs are available in a variety of pharmaceutical forms, including oral tablets, orally disintegrating tablets, oral liquids, and i.m injections.

ADASUVE (loxapine) is a pre-dispensed inhalation powder. The product is a hand-held device with a mouthpiece for single use by inhalation of a 4.5 mg or a 9.1 mg delivered doses of the antipsychotic loxapine. The product is based on the applicant's Staccato® delivery system. Oral inhalation through the product initiates the rapid heating of a thin film of loxapine to form a drug vapour, which condenses into aerosol particles. This new method of administration (oral inhalation) is intended to ensure peak plasma levels in the systemic circulation within minutes after administration thus according to the applicant addressing the unmet need for rapid onset of sedation by non-invasive administration.

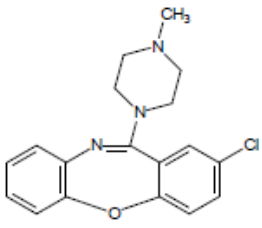
2.2. Quality aspects

2.2.1. Introduction

The drug product Adasuve contains the active substance loxapine. This is presented as a fully-integrated drug-device combination product, for single use. It is available in two doses: 4.5 mg and 9.1 mg of Loxapine. There are no excipients in the drug product and no drug overages. Fully assembled Staccato Loxapine devices are packaged in a multi-laminate foil pouch.

2.2.2. Active Substance

The active substance, loxapine (INN) or 2-Chloro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4] oxazepine, is a known active substance not described in any pharmacopeia. Loxapine is a white to yellowish, odourless crystalline powder, slightly soluble in water, sparingly soluble in methanol and freely soluble in acetone, chloroform, dichloromethane and ethyl acetate. Loxapine base exists at least in two different crystal phases, polymorph I and polymorph II. The two polymorphic forms of the drug substance can be distinguished by means of IR spectroscopy, and the batch data demonstrate that the manufacturer of the active substance produces consistently the crystalline form corresponding to the polymorph II. The molecular structure is as depicted below:



Manufacture

Starting materials are clearly defined and characterized. Detailed information is included in the Restricted Part of the ASMF. The drug substance was adequately characterised with regard to structure and impurities. One of the loxapine API impurities may have genotoxic potential, but it has been demonstrated that this impurity is not present in the drug substance.

Specification

The drug substance specification was established in-house by the Applicant. It is based on the release specification provided by the active substance manufacturer, supplemented with tests for impurities and microbial limits and some differences in the acceptance criteria. The Applicant will accept only those loxapine base lots from the active substance manufacturer that meet all specification acceptance criteria. The active substance specification is in general acceptable, and includes tests for appearance, Identification (IR and HPLC), heavy metals (Ph Eur), assay (HPLC), impurities (HPLC), lost on drying (PH Eur), residue on ignition or sulfated ash (Ph Eur), melting point (Ph Eur), residual solvent (GC). Batch analysis data demonstrating compliance with the proposed active substance specification were provided for 3 production scale batches. Supporting data of several development batches was also provided.

Stability

Stability data on the active substance were provided for five batches stored at 25°C/60% RH (6-36 months) and three batches stored at 40°C/75%RH (6 months). The batches were stored in the commercial packaging (double LDPE bag/PE drum). Storage under long-term and accelerated conditions did not show any up- or downward trends, indicating that the batches remain stable throughout the tested period. Stress testing and photo degradation studies showed no significant degradation. Based on the stability data presented the justified retest period has been accepted.

Comparability exercise for Active Substance

N/A

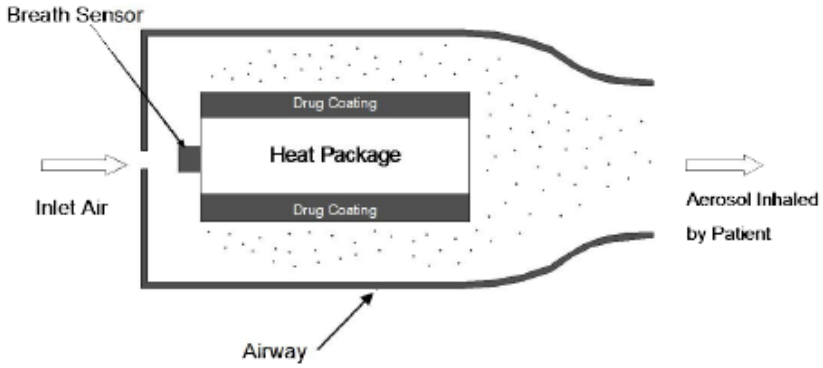
2.2.3. Finished Medicinal Product

Pharmaceutical Development

The objective was to develop a rapid systemic delivery of loxapine by inhalation of a thermally generated aerosol.
The pharmaceutical development of the product was adequately performed. Loxapine base was selected over the salt form because the properties of the base form are more suitable for the requirements of the Staccato Loxapine for Inhalation design. In particular, the base form is more volatile and therefore can be vaporized at a lower temperature, giving higher aerosol purity.

The Staccato Loxapine system for inhalation is a fully integrated drug-device combination product, for single use. It consists of a breath actuation mechanism, active substance coated onto a heat package (which produces a thermally generated aerosol) and a medical-grade plastic housing that forms the airway, which controls and directs the airflow of the vaporized drug. A schematic view of the Staccato Loxapine system is presented in Figure 1.

Figure 1. Schematic Side-View of *Staccato* Loxapine



When a user inhales through the Staccato Loxapine mouthpiece, their breath deflects a battery activated starter and this in turn initiates a controlled, gasless, oxidation-reduction (redox) reaction that liberates heat. Following heat generation, the thin film of loxapine that is coated onto the heat package vaporises completely and instantly. The vapour then cools in the airflow and condenses to form aerosol particles.

The active substance properties that may impact drug product performance have been identified and taken into account during product development. These include solubility, solution stability, compatibility with the heat package substrate, thermal stability during aerosolisation and impurities. Loxapine particle size and morphology do not affect the performance of the drug product, since loxapine is fully dissolved prior to further processing during drug product manufacture.

The following finished product critical quality attributes (CQA) that can impact product quality, safety and efficacy, were identified as part of the development process: mean emitted dose and uniformity, aerosol impurities and particle size distribution.

The applicant has provided ample information on the device, its specifications, design, purpose and operation. For the evaluation of the safety and performance of the device the requirements of the European Medical Devices Directive 93/42/EEC (MDD) were used as the reference. The manufacturer has extensively tested the performance and the safety of the device. The heat package temperature directly impacts the performance of the device. Adequate data have been provided to show that the heat package consistently produces heat to evaporate the active substance that is coated on the outer surfaces. The system proved to remain reliable under shipping and storage conditions

Safety testing further included the release of particulates other than the active substance, e.g coming from a leaking heat package, the temperature of the outside of the device and the temperature of the aerosol generated by the device.

The usability of the device has been extensively tested with placebo devices.

Overall, all relevant material and device attributes and process parameters have been evaluated for their potential impact on each of the CQAs of the finished product and, where required, appropriate in-process controls have been put in place.

Changes made to the device during product development and clinical studies are well described. All device versions were compared with regard to the impact on the finished product CQAs and key user interface characteristics (inhalation resistance of the drug product, performance of the breath actuation mechanism). The equivalence of the main clinical version and the commercial version of the device has been adequately demonstrated.

Adventitious agents

N/A

Manufacture of the product

The manufacturing process of the drug product involves loxapine solution preparation, heat package cleaning, drug deposition, final assembly and primary packaging. The manufacturing process is a non-standard process. Loxapine solution and the heat package are considered process intermediates. The holding times are supported by stability data. Information provided on manufacturing process development shows that all parameters that may impact the critical quality attributes of the final drug product are controlled.
Batch data on 6 primary batches (30% - 50% of commercial scale) produced at the commercial production facility under normal operating conditions was provided. The batch data of all development batches show that the quality of the pilot scale batches is predictive for the commercial scale batches. The commercial scale production process is adequately validated.

Product specification

The product specification includes tests for appearance, primary package leakage detection (Ph Eur), seal strength, identification of coated drug (IR and HPLC), coated dose assay (UPLC), mean emitted dose and emitted dose content uniformity (Ph Eur), aerosol impurities (DUSA), aerosol particle size distribution (fine particle mass) (Ph Eur), residual solvents (GC) and particulates in emitted dose (Ph Eur). The analytical procedures are well described and validated. Batch analytical data from the proposed commercial manufacturing site were provided on three primary batches per strength and of several supporting batches are provided, demonstrating compliance with the proposed release specification.

Stability of the product

Stability data on Adasuve was provided for three primary batches of each strength stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months) and for three registration batches per strength stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months).

The batches were stored in the primary packaging for commercial supply. The drug product met all acceptance criteria and remained well within the proposed limits. No clear trends were observed for any of the test attributes. The critical quality attributes (emitted dose, aerosol particle size distribution, and aerosol impurities) have remained stable and consistent. Light stress studies demonstrated that the product is not sensitive to light. Forced degradation of loxapine base required unusually strong stress conditions in order to generate degradation products. The two major loxapine degradation products were identified after acid stress and oxidation stress.

Seal strength will be monitored during the ongoing stability studies. In case the updated stability data support the removal of this test from the stability protocol, this will be done by the variation procedure. This proposal is acceptable.

The proposed shelf-life as described in the SmPC is considered acceptable. No special temperature storage conditions are required. The product should be stored in the original pouch until ready for use.

Comparability Exercise for Finished Medicinal Drug Product

N/A

GMO

N/A

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The quality of Adasuve is adequately established. Satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorisation. The drug substance was adequately characterized and the specification is acceptable in view of the route of synthesis and the various ICH guidelines. Concerning the finished product, the development studies adequately support the specification and acceptance criteria proposed. The drug product is stable with respect to degradation. Issues concerning the device reliability and performance have been addressed satisfactorily. The results of tests carried out indicate 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.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

N/A

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

Loxapine is a known active substance and literature data have been submitted to support the non clinical dossier in addition to a number of studies specifically conducted by the applicant.

2.3.2. Pharmacology

A limited pharmacology programme has been conducted by the applicant including in vitro and in vivo tests i.e. in vitro study to characterise the receptor binding of one of its primary metabolite (loxapine N-oxide) and in vitro/in vivo safety pharmacology in addition to the literature data submitted to support this part of the dossier.

2.3.2.1. *Primary pharmacodynamic studies*

Based on literature data, the binding profile of loxapine has revealed affinity to a range of neurotransmitter receptors (Ki, nM): D1 (18), D2 (9.8), 5-HT_{2A} (2), α_1 (250), M_1 (117). In a separate

study using guinea pig cerebral cortex receptors, loxapine also exhibited a K_i value of 14.9 nM for the histamine H_1 receptor.

Loxapine has shown to prevent the stimulation of adenylate cyclase by dopamine in rat striatal homogenates by 60% of inhibition. IC_{50} values for rat striatal [^{3}H]-spiroperidol binding were 101, 196 and 5870 nM for loxapine, amoxapine and imipramine, respectively.

Loxapine, amoxapine and their 8-hydroxylated metabolites displayed moderate strength in inhibiting striatal [^{3}H]-spiperone binding. Loxapine exhibited the strongest inhibition for [^{3}H]-spiperone whereas amoxapine and its 8-hydroxylated metabolite were stronger inhibitors of [^{3}H]-imipramine binding and of serotonin uptake. These data suggested properties of both tricyclic antidepressant and antipsychotic agent for the studied compounds.

In rats, pED50 values for loxapine were respectively 7.0, 6.8 and 6.7 for the occupancy of the 5-HT_2 receptors (cortex) and D_2 receptors (striatum and olfactory tubercle). *In vitro* data suggested more potency for loxapine at these receptors. In male NMRI mice, the ED50 value for loxapine was 0.3 mg/kg for inhibition of [^{3}H] SCH 23390, D_1 receptor antagonist.

In rats, a significant decrease in 5-HT_2 receptor binding (cortex) was observed due to a decrease in receptor density, but no change in K_D following single or repeated intraperitoneal (i.p.) administration of up to 28 days treatment with loxapine 5 mg/kg. After a single dose, loxapine also reduced dopamine receptor density (38% reduction) and greatly reduced serotonin receptor density (47% reduction). There were no significant effects on receptor affinities (K_D). After multiple doses, loxapine did not produce any significant increase in dopamine receptor density but induced a very significant reduction in serotonin receptor density.

In rats, K_i value for loxapine was 1.8 nM for serotonin 2 receptor (cortex) following i.p. administration at a dose of 10 mg/kg. As compared to the vehicle, a significant decrease in maximal binding capacity (Bmax: 9.67 vs. 21.97 pmol/g) and increased K_D (0.773 vs. 0.500 nM) were observed.

In rats, after subcutaneously (s.c.) administration at doses ranging up to 1 mg/kg, there was 50% occupancy at 0.05 mg/kg and 0.04 mg/kg for D_2 and 5-HT_2 receptors, respectively with a ratio 5-HT_2/D_2 was close to 1.

Loxapine also significantly increased FOS positive cells both in the nucleus accumbens and the dorso-lateral striatum.

After repeated administration, loxapine (4mg/kg/day) elicited increases of 180% in dopa decarboxylase (DDC) mRNA levels but had no effect on tyrosine hydroxylase (TH) mRNA levels suggesting that DDC may be more important than TH in the long term regulation of dopamine production. Increases of 450%, 150% and 550% in D_1, D_2 and D3 receptor mRNA levels, were also respectively observed after multiple doses of loxapine (2mg/kg/day).

In vivo data suggested a number of pharmacological effects for loxapine including decreased spontaneous locomotor activity, sedation, depression and catalepsy. Loxapine also inhibited conditioned avoidance, potentiated narcosis induced by thiopental sodium and protected against amphetamine mortality. Other pharmacological effects included: inhibition of apomorphine-induced stereotypic behaviour (gnawing, emesis), partial antagonism of 2,5-dimethoxy-4-methamphetamine discriminative stimulus, induction of dose dependent hypothermia and hypophagia, and at high doses, induction of clonic/tonic convulsions and aggressive behaviour.

As compared to its primary metabolites, loxapine had approximately one fifth the potency of 7-OH-loxapine and 8-OH-loxapine was essentially inactive suggesting that hydroxylation of loxapine at position 7 increased the dopamine receptor blocking potency of loxapine, whereas hydroxylation at

position 8 abolished this effect. In another study, IC_{50} values for rat striatal [^{3}H]-spiroperidol binding were 9, 140 and 1300 nM for 7-OH-loxapine, loxapine and 8-OH-loxapine, respectively.

Literature data suggested that another primary metabolite (amoxapine) had a different spectrum of pharmacological effects than loxapine acting as an inhibitor of reuptake of norepinephrine, a potent antagonist at 5-HT_2 sites, and a weak D_2 antagonist (Coupet et al, 1979). Amoxapine is also considered as relatively potent histamine H_1 and α_1 receptor antagonist, and a weak muscarinic acetylcholine and α_2 receptor antagonist.

No information was obtained from the published literature on the pharmacological activity of loxapine N-oxide. An *in vitro* receptor binding study of loxapine N-oxide conducted by the applicant showed that this metabolite was inactive at relevant receptors that were studied: α_1, D_1, D_{2S} H_1 M_1, $5HT_{2A}$.

2.3.2.2. *Secondary pharmacodynamic studies*

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

2.3.2.3. *Safety pharmacology programme*

The safety pharmacology programme consisted of two in vitro hERG channel assays and an in vivo cardiovascular and respiratory safety study in dogs. All other data are derived from the literature.

CNS system

In mice, hypothermia was observed after loxapine administration with a total decrease of approximately 5ºC, which was comparable to hypothermia induced with chlorpromazine and haloperidol administration. Like other antipsychotics, loxapine potentiated pentobarbital-induced sleep and did not reverse most CNS effects of the vesicular monoamine transport inhibitor tetrabenazine.

In cats, loxapine has shown to slow EEG waves after iv doses lower than 5 mg/kg. Catalepsy and “rage-like” behaviour were noted after iv dose of 1-1.5 mg/kg, whereas after 2-5 mg/kg, facial spasms and twitches of the whole body with occasional convulsions after the highest dose were observed.

Loxapine has not shown any protective effects against convulsions induced by strychnine, pentylenetetrazole, or electroshock. In contrast to chlorpromazine, loxapine did not offer protection against audiogenic seizures, and with prolonged treatment, loxapine increases susceptibility to audiogenic seizures. The pro-convulsive effects of loxapine were observed after administration of high doses in cats and audiogenic seizures were noted in repeated dose toxicity studies in rats.

Cardiovascular system

Based on literature data, loxapine treatment resulted in decreased amplitude of heart movements by 10% after 0.1 mg, by 24% after 0.5 mg, and by 60% after 2.5 mg of loxapine per heart in isolated rabbit hearts. Coronary flow was affected only marginally by the two lower loxapine doses but was decreased by 69% after administration of 2.5 mg of loxapine per heart. This dose of loxapine, however, did not induce heart arrest.

In isolated and perfused guinea pig atria, loxapine did not exert any significant effects at a concentration of 0.002 mg/ml. At a concentration of 0.01 mg/ml there was a heart rate decrease of approximately 21%, with inconsistent effects on heart contractility. At a concentration of 0.05 mg/ml, loxapine decreased heart rate by 33% and contractile tension by 31%, with complete arrest after 12 minutes of exposure.

In isolated rabbit auricular vessels, increases in perfusion volume were observed after loxapine administration. These were minor after 1 and 10 µg of loxapine per auricular vessel (8% and 15% respectively). However, a 51% increase in perfusion volume was achieved following exposure to 100 µg of loxapine per auricular vessel.

In in vitro hERG channel assays conducted by the applicant, loxapine and 8-OH loxapine were found to dose dependently block hERG channel current, yielding an IC_{50} value of 1.8 µM and 3.6 µM, respectively.

In anesthetized cats, loxapine administration produced dose-dependent decreases in carotid blood pressure (systolic blood pressure decreased by 7% after 0.1 mg/kg, by 18% after 0.5 mg/kg, and by 38% after 2.5 mg/kg). Carotid blood pressure returned to baseline 4 minutes following 0.1 mg/kg loxapine, after more than 16 minutes following 0.5 mg/kg loxapine, and after more than 60 minutes following 2.5 mg/kg loxapine. Loxapine had little effect on femoral blood flow at the two lower loxapine doses, but produced transient and marked decreases (approximately 76%) in blood flow after 2.5 mg/kg, followed 1 minute later by marked increases. Loxapine administration did not have any significant effects on heart rate, PR interval, or ECG patterns.

In anesthetized cats, a transient hypotensive response, with an immediate return to control blood pressure values was also observed after intravenous loxapine administration (0.25 - 5 mg/kg). In decerebrated cats, subjected to the same treatment, initial hypotensive response was followed by a period of sustained hypertension which was partially inhibited by the non-selective alpha blocker phenoxybenzamine.

In cats, loxapine did not cause disturbances in cardiac rhythm at an iv dose of 5mg/kg and did not block or attenuate the vasopressor effects of amphetamine at an iv dose of 2mg/kg.

In dogs, effects of loxapine usually trended towards decreased blood pressure, reduced arterial blood flow, increased cardiac contractility, and increased cardiac output at a dose ranging from 0.5-4mg/kg. Heart rate was not affected by loxapine treatment and there were no consistent changes in ECG parameters. However, when the dose of loxapine was increased to 7.5 mg/kg (cumulative intravenous dose), one dog developed markedly elevated T-waves and expired in cardiac arrest. In subsequent studies in conscious dogs with loxapine administered orally at doses up to 10 mg/kg/d for 6 months and 20 or 30 mg/kg/d for 3 months, however, it was noted that no clinical or histopathological signs of cardiotoxicity were seen.

In a cardiovascular and respiratory safety study specifically conducted by the applicant, conscious (non-anesthetized) telemetered dogs were used and 3 doses of loxapine were tested (0.15, 0.5, and 1.5 mg/kg). As single-breath rapid inhalation delivery in unrestrained dogs was not feasible, a rapid intravenous bolus (over 5 seconds) was used to mimic inhalation exposure to the drug. Following administration, all animals survived and none exhibited significant adverse reactions. No changes in heart rate or mean arterial blood pressure were observed following vehicle administration or following the lowest loxapine dose tested (0.15 mg/kg). Following the intermediate loxapine dose (0.5 mg/kg), mild increases in heart rate were recorded but no changes in mean arterial blood pressure were noted. After the highest loxapine dose (1.5 mg/kg), mean arterial blood pressure transiently decreased at 20 seconds post dose by approximately 22%. This decrease in mean arterial blood pressure was followed by an immediate increase, which lasted until approximately 6 minutes post dose. This increase in blood pressure was accompanied by a decrease in heart rate, which lasted until 15 minutes following dosing. None of these changes in cardiovascular parameters reached statistical significance as compared to treatment with vehicle after any loxapine dose, with the exception of a significant decrease in heart rate 6 minutes after administration of 1.5 mg/kg loxapine. No changes in ECG intervals attributable to loxapine or vehicle administration were observed. Loxapine administration did not lead to QT or QTc

prolongation. Peak plasma levels of loxapine in venous blood were recorded at the first two collection time points (either 30 or 120 seconds) and averaged 177 ng/mL (range 64-392 ng/mL) following the 0.15 mg/kg dose; 1,398 ng/mL (range 253-2,830 ng/mL) following the 0.5 mg/kg dose; and 1,438 ng/mL (range 841-2,650 ng/mL) following the 1.5 mg/kg dose of loxapine.

Respiratory safety

Based on literature data, antipsychotics did not induce any significant changes in respiration in humans at rest but appeared to enhance ventilatory response to hypoxia. This effect is said to be likely attributable to their action in the carotid body. Cases of respiratory depression following administration of antipsychotics (including loxapine) have been reported and involved co-administration of other drugs known to cause respiratory impairment such as benzodiazepines.

The respiratory effects of loxapine were evaluated in several non clinical studies. Intraperitoneal injections of loxapine at 50 mg/kg in rats did not induce any significant respiratory changes in blood pH and pCO_2. In anesthetized cats, loxapine (0.5 mg/kg) increased respiratory rate but decreased amplitude of respiratory movements. Higher dose of loxapine (2.5 mg/kg) induced transient (typically lasting seconds) respiratory arrest in some animals followed immediately by a marked increase in respiratory rate to up to 400% of baseline, with a gradual return to normal over 10 minutes.

In the cardiovascular and respiratory safety study specifically conducted by the applicant, previously discussed (see cardiovascular system), loxapine did not lead to any significant changes in respiratory rate, with the exception of mild increases following the highest loxapine dose of 1.5 mg/kg, which reached statistical significance as compared to vehicle at 15 minutes post dose. The mean respiratory rate at this time point (33 breaths per minute) was, however, within the normal range for the species. Analysis of blood gases revealed transient decreases in pCO_2 levels following the lowest loxapine dose (0.15 mg/kg) and transient increases in pO_2 levels following the 0.15 and 0.5 mg/kg doses of loxapine, with no changes at the highest dose of loxapine (1.5 mg/kg).

Gastrointestinal and renal safety

Based on literature data, *in vitro* studies suggested that loxapine has direct effects on intestinal motility (likely due to its antagonistic action at $5\text{-}HT_7$ receptors) as its administration prevented 5-HT induced contractions of isolated rat jejunum.

In rats, loxapine (1 - 20 mg/kg) did not increase the number of animals that developed stress-induced gastric ulcers suggesting its lack of ulcerogenic effects. Loxapine was also shown to produce mild diuretic effects when administered alone.

2.3.2.4. *Pharmacodynamic drug interactions*

Based on literature data, interactions of loxapine succinate with diuretic, antihypertensive and antiparkinson agents were studied in rats. Loxapine (1 to 8 mg/kg, route not specified) failed to reduce blood pressure in normotensive rats but enhanced the anti-hypertensive effect of guanidine. Loxapine in combination with hydralazine, guancidyne or methyldopa caused a slower heart rate than guanidine or methyldopa alone and a decrease in pressor response to epinephrine greater than guanidine or hydralazine alone; the effects disappeared in 24 h. Loxapine succinate alone produced a mild increase in urinary volume in rats and in combination with furosemide or hydrochlorothiazide, the diuretic activity was additive.

2.3.3. Pharmacokinetics

The metabolism and pharmacokinetics of loxapine and its metabolites were investigated by the applicant, mainly in rats and dogs. Organ and tissue distribution studies used also cats. Metabolism studies using liver microsomes included other species: mouse, guinea pig, rabbit and monkey.

After inhalation, the bioavailability of loxapine was around 20-30% in male rats, 53% in female rats and greater than 100% in dogs. After oral administration, loxapine was not detectable in dogs and the bioavailability was around 2-10% in rats indicating a much higher bioavailability using the inhalation route in animals. In humans, oral bioavailability was higher than in animals with approximately 33%. No bioavailability data after inhalation were available in humans, however, an inhalation dose 5 times lower than the oral dose resulted in comparable systemic exposure.

After inhalation, maximum plasma concentrations for loxapine were reached very rapidly in the studied species (around 1-1.5 minutes). C_{max} and AUC increased dose-proportional and loxapine plasma exposure was linear over the dose range of 2 to 17 mg/kg in rats and 0.10 to 2.16 mg/kg in dogs. There were no signs of plasma accumulation of loxapine or its metabolites after repeated dosing. Half-lives of loxapine and metabolites were around 1-11 hours for loxapine, 3-11 hours for 7-OH loxapine, 3 hours for amoxapine and 0.3-2 hours for loxapine N-oxide. In rats, the clearance of inhaled loxapine was around 20-30 L/h/kg indicating rapid elimination.

After single intravenous dosing, half-lives of loxapine and metabolites were around 2- 9 hours for loxapine, 6 hours for amoxapine, 6-7 hours for 7-OH-loxapine, 4-9 hours for 8-OH-loxapine and 7 hours for loxapine-N-oxide. Loxapine plasma exposure was linear in the dose range of 2 to 8 mg/kg in rats and 0.15 to 0.5 mg/kg in dogs. In rats, the volume of distribution was estimated as around 23-26 L/kg and total plasma clearance was approximately 6.2-6.5 L/h/kg.

The radioactive drug was rapidly and widely distributed over the body. Thirty minutes after an intravenous dose of 5 mg/kg of loxapine in rats, tissues concentrations were found to be higher in brain and lungs than in the spleen, pancreas, liver, kidneys and other body organs. At 4 hours, these concentrations had fallen to 10-30% of the initial value dose indicating rapid clearance except for the liver and fat tissues. In studies analysing the brain distribution of loxapine in rats, dogs and cats, the cortex contained the least amount of loxapine, whereas the subcortical structures maintained high relative concentrations in all three species. Loxapine had relatively high binding to animal and human plasma proteins (>97%) and was equally distributed between red blood cells and whole blood plasma at concentration of 100 ng/mL , with a whole blood to plasma ratio greater than 1 (1.1). Loxapine was not found to be a substrate of the protein P-glycoprotein (P-gp) but did moderately inhibit P-gp.

Loxapine metabolism involved formation of 7-OH-loxapine, 8-OH-loxapine, amoxapine and loxapine N-oxide via flavin-containing monooxygenases (FMOs) and several cytochrom (CYP) isoforms. 7-OH-loxapine is mainly formed by CYP3A4 and 2D6, 8-OH-loxapine mainly by CYP1A2, and amoxapine by CYP3A4 and 2C19. Loxapine N-oxide is suggested to be mainly formed by FMOs. In rats and dogs, 7-OH-loxapine was the major metabolite. 8-OH-loxapine was not present in rats. In dogs, another main metabolic pathway was the formation of loxapine-N-oxide, possibly due to the presence of FMOs in the lungs. In rats, the secondary metabolism of 7-OH-loxapine primarily to 7-OH-amoxapine, by CYPs and in smaller amounts to 7-OH-loxapine N-oxide, by FMOs was found to be gender-specific with males forming both metabolites faster than females. In contrast, in humans the main metabolite is 8-OH-loxapine whereas 7-OH-loxapine is formed to a much lesser extent. However, the metabolic pathway forming loxapine-N-oxide cannot be excluded in humans since at present the responsible FMO has not been identified. The other pharmacological active metabolite, amoxapine, is found in small percentages in all studied species and man. Compared with the oral route, loxapine inhalation led to lower metabolites levels in humans due to the absence of the first-pass effect.

Loxapine related material was mainly excreted in the faeces (61%) after intravenous dosing in dogs. Loxapine and/or its metabolites were also found to be excreted in the milk of dogs.

2.3.4. Toxicology

A limited toxicology programme has been conducted by the applicant including single dose and repeated toxicity studies using the inhalation/intravenous routes in rats and dogs in addition to the literature data submitted to support this part of the dossier.

2.3.4.1. *Single dose toxicity*

Acute toxicity studies (single dose and/or escalating dose) were conducted in both rats and dogs. Different routes of administration were tested (rats: intravenous, nose inhalation; dogs: oral inhalation) using intravenous loxapine succinate and inhaled loxapine base. Non-lethal effects were observed up to the maximum tested dose (rats 24 and dogs 2.5 mg/kg). Clinical signs consisted mainly of lethargy, unresponsiveness, decreased activity, and at the higher dose levels, tremors, clenched forelimb (rats), and weakness, and were considered to be related to the pharmacological effects of loxapine. The signs appeared to be less severe than those reported in the literature for acute toxicity studies using different routes of administration (oral, subcutaneous), however, this finding may be due to the lower non-lethal dose levels applied in the studies performed by the applicant.

2.3.4.2. *Repeat dose toxicity*

Repeated dose toxicity studies were conducted for 5 and 28 days in dogs, and 14 days in rats.

In male and female rats, mean dose levels of 1.7, 6.4 and 13 mg/kg/day caused dose related CNS clinical signs consisting of lethargy, hunched posture and tremors after nose inhalation. Other effects included mammary hyperplasia in both sexes, ovarian follicular cysts that were reversible at the end of the recovery period and mucification of vaginal epithelium in females. Mammary hyperplasia was reversible at the end of the recovery period for males. Treated animals in the mid and high dose groups showed significant gender-specific decreases in mean body weight and weight gain patterns, but these were considered secondary to the lethargy effect. Histological changes related to inhalation exposure included squamous metaplasia of the larynx, possibly due to the particle impaction associated with the delivery route and this effect was also reversible. Based on the persistence of the clinical signs until the morning following dosing, the slow recovery of body weight decreases and the partial recovery of the histological findings at the high dose, the no-observed-adverse-effect level (NOAEL) was considered to be 1.7 mg/kg/day.

In dogs, loxapine treatment related clinical signs included decreased activity, lack of coordination, limited use of hind limbs, lying on the side and an increase in frequency of tremors and weakness as compared to controls at a dose of 2 mg/kg/day administered for 5 days. These signs, slight to moderate in degree, were noted immediately after completion of exposure, and diminished in incidence and severity by 9 hours post exposure. Except for weakness noted in some dogs, the clinical signs had resolved by 24 hours post exposure. Slight decreases in body weight and food consumption were noted in dogs given loxapine at a dose of 2.0 mg/kg/day. There were no treatment related macroscopic or microscopic changes. The no-observed-adverse-effect level (NOAEL) was considered to be 0.16 mg/kg/day. In another study with mean achieved doses of 0.12, 0.95 and 1.8 mg/kg/day for 28 days, decreased activity, lack of coordination, tremors, lying on side and weakness were noted. Incidence, severity and duration of these clinical signs decreased with repeated exposure. The NOAEL was considered to be 1.8 mg/kg/day.

2.3.4.3. *Genotoxicity*

Loxapine and its metabolites (8-OH loxapine, amoxapine) were evaluated in vitro using gene mutation assay in bacteria and chromosome aberration tests in human blood lymphocytes. All of these tests were negative and did not suggest a genotoxic potential of these compounds.

2.3.4.4. *Carcinogenicity*

No carcinogenicity studies were performed.

2.3.4.5. *Reproduction toxicity*

No specific fertility and early embryonic developmental, pre-and postnatal developmental toxicity studies or juvenile animal studies were conducted with loxapine.

Based on literature data, female rats did not mate due to persistent diestrus after oral treatment with loxapine.

Embryo/fetal and perinatal development were studied in several species: rats, rabbits, mice. In rats, embryo/foetal toxicity was observed: loss of conceptuses, reduced foetal weight, increased number of anomalies/variations and decreased ossification. This was associated with signs of maternal toxicity: loss of maternal weight and/or decreased body weight gain. Observed malformations appeared to be incidental, hydroureter and hydronephrosis occurred and were found to be not dose-related. A similar pattern of developmental delay associated with maternal toxicity was observed in mice. Rabbits appeared to be less susceptible as decreased maternal weight gain and implantation counts were only observed at the highest dose (60 mg/kg/day) per oral gavage whilst retarded ossification of sternebrae per i.m. administration, but no teratogenic effects were noted. Postnatal survival of offspring of rabbits treated with loxapine during all or a portion of organogenesis also was reduced during the first week following birth.

Prenatal and postnatal development was investigated in rats and dogs. In rats, parturition difficulty (dystocia) occurred in 3 of 20 mated dams from the high dose group. Increased numbers of perinatal and neonatal deaths as well as decreased birth and weaning weights were noted. These effects, as well as reduced ossification and renal findings, consisting of distended renal pelvis with reduced or absent papillae, suggested again a developmental delay. This was also associated with signs of maternal toxicity: lacrimation, perineal staining and decreases in body weight gain and food consumption. In dogs, postnatal survival of offspring was found to be markedly reduced in all treated groups for the first week following parturition. No morphologic effects due to maternal loxapine treatment were observed in the offsprings.

2.3.4.6. *Toxicokinetic data*

The toxicokinetic data were summarised in section 2.3.3.

2.3.4.7. *Local Tolerance*

Single and repeated dose toxicity studies addressed local tolerance (see above).

2.3.4.8. *Other toxicity studies.*

The toxicity profile of a number of degradation products and device components (metals, leachables) were studied and did not show any relevant findings. Impurities were adequately qualified and those with respiratory sensitising or irritating potential were considered below the clinical safety threshold.

No other toxicity studies were performed which was considered acceptable by the CHMP, given the repeated toxicity data and the absence of non clinical model to evaluate respiratory sensitisation potential.

2.3.5. Ecotoxicity/environmental risk assessment

Table 1. Summary of main study results

Substance (INN/Invented Name): loxapine			
CAS-number (if available): 1977-10-2			
PBT screening		Result	**Conclusion**
Bioaccumulation potential log K_{ow}	MEEKC in comparison with ClogP and literature log P data.	3.86 - 3.98	not PBT nor vPvB
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default F_{pen}	0.005	µg/L	< 0.01 threshold

During the evaluation, the CHMP questioned the Fpen refinement and hence the calculated PEC surfacewater of 0.005 µg/L. However, using prevalence values of 0.8% (schizophrenia) and 1.3% (Bipolar Disorder I) and 0.4% (Bipolar Disorder II), with 12, 6 and 6 episodes per year, respectively, and a treatment duration of 2 days in all cases, F_{pen} values are 0.000526, 0.000427 and 0.000132. The summed F_{pen} is 0.00108. With DOSE*ai* = 9.1 mg/patient/day, the resulting $PEC_{surface\ water}$ is 4.9 ng/L, which is below the action limit. In addition, the CHMP considered that these values would slightly change if calculated for a duration period of 1 day in which 2 doses are administered, but would still be well below the action limit. Hence the CHMP concluded that loxapine PEC surfacewater value was below the action limit of 0.01 µg/L and was not a PBT substance as log Kow does not exceed 4.5. Therefore loxapine is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

Literature data adequately characterised the properties and principal effects of loxapine as well as potential harmful effects on vital organ systems. Receptor binding and functional studies demonstrated that loxapine has the highest affinity for serotonin (5-HT_{2A}) receptor, followed by dopamine (D_2 and D_1) receptors. Loxapine has also affinity for muscarinic (M_1) and adrenergic (α_1) receptors. 7-OH-loxapine, a major metabolite found in rats and dogs, but of lesser importance in humans, has a 5-fold higher affinity for the D_2 receptor.

Difference between *in vitro* studies and *in vivo* occupancies of 5-HT_2/D_2 receptors could be influenced by active metabolites. Loxapine was considered to mainly contribute to the pharmacological activity in vitro whereas active metabolites, including amoxapine and hydroxylated metabolites, were suggested to influence the *in vivo* behavior. It was generally stated in the literature that 7-OH loxapine, a major metabolite in rats and dogs, contributes to the pharmacology of loxapine. Considering no data were available on the distribution of this metabolite to the brain, it is difficult to determine to which extent this metabolite or others play a role *in vivo*.

Animal studies demonstrated a number of effects characteristic of antipsychotic drug profile, including decreased spontaneous locomotor activity, sedation, depression and catalepsy. Loxapine also exhibited analgesic activity, inhibited conditioned avoidance, potentiated narcosis and protected against amphetamine mortality. Other pharmacological effects included: inhibition of apomorphine-induced stereotypic behavior (gnawing, emesis), partial antagonism of 2,5-dimethoxy-4-methamphetamine

discriminative stimulus, induction of dose dependent hypothermia and hypophagia, and at high doses, induction of clonic/tonic convulsions and aggressive behaviour.

The safety pharmacology identified mainly CNS (e.g. hypothermia, potentiation of pentobarbital-induced sleep and slowing of EEG waves) and cardiac (e.g. transient hypotension, decreased arterial blood flow, increased cardiac contractility and increased cardiac output) as possible targets for loxapine regarding potential adverse effects in mans. No significant gastrointestinal or renal effects were observed. The CHMP noted that the effect on EEG rhythms have also been observed with chlorpromazine. Seizures have also been reported in humans following cases of overdose with loxapine.

Non clinical QT findings were consistent with a IC_{50} value (1.8 µM) of loxapine in the hERG channel assay and a lack of QT prolongation in dogs. However a mild prolongation of QTc was observed in a specific clinical study. This is further discussed in the clinical pharmacology (see 2.4.3).

Animal studies did not indicate a direct effect of loxapine on respiratory function under normal conditions. However, it has been shown that administration of another antipsychotic drug (prochlorperazine) increased ventilatory response (minute ventilation, tidal volume and breathing rate) under hypoxic conditions. It could be hypothesised that the underlying mechanism could play a role in the serious adverse ventilatory responses observed in asthma and COPD patients. This is further discussed in the clinical pharmacology (see 2.4.3).

Non clinical data suggested drug interactions of loxapine succinate with diuretic, antihypertensive and antiparkinson agents. There is no available clinical data to suggest relevance of such interactions in humans and no additional drug interactions were considered necessary by the CHMP.

The results of pharmacokinetic studies in animals showed: rapid inhaled absorption (due to the absence of the first pass effect experienced with the oral route), extensive tissue distribution, high protein binding and rapid elimination. Loxapine drug related material was mainly excreted in faeces and notably in milk. While the patterns of metabolites were relatively similar in the studied animal species, it substantially differs from the human pattern. On this basis, extrapolation from animal data to man was considered limited.

The majority of the findings in the repeated dose toxicity studies were related to the pharmacological CNS activity of loxapine except for changes to reproductive tissues related to the extended pharmacology of loxapine. Similar changes, e.g., gynecomastia, are known in humans, but only after long-term administration of medicines causing hyperprolactinaemia.

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

No carcinogenicity studies were performed and this can be considered acceptable in view of the maximum duration of treatment of up to 2 doses in 24 hours.

Data on fertility and early embryonic development are limited. Female rats did not mate due to persistent diestrus after oral treatment with loxapine. Embryo/fetal developmental and perinatal studies indicated developmental delay (reduced weights, delayed ossification, hydronephrosis, hydrourether, and/or distended renal pelvis with reduced or absent papillae) as well as increased numbers of perinatal and neonatal deaths in offspring of rats treated from mid-pregnancy after oral dosing of loxapine, that were below the maximum recommended dose in humans. Based on these data and in the absence of information on pregnancy exposure with loxapine, a recommendation to use loxapine during pregnancy only if the potential benefit justifies the potential risk to the fetus, has been reflected into the SmPC.

Loxapine PEC surfacewater value was below the action limit of 0.01 µg/L and was not a PBT substance as log Kow does not exceed 4.5. Therefore loxapine is not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non clinical aspects of loxapine have been adequately documented and meet the requirements to support this application.

2.4. Clinical aspects

2.4.1. Introduction

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.

2.4.2. Pharmacokinetics

The phase I clinical pharmacology programme has been conducted using single or multiple doses of Adasuve, in healthy volunteers (including smokers), subjects with asthma and COPD and in patients on chronic, stable, antipsychotic regimens. In addition to phase I studies, pharmacokinetic characteristics derived from literature data on oral loxapine were also considered.

Plasma concentrations of loxapine and its analysed metabolites was determined using LC/MS/MS methods in the PK studies. Pharmacokinetics parameters were determined using non compartmental models.

2.4.2.1. *Absorption*

Loxapine was rapidly absorbed upon oral inhalation with a median time of maximum plasma concentration (Tmax) values of 2-3 minutes. The absolute biovailability of inhaled loxapine was not studied. Loxapine exposure in the first 2 hours after administration (AUC0-2h, a measure of early exposure that is relevant to the onset of therapeutic effect) was 25.6 ng*h/mL for the 5 mg dose and 66.7 ng*h/mL for the 10 mg dose in healthy subjects.

Based on literature data, similar systemic exposures to oral loxapine 50 mg and inhaled loxapine 10 mg were observed indicating a good bioavailability using the inhalation route while the Cmax was about 4 to 5 –fold higher. In addition, the exposure to metabolites after an oral dose was higher than after inhalation, due to the high first pass effect.

Bioequivalence between inhalation powder applied for and the formulation used during phase III studies for 5 mg and 10 mg was demonstrated for the exposure parameter (AUC) but not for the maximum plasma concentration (Cmax). Higher Cmax were observed in the formulation applied for.

2.4.2.2. *Distribution*

No specific study has been performed to estimate the volume of distribution after inhalation in man and this was not considered necessary, considering loxapine inhalation powder is intended for short term use. Loxapine was found to be highly bound to human plasma proteins (96.6%). In these assays,

the drug recovery was low, the applicant suggested that a binding to lipoproteins, as observed with clozapine and haloperidol cannot be excluded with loxapine and could explain this finding.

2.4.2.3. *Elimination*

No specific study has been performed with loxapine inhalation powder and this was considered not necessary, considering loxapine inhalation powder is intended for short term use. Taking into account the elimination profile of oral loxapine, excretion is suggested to occur mainly in the first 24 hours. Metabolites are excreted in the urine in the form of conjugates and in the faeces unconjugated. The mean elimination half-life between loxapine inhalation and oral loxapine were found to be comparable and up to 8 hours.

2.4.2.4. *Dose proportionality and time dependencies*

A dose proportional increase in exposure for loxapine was observed over the 0.625 – 30 mg dose range. For the maximum plasma concentration, this increase was less than dose proportional. No data were available on time dependency and this was considered acceptable given that loxapine inhalation powder is intended for short term use.

After repeat administration of inhaled loxapine every 4 hours for a total of 3 doses (either 5 mg or 10 mg) in subjects on chronic, stable, antipsychotic regimens, mean peak plasma concentrations were similar after the first and third dose, indicating minimal accumulation during the 4-hour dosing interval.

2.4.2.5. *Special populations*

Population pharmacokinetic analyses were provided to evaluate the effect of race, gender, weight, smoking and age. No specific phase I studies evaluating renal and hepatic functions, elderly population were conducted and these were considered not necessary, given that loxapine inhalation powder is intended for short term use.

A specific phase I study evaluating the effect of smoking did not reveal relevant differences in the pharmacokinetic profile of smokers versus non smokers and no dosage adjustment is recommended based on the smoking status.

No data are available in the paediatric population as the studies included in the PIP have been deferred.

Given the known increased risk of death in elderly patients with dementia-related psychosis using antipsychotics, the elderly population was not studied and no data are available.

Population pharmacokinetic analyses did not reveal any significant effects of race, gender, weight, smoking and age. However it is noted that in female smokers exposure (AUC_{inf}) to loxapine and its active metabolite 7-OH loxapine is lower than in female non-smokers (84% vs 109% 7-OH-loxapine/Loxapine Ratio), which is probably due to an increase in loxapine clearance in smokers.

2.4.2.6. *Pharmacokinetic interaction studies*

In vitro studies with human hepatocytes showed that loxapine and/or its metabolites did not significantly inhibit CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4. The formation of the metabolites was inhibited by inhibitors of CYPs 1A2, 2B6, 2C8 and 2C19 inhibitors for 8 OH loxapine ; 2C8 and 2C19 inhibitors for 7-OH loxapine; CYPs 2C8, 2C9 and 3A4/5 for amoxapine.

Loxapine was not found to be a substrate for P-glycoprotein (P-gp) , however it has shown to act in vitro as an inhibitor of P-gp, with an IC_{50} of 9.1 µM (about 3 µg/ml). Considering the maximal plasma concentrations observed in vivo of about 120 – 140 ng/ml after multiple dosing, the possible impact on P-gp-mediated transport of other drugs is not considered of clinical significance.

No other additional interaction studies have been performed.

Given the metabolism pathways of loxapinem further investigation on the potential for drug interactions with drug product and metabolites (loxapine and 8-OH loxapine) that induce the levels of CYPs 1A2, 3A4 and 2D6 or inhibit the levels of UDP-glucuronosyltransferases (including UGT1A1, UGT1A3) was recommended by the CHMP.

2.4.3. Pharmacodynamics

2.4.3.1. *Mechanism of action*

Loxapine is a dibenzoxazepine compound. As for other antipsychotic agents, the efficacy of loxapine in the claimed indication is proposed to be mediated through high affinity antagonism of dopamine D2 receptors and serotonin 5-HT2A receptors. Loxapine binds with noradrenergic, histaminergic, and cholinergic receptors, and its interaction with these systems may influence the spectrum of its pharmacological effects. Changes in the level of excitability of subcortical inhibitory areas have been observed in several animal species, associated with calming effects and suppression of aggressive behaviour.

2.4.3.2. *Primary and Secondary pharmacology*

Five clinical studies were conducted (4 in healthy subjects, 1 in patients on chronic, stable, antipsychotic regimens) to investigate the sedative effects of loxapine as measured by the Visual Analogue Scale (VAS) scores for sedation. Two studies (1 in healthy subjects, 1 in asthma and COPD patients) evaluated the effects on respiratory function and used 2 inhaled doses of loxapine administered 8-10 hours apart. A QT/QTc study was also conducted by the applicant. Some of these studies were previously discussed in relation to the pharmacokinetic profile of loxapine. Available literature data on receptors binding studies in man using Positron Emission Tomography (PET) were also submitted.

Sedative effects

Sedation was considerably more pronounced in the healthy subjects than in the subjects on chronic, stable antipsychotic regimens. There was a rapid onset of a measurable sedative effect as early as 2 minutes, reaching a peak effect at 30 minutes to 1 hour, and declining to halfway at approximately 2 hours post dose. The peak effect was found to be greater after the second dose.

Respiratory effects

A decreased FEV1 suggestive of expiratory difficulty was observed more significantly in the loxapine group as compared to the placebo group in both asthma and COPD patients. In asthma patients, FEV1 decrease of at least 10, 15, or 20% were respectively 84.6%, 61.5% and 42.3% for the loxapine group and 11.5%, 3.8% and 3.8% for the placebo group. In COPD patients, FEV1 decrease of at least 10, 15, or 20% were respectively 80.0%, 56.0% and 40.0% for the loxapine group and 66.7%, 33.3% and 11.1% for the placebo group.

In healthy subjects, sedation was observed accompanied by an increased FEV1/FVC ratio in spirometry measurement after each of 2 doses of loxapine with an 8-hour interval. This finding indicated a decreasing end-of-expiration effort. A 15% or larger decrease in FEV1, occurred after loxapine

treatment in 19.2% as compared to 3.8% of all subjects after placebo treatment, suggesting expiratory difficulty. One subject had a decrease of 20% or more after loxapine treatment. In 5 of the 7 subjects experienced a 10% or more decrease, as measured soon after loxapine administration. There were no vital signs or SpO2 changes or indications of bronchospasm to explain these differences.

Cardiac effects

In a QT/QTc study, there was no significant effect of a single dose of loxapine 10 mg on cardiac repolarization as compared to placebo. The upper bound of the 95% 1-sided CI for the largest time-matched mean effect of loxapine on the difference from placebo in the change from baseline in the QTcI interval excluded 10 milliseconds. The QTc interval prolongation as compared to placebo showed a maximum of 5.418 msec, as compared to 8.356 msec prolongation for the active comparator (moxifloxacin 400 mg).

PET findings

Based on literature data, the dose of loxapine to occupy 50% of D_2 receptors was 9.6 mg/day for D_2 receptors and 13.6 mg/day for 5-HT_2 receptors in man. Loxapine was also found to be equipotent at the 5-HT_2 and D_2 receptors. At the dose range tested (10-100 mg/day), D_2 receptor occupancy ranged from 43 to 90% whereas 5-HT_2 occupancy varied from 27% to near saturation suggesting different profile in vivo as compared to in vitro data.

2.4.4. Discussion on clinical pharmacology

Limited characterisation of the pharmacokinetic profile of oral inhalation route for loxapine has been performed with the absorption phase specifically studied. Based on literature data, similar systemic exposure for oral loxapine 50 mg and inhaled loxapine 10 mg were observed indicating a good bioavailability using the inhalation route.

Bioequivalence between inhalation powder applied for and the formulation used during phase III studies for 5 mg and 10 mg was demonstrated for the exposure parameter (AUC) but not for the maximum plasma concentration (Cmax). Higher Cmax were observed in the formulation applied for. The CHMP however agreed that this finding was not clinically impacting on the safety profile of the product based on the available clinical data using this formulation.

Subjects with hepatic/renal impairment and the elderly population were not studied and no data are available. A specific phase I study evaluating the effect of smoking did not reveal relevant differences in the pharmacokinetic profile of smokers versus non smokers and no dosage adjustment is recommended based on the smoking status.

No data are also available in the paediatric population as the studies included in the PIP have been deferred.

Population pharmacokinetic analyses did not reveal any significant effects of race, gender, weight, smoking and age. However it is noted that in female smokers exposure (AUC_{inf}) to loxapine and its active metabolite 7-OH loxapine is lower than in female non-smokers (84% vs 109% 7-OH-loxapine/Loxapine ratio), which is probably due to an increase in loxapine clearance in smokers.

The presented clinical pharmacokinetic data were considered sufficient, given that loxapine inhalation powder is intended for a short term use.

The PK/PD profile in the following populations was studied: healthy subjects, patients on chronic, stable, antipsychotic regimens, patients with asthma and COPD patients.

Pharmacodynamic data confirmed the fast onset of sedative effect achieved with loxapine inhalation. However this effect appeared much weaker in patients on stable, chronic antipsychotic regimens as compared to healthy subjects. In addition, expiratory difficulty was observed after loxapine administration in patients with asthma and COPD patients. This is further discussed in the clinical safety (see 2.6).

A combined sedative and respiratory effect was also observed and this may predispose to over-sedation in case of co-administration with other ventilation depressants such as hypnosedatives including benzodiazepines. The CHMP therefore recommended to include a number of warnings in patients at risk ie patients with hypovigilance, with CNS-depression due to alcohol or other centrally acting medicinal products (anxiolytics, antipsychotics, hypnotics, opiates), with agitation due to intoxication or physical disease (delirium). The CHMP also recommended to conduct a phase I study to assess the safety and PD profile of concomitant administration of single doses of inhaled loxapine and lorazepam (i.m.) compared to the administration of each agent alone. This study is part of the risk management plan (see 2.7.2).

A QT/QTc study did not reveal significant effect of a single dose of loxapine 10 mg on cardiac repolarization as compared to placebo. However, the effect on QT was not evaluated after repeated administration. Whilst similar systemic exposures to oral loxapine 50 mg and inhaled loxapine 10 mg were observed, the recommended daily dose for oral loxapine was found to be much more higher than 50 mg with 200 mg/day (up to 600 mg/day in certain cases) which can be given once a day in the evening or in fractionated doses during the day. The posology of oral loxapine hence suggested a much higher exposure to loxapine and its active metabolites (due to the high first pass effect) as compared to the proposed posology for inhaled loxapine, hence the CHMP considered that on this basis and the safety profile of oral loxapine, the risk for QTc prologation appeared to be limited and manageable in clinical practice. Following the SAG-Psychiatry conclusions (see 2.5.7), the CHMP recommended to include a warning on QT interval as follows:

"Clinically relevant QT prolongation does not appear to be associated with a single dose of ADASUVE. Caution should be exercised when ADASUVE is administered in patients with known cardiovascular disease or family history of QT prolongation, and in concomitant use with other medicinal products known to prolong the QT interval. The potential risk of QTc prolongation following repeat dosing or interaction with medicinal products known to prolong QTc interval is unknown. "

In addition, the CHMP recommended to conduct a post-approval study investigating a 2 doses of 10 mg of ADASUVE given 2 hours apart, including a positive control with known QT/QTc prolongation (oral moxifloxacin, 400 mg), an oral placebo and inhaled placebo, as proposed by the applicant. This study is part of the risk management plan (see 2.7.2).

2.4.5. Conclusions on clinical pharmacology

Overall, the pharmacological profile of loxapine in human studies has been adequately characterised for its intended use.

2.5. Clinical efficacy

The initial indication applied for was: rapid control of agitation in adult patients with schizophrenia or bipolar disorder.

The clinical development consisted of 3 clinical studies (004-201, 004-301 and 004-302) that were multicenter, randomised, double blind, parallel group and placebo controlled. All study centres were in the US. These studies were performed in patients with schizophrenia (004-201,004-301), bipolar I

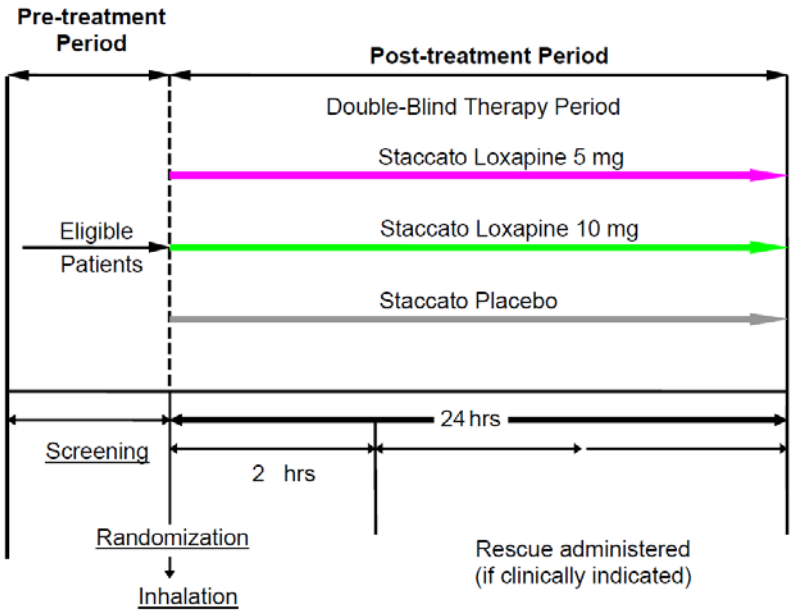
disorder (study 004-302) and schizoaffective disorder (004-201) and evaluated the 5 mg and 10 mg dose of loxapine with a maximum of 1 (004-201) to 3 doses administered (004-301, 004-302) during a 24-hour study period. Studies 004-301 and 004-302 are identified as the pivotal phase III studies.

An indirect comparison of the efficacy results of loxapine versus i.m. aripiprazole and i.m. olanzapine was also presented taking into account the CHMP reflection paper on the need for active controls (draft, EMA/759784/2010).

2.5.1. Dose response study

Study 004-201 was designed to evaluate the dose response and included 2 periods (pre/post treatment) as shown in Figure 1.

Figure 1



In this study, the population included adults, 18 to 65 years of age, who had met the DSM-IV criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder. Loxapine was administered via inhalation using the Staccato delivery system. Treatment was administered using 3 devices, each containing 0 mg, 5 mg, or 10 mg of Loxapine.

Patient disposition and demographics are presented in figure 2 and Table 2.

Figure 2

Figure 10-1. Flow Chart of Patient Disposition

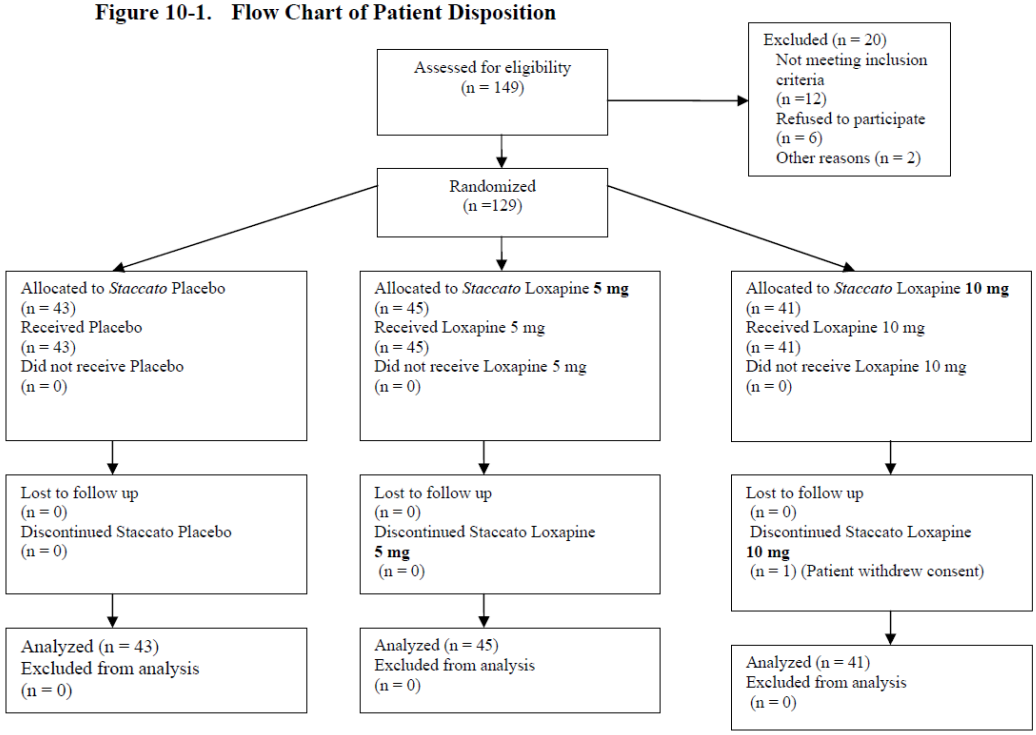


Table 2

Table 11-1. Patient Demographics (Safety Population)

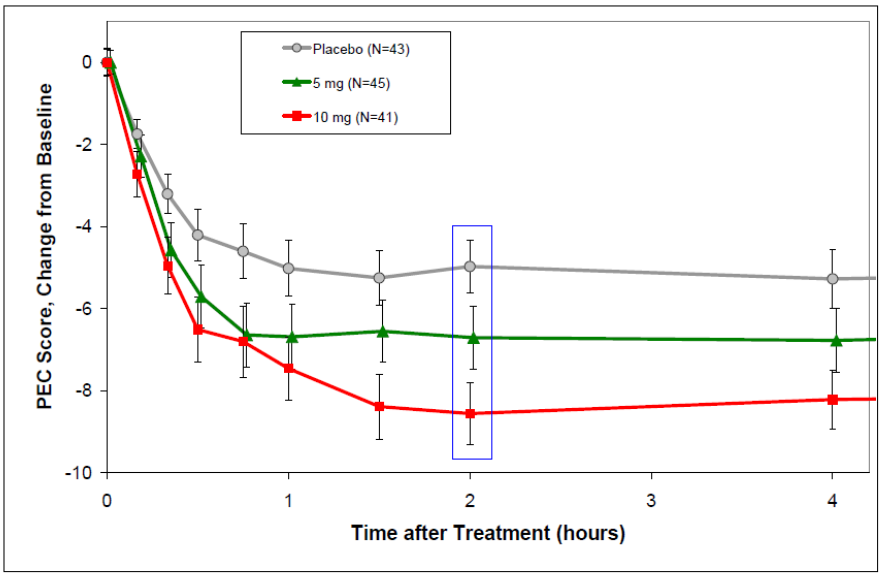
		Placebo (N = 43)	*Staccato* Loxapine 5 mg (N = 45)	*Staccato* Loxapine 10 mg (N = 41)	Overall (N = 129)
Age					
Mean (SD)		43.5 (7.70)	40.8 (7.45)	39.3 (8.77)	41.2 (8.09)
Median		44.0	42.0	37.0	41.0
Minimum, Maximum		21.0, 57.0	26.0, 57.0	23.0, 61.0	21.0, 61.0
Gender					
Male	N (%)	33 (77%)	38 (84%)	34 (83%)	105 (81%)
Female	N (%)	10 (23%)	7 (16%)	7 (17%)	24 (19%)
Race					
Caucasian	N (%)	21 (49%)	19 (42%)	15 (37%)	55 (43%)
Black	N (%)	16 (37%)	20 (44%)	21 (51%)	57 (44%)
Hispanic	N (%)	4 (9%)	5 (11%)	4 (10%)	13 (10%)
Asian	N (%)	1 (2%)	0	1 (2%)	2 (2%)
Other	N (%)	1 (2%)	1 (2%)	0	2 (2%)
Height (in)					
Mean (SD)		67.9 (3.73)	68.6 (3.31)	69.4 (3.46)	68.6 (3.53)
Median		68.0	70.0	69.0	69.0
Minimum, Maximum		61.0, 74.0	60.0, 74.0	62.0, 80.0	60.0, 80.0
Weight (lb)					
Mean (SD)		193 (42.89)	206 (48.13)	199 (46.72)	199 (45.91)
Median		185	195	193	191
Minimum, Maximum		120, 320	115, 321	128, 316	115, 321

SD = standard deviation
Data Source: Table 14.2.1.1

The primary efficacy endpoint was defined as the absolute change in Positive and Negative Syndrome Scale (PANSS) Excited Component (PEC) score from baseline at 2 hours following Staccato Loxapine administration. Change from baseline in PEC score over time are presented in Figure 3.

Figure 3

Figure 11-1. Change from Baseline in PEC Score over 4 hours by Treatment (Mean ± SEM) (ITT w/LOCF Population)



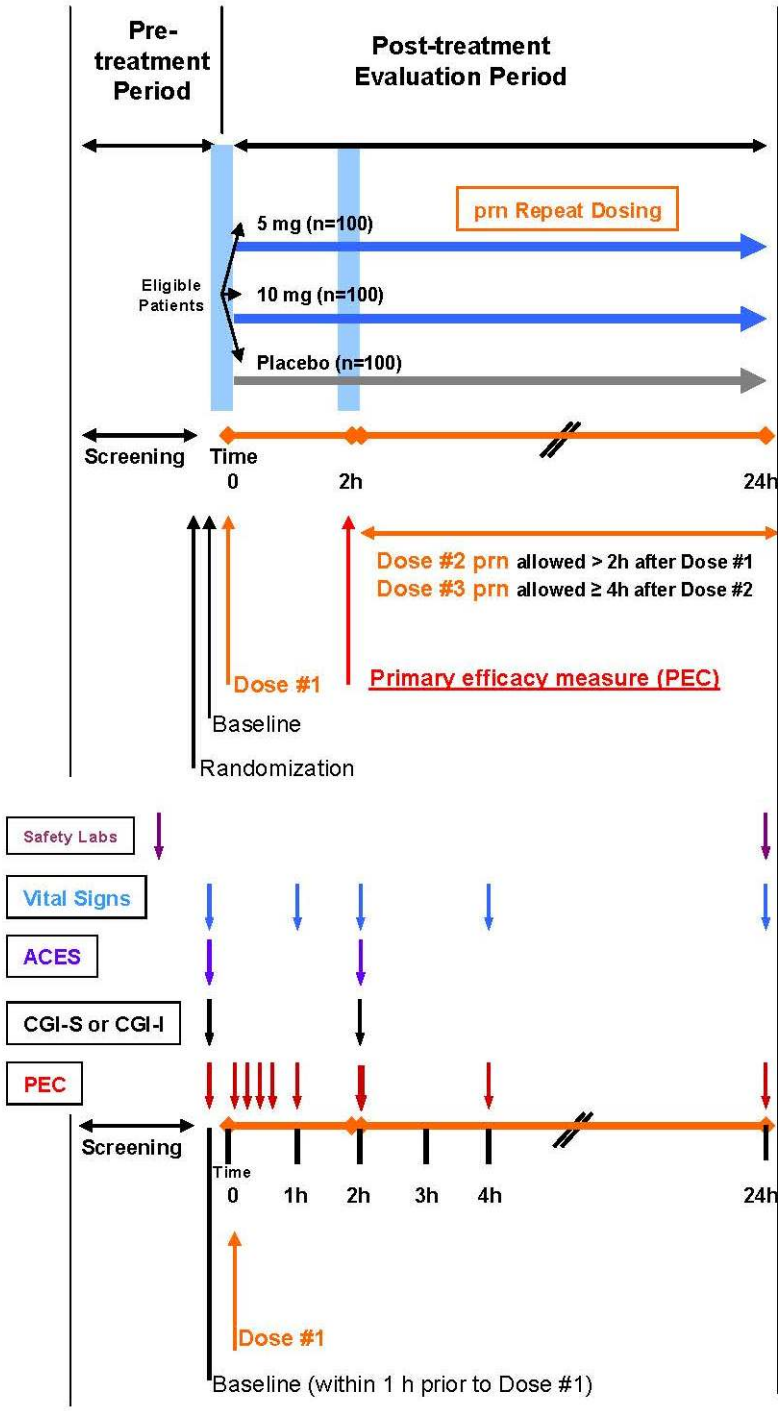
		Time after treatment								
Treatment	Baseline	10 min	20 min	30 min	45 min	1 hr	1.5 hr	2 hr	4 hr	24 hr
Placebo (N=43)										
Mean	0	-1.74	-3.21	-4.21	-4.6	-5.02	-5.26	-4.98	-5.28	-3.77
Std Dev	2.23	2.27	3.14	4.10	4.37	4.47	4.41	4.13	4.75	4.39
5 mg (N=45)										
Mean	0	-2.29	-4.58	-5.71	-6.64	-6.69	-6.56	-6.71	-6.78	-4.84
Std Dev	1.94	3.48	4.55	5.14	5.22	5.26	5.05	5.14	5.22	4.30
p-value*		0.3893	0.1056	0.1345	0.0507	0.1139	0.2028	-	0.1631	0.2477
p-value#								0.0880		
10 mg (N=41)										
Mean	0	-2.73	-4.95	-6.51	-6.8	-7.46	-8.39	-8.56	-8.22	-7.17
Std Dev	2.02	3.51	4.48	5.09	5.54	4.89	5.05	4.90	4.63	4.69
p-value*		0.1276	0.0415	0.0248	0.0461	0.0193	0.0032	-	0.0052	0.0009
p-value#								0.0002		
p-value = 0.0005 for overall treatment effect at 2 hr (by ANCOVA with terms for baseline PEC, treatment and pseudocenter)										

* p-values using Student's t-test for pairwise comparisons of 10 & 5 mg to placebo (unadjusted for multiple comparisons).
# p-values (adjusted) using Dunnett's t-test with ANCOVA model with terms for baseline PEC, treatment and pseudocenter
Source: Tables 14.9.1 (means and SDs with unadjusted p-values by Student's t-tests for secondary endpoints) & 14.10.1 (overall p-value and Dunnett's adjusted p-values for primary endpoint)

2.5.2. Main studies

The 2 main studies (**004-301 and 004-302**) were designed as a double-blind, randomised, placebo-controlled, parallel-group study evaluating the efficacy and safety over 24 hours of loxapine 5 mg and 10 mg inhalation powder administered orally once daily versus placebo. Study 004-301 was conducted in patients with schizophrenia and study 004-302 included patients with Bipolar I disorder (see Figure 4).

Figure 4



Several types of patients could be enrolled: 1) those admitted to a hospital setting or a research unit for the purpose of the study, 2) those already hospitalized for treatment of schizophrenia who had acute agitation, 3) those treated at a psychiatric emergency room setting that allowed extended patient stays in a secluded observation room for the period of the study. Only patients willing and able to stay in the hospital or clinic throughout the post-treatment evaluation period and for at least 12 hours after the last dose of study medication were enrolled.

2.5.2.1. *Methods*

Study Participants

Main inclusion criteria

Male and female patients between the ages of 18 to 65 years inclusive; with DSM-IV diagnostic criteria for schizophrenia in study 004-301; who met DSM-IV criteria for bipolar I disorder, manic or mixed episodes (as confirmed by administration of the Mini International Neuropsychiatric Interview) and with or without psychotic features in study 004-302; judged to be clinically agitated at baseline (with a total score of ≥14 on the 5 items "poor impulse control, tension, hostility, uncooperativeness, and excitement" comprising the PEC scale), with a value of ≥4 (out of 7) on at least 1 of the 5 items on the PEC scale, who read and understand English and provided written informed consent, in good general health prior to study participation as determined by a detailed medical history, physical examination, and 12-lead electrocardiogram (ECG); using appropriate contraceptive methods during the study and for 1 week following the end of the study.

Main exclusion criteria

Patients who met any of the following criteria were excluded: agitation caused primarily by acute intoxication upon investigator opinion ; positive urine drug screen for psychostimulants (eg, cocaine, phencyclidine [PCP]) ; history within the past 2 months of drug or alcohol dependence as defined by DSM-IV; judged to be at serious risk for suicide; treatment with benzodiazepines or other hypnotics or oral or short-acting i.m. antipsychotics within 4 hours prior to study drug; treatment with injectable depot neuroleptics within 1 dose interval prior to study drug administration; history of allergy or intolerance to loxapine or amoxapine were to be excluded; female patients who had a positive pregnancy test at screening or were breast-feeding;laboratory or ECG abnormalities considered significant by the investigator that would have clinical implications for the patient's participation in the study ; significant hepatic, renal, gastroenterologic, respiratory, cardiovascular (including ischemic heart disease and congestive heart failure), endocrinologic, neurologic, or hematologic disease; clinically significant acute or chronic pulmonary disease (eg, clinically apparent asthma, chronic bronchitis, emphysema); treatment with an investigational drug within 30 days prior to screening were to be excluded; unsuitable candidate for receiving Staccato Loxapine, or likely to be unable to use the inhalation device, as judged by the investigator.

In study 004-301, additional exclusion criteria were: patients with a diagnosis of schizophrenia, schizoaffective disorder, delirium, dementia, or any psychiatric diagnosis other than bipolar I disorder that required pharmacotherapy; who had taken fluoxetine (Prozac) during the 30 days prior to randomization, or other antidepressants during the 7 days prior to randomization; who have taken anticonvulsants with the exception of stable doses of valproate in the 7 days prior to randomization.

Treatments

Patients were randomized to treatment in a 1:1:1 ratio. As part of the screening process, patients were evaluated for their ability to properly perform the inhalation maneuver required to use Staccato Loxapine/Staccato Placebo. Post-treatment period started with the administration of Dose 1 (Time 0) and continued for 24 hours. If required, a maximum of 3 doses of study medication were allowed during that 24-hour period. If agitation did not subside sufficiently after the first dose of study medication or if it recurred, a second dose could be given >2 hours after Dose 1 (after completion of

the 2-hour efficacy assessments). If necessary, a third dose could be given ≥4 hours after the second dose. Unless medically required, rescue medication (i.m. lorazepam) was not to be used until after the 2-hour efficacy assessments had been completed, the second dose of study medication had been given, and at least 20 minutes had elapsed after administration of study medication.

Outcomes/endpoints

The primary efficacy measure was the absolute change in PEC score from baseline to 2 hours following the first dose (Dose 1).

Main secondary efficacy measure was the value of the Clinical Global Impression – Improvement Scale (CGI-I) score 2 hours after Dose 1. Other secondary efficacy measures included changes from baseline in PEC scores at 10, 20, 30, and 45 minute after first dose for 10 mg dose only.

Tertiary Endpoints included: CGI-I responders 2 hours after Dose 1 [defined as patients with a score of 1 (very much improved) or 2 (much improved) on the CGI-I scale; CGI-I non-responders were defined as patients with scores from 3 (minimally improved) through 7 (very much worse); a value of 0 (not assessed) was considered missing]; changes from baseline in PEC score at 60 minutes, 90 minutes, 4 hours, and 24 hours after Dose 1 for 10 mg dose only; total number of patients per group who received 1, 2, or 3 doses of study medication with and without rescue medication by 4 hours and 24 hours after Dose 1; time to rescue medication during the entire 24-hour post-treatment evaluation period; time to the second dose 2 (Dose 2) during the 24-hour post-treatment evaluation period (prn); Agitation-Calmness Evaluation Scale (ACES) score 2 hours after Dose 1.

Sample size

The planned enrolment of approximately 300 patients (100 per group) would provide 99 % statistical power for the 10 mg dose Placebo pairwise comparison and 79 % statistical power for the 5 mg dose pairwise comparison for the primary efficacy analysis based on study 004-201 results.

Randomisation

Patients were assigned a unique number corresponding to the patient number on the study drug label. A computer-generated randomization schedule was used to package and label the study medication with sequential patient number.

Blinding (masking)

Study medication was packaged into labelled kits containing 3 single dose devices with an identical, blinded label. The label on the kit was detachable, to be removed and affixed in the drug accountability log at randomization. All labels included protocol number and patient number. In case of emergency treatment information could be accessed from the blinded label in the drug accountability log.

Statistical methods ANCOVA/ANOVA

The primary analysis was evaluated in the intent-to-treat population with last observation carried forward (ITT with LOCF). It included all patients who received any study medication and had both baseline and at least one post-dose efficacy assessment or used rescue medication before 2 hours after dosing. Missing values were replaced using the LOCF algorithm. Any observations recorded after the use of rescue medication were considered missing and subject to the LOCF algorithm. The LOCF

approach was not required for survival analyses, in which the standard right-censoring approach was applied. The safety population included all patients who received any study medication.

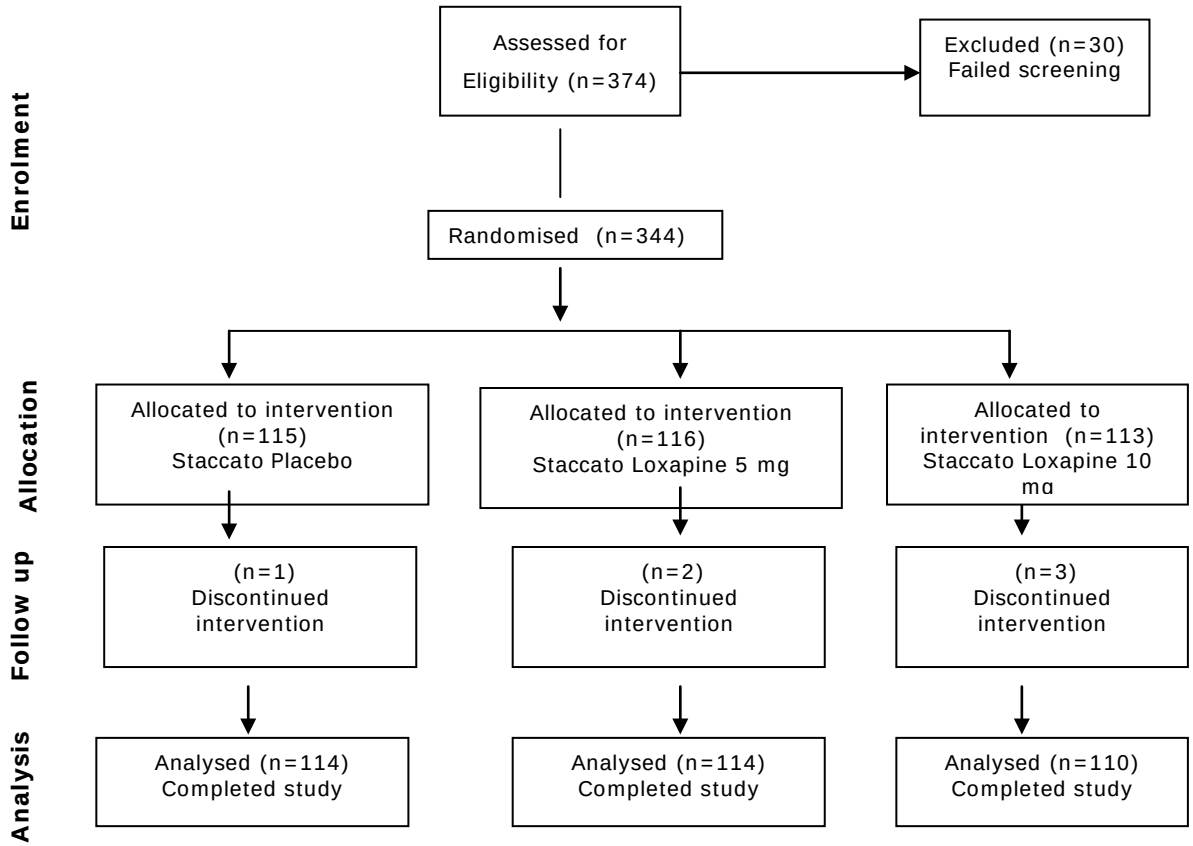
The primary and secondary outcome measures were analysed using ANCOVA model, with a global F-test and Dunnett's t-tests for the follow-up active/placebo pairwise comparisons (adjusted for multiple comparisons). A main-effects ANCOVA model including terms for baseline PEC score, treatment, and center (ie, pseudocenter) was used to assess the overall treatment effect. Treatment and pseudocenter effects were considered statistically significant if $p \leq 0.05$. A family-wise α-level of 0.05 was maintained for the primary and secondary analyses using a global "gatekeeper" tests with follow-up (adjusted) pairwise testing, and a closed-method hierarchical testing strategy. Sensitivity analyses on primary and secondary outcome measures were also performed to test the robustness of the adjusted p-values derived from the multiplicity testing procedure. Tertiary efficacy outcome measures were analysed using a 2-sided test at a nominal $\alpha=0.05$ level.

2.5.2.1.1. **Results**

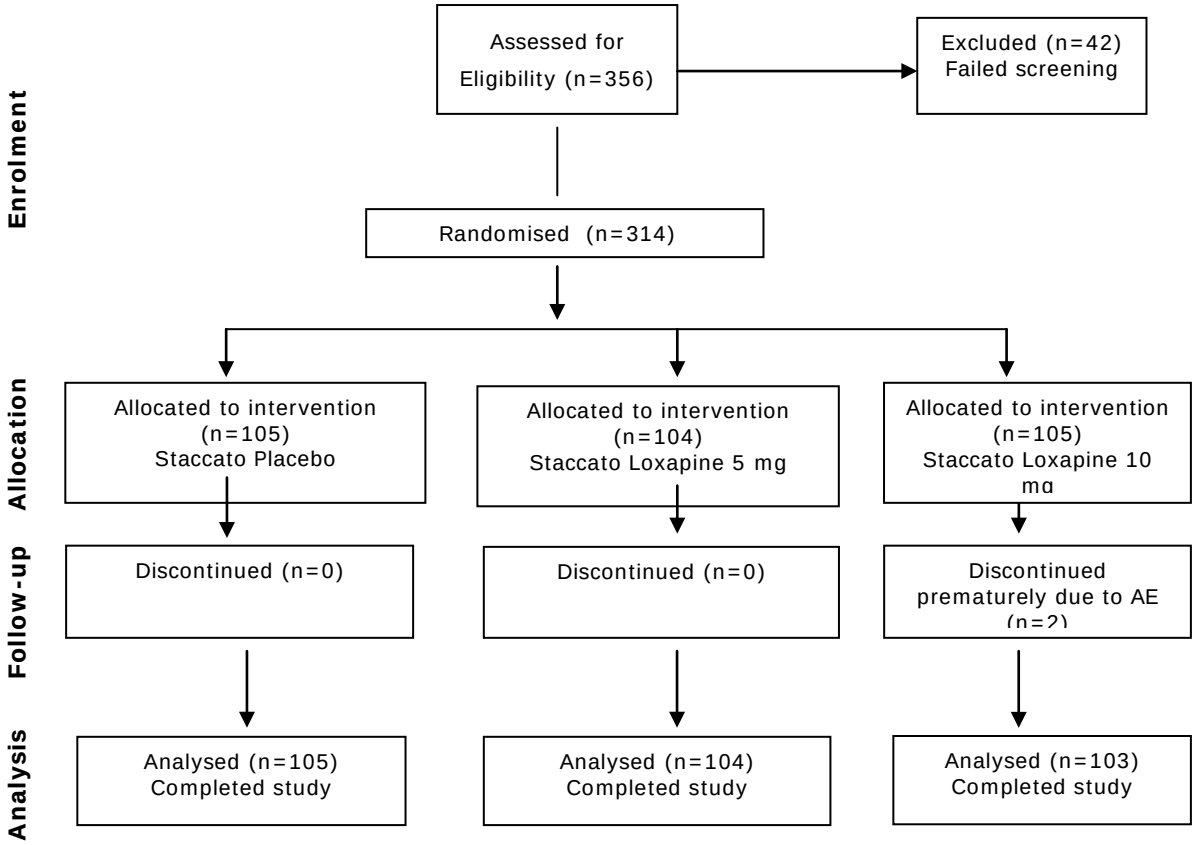
Participant flow

This is presented in Figures 5 and 6.

Study 004-301- Figure 5



Study 004-302- Figure 6



Recruitment

Study period was from 22 February 2008 to 27 June 2008 for study 004-301 and from 24 July 2008 to 2 November 2008 for study 004-302.

Conduct of the study

In both studies, the original protocol was not amended and important protocol deviations were related to enrolment criteria, the study and rescue medication regimens, the use of prohibited concomitant medications, a failure to manage a patient according to withdrawal criteria, and any other deviation judged by the medical monitor to warrant inclusion in the clinical study report. In study 004-301, important protocol deviations were identified for 11 patients (3.2%) in study 004-301 and 28 patients (8.9%) in study 004-302. These were not considered to significantly influence the results of both studies.

Baseline data

In study 004-301, mean age was 43.1 years, and the majority were male (73.5%). Most were either Black (57.6%) or Caucasian (33.7%), with a slightly higher percentage of Caucasians in the 5 mg group (41.4%) compared with the 10 mg and placebo groups (31.9 and 27.8% , respectively). Most patients had a history of smoking (current smokers, 81.7%; ex-smokers, 7.8%).

In study 004-302, males (49.7%) and females (50.3%) had their mean age value as 40.8 years. Most patients were either Black (44.3%) or Caucasian (43.9%) and had a history of smoking (current smokers, 74.5%; ex-smokers, 8.0%).

All patients had bipolar I disorder (manic in 68.8% of patients, and mixed in the remaining 31.2%). Across treatment groups, the mean time since diagnosis of bipolar disorder ranged from 11.7 to 12.8 years. At screening the mean duration of the current episode of agitation ranged from 9.7 to 16.0 days (medians ranged from 5.0 to 6.2 days).

Other baseline data are presented in Tables 3-6 and Figures 7-8.

Study 004-301

Table 3. Baseline Disease Characteristics (Safety Population)

Baseline Disease Characteristic	Staccato Placebo (N=115)	Staccato Loxapine 5 mg (N=116)	Staccato Loxapine 10 mg (N=113)
Diagnosis, n (%):			
Schizophrenia	115 (100%)	116 (100%)	113 (100%)
PEC score at baseline			
Mean (SD)	17.4 (1.80)	17.8 (2.34)	17.6 (2.06)
Median	17	18	17
Min, max	14, 24	14, 28	14, 27
CGI-S score at baseline			
Mean (SD)	3.9 (0.53)	4.0 (0.56)	4.1 (0.60)
Median	4	4	4
Min, max	2, 5	3, 6	2, 6
Time since diagnosis (years)			
Mean (SD)	18.8 (10.34)	16.5 (10.80)	18.2 (10.03)
Median	18	15.5	18
Min, Max	0, 40	0, 41	1, 49
No. of previous hospitalizations			
Mean (SD)	9.6 (8.96)	9.2 (12.22)	9.7 (11.26)
Median	8	6	6
Min, Max	0, 50	0, 99	0, 90
Duration of current agitation episode at screening (days)			
Mean (SD)	6.9 (9.21)	6.1 (7.50)	7.6 (11.52)
Median	4	4	4
Min, Max	<1, 72	<1, 45	<1, 90

CGI-S=Clinical Global Impression - Severity Scale; PEC=Positive and Negative Symptom Scale, Excited Component
Source: Section 11.1, Tables 1.12.1, 2.4, 2.7; Appendix 12.2, Listings 1.15, 2.1.2, 2.2

Figure 7

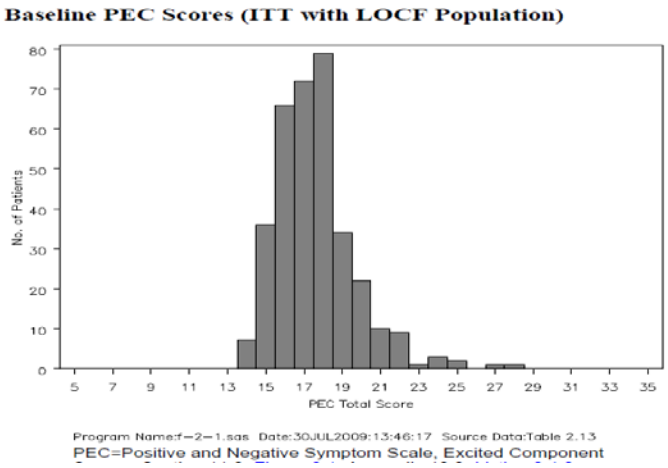


Table 4. ATC Medication Classes Taken Before Screening by at Least 5% of Patients in Any Treatment Group (Safety Population)

ATC Class	*Staccato* Placebo (N=115)	*Staccato* Loxapine 5 mg (N=116)	*Staccato* Loxapine 10 mg (N=113)
Antipsychotics	9 (7.8%)	9 (7.8%)	9 (8.0%)
Benzodiazepine derivates	12 (10.4%)	6 (5.2%)	10 (8.8%)
Benzodiazepine-related drugs	8 (7.0%)	7 (6.0%)	4 (3.5%)
Butyrophenone derivatives	6 (5.2%)	9 (7.8%)	4 (3.5%)
Diazepines, oxazepines, and thiazepines	44 (38.3%)	39 (33.6%)	34 (30.1%)
Ethers of tropine or tropine derivatives	8 (7.0%)	14 (12.1%)	14 (12.4%)
Fatty acid derivatives	3 (2.6%)	10 (8.6%)	7 (6.2%)
Other antidepressants	10 (8.7%)	10 (8.6%)	5 (4.4%)
Other antipsychotics	13 (11.3%)	14 (12.1%)	15 (13.3%)
Phenothiazines with piperazine structure	4 (3.5%)	5 (4.3%)	7 (6.2%)
Selective serotonin reuptake inhibitors	7 (6.1%)	9 (7.8%)	9 (8.0%)

ATC=Anatomical, Therapeutic, Chemical (classification)
Medications taken in the 30 days before screening
Source: Section 11.1, Table 1.9; Appendix 12.2, Listing 1.13

Study 004-302

Table 5. Baseline Disease Characteristics (Safety Population)

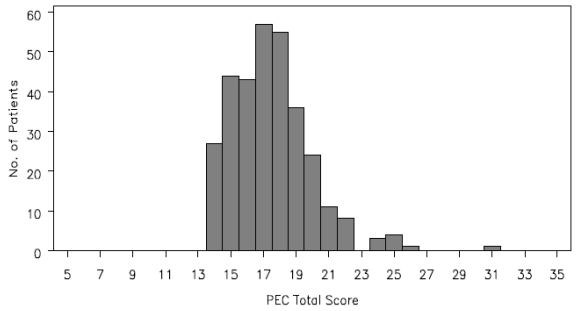
Baseline Disease Characteristic	*Staccato* Placebo (N=105)	*Staccato* Loxapine 5 mg (N=104)	*Staccato* Loxapine 10 mg (N=105)
Diagnosis, n (%):			
Bipolar I disorder, manic episodes	72 (68.6%)	68 (65.4%)	76 (72.4%)
Bipolar I disorder, mixed episodes	33 (31.4%)	36 (34.6%)	29 (27.6%)

PEC score at baseline			
Mean (SD)	17.7 (2.80)	17.4 (2.23)	17.3 (2.25)
Median	17	17	17
Min, max	14, 31	14, 26	14, 25
CGI-S score at baseline			
Mean (SD)	4.1 (0.57)	4.0 (0.53)	4.0 (0.49)
Median	4	4	4
Min, max	2, 6	3, 6	3, 5
Time since diagnosis (years)			
Mean (SD)	18.8 (10.34)	16.5 (10.80)	18.2 (10.03)
Median	10	10	9
Min, Max	0, 45	0, 38	0, 38
No. of previous hospitalizations			
Mean (SD)	5.9 (6.57)	5.5 (6.55)	5.1 (6.41)
Median	4	3	3
Min, Max	0, 30	0, 30	0, 30
Duration of current agitation episode at screening (days)			
Mean (SD)	14.2 (21.52)	16.0 (32.36)	9.7 (10.19)
Median	6.2	6.2	5
Min, Max	0.25, 146	0.25, 210	0.25, 45

CGI-S=Clinical Global Impression - Severity Scale; PEC=Positive and Negative Symptom Scale, Excited Component
Source: Section 11.1, Tables 1.11.1, 2.4, and 2.7; Appendix 12.2, Listings 1.15, 2.1.2, and 2.2

Figure 8

Baseline PEC Scores (ITT Population with LOCF)



Program Name:f-2-1.sas Date:23APR2009: 8:03:10 Source Data:Table 2.13
PEC=Positive and Negative Symptom Scale, Excited Component

Table 6. ATC Medication Classes Taken Before Screening by at Least 5% of Patients in Any Treatment Group (Safety Population)

ATC Class[a]	*Staccato* Placebo (N=105)	*Staccato* Loxapine 5 mg (N=104)	*Staccato* Loxapine 10 mg (N=105)
ACE inhibitors, plain	1 (1.0%)	8 (7.7%)	5 (4.8%)
Antipsychotics	12 (11.4%)	12 (11.5%)	10 (9.5%)
Benzodiazepine derivates	11 (10.5%)	15 (14.4%)	10 (9.5%)
Benzodiazepine-related drugs	4 (3.8%)	11 (10.6%)	8 (7.6%)
Diazepines, oxazepines, and thiazepines	28 (26.7%)	37 (35.6%)	26 (24.8%)
Drugs used in nicotine dependence	1 (1.0%)	4 (3.8%)	6 (5.7%)
Fatty acid derivatives	18 (17.1%)	16 (15.4%)	24 (22.9%)
Indole derivatives	7 (6.7%)	8 (7.7%)	3 (2.9%)
Lithium	12 (11.4%)	15 (14.4%)	19 (18.1%)
Other antidepressants	4 (3.8%)	9 (8.7%)	12 (11.4%)
Other antiepileptics	5 (4.8%)	6 (5.8%)	3 (2.9%)
Other antipsychotics	3 (2.9%)	4 (3.8%)	12 (11.4%)
Other hypnotics and sedatives	5 (4.8%)	1 (1.0%)	7 (6.7%)
Propionic acid derivatives	9 (8.6%)	11 (10.6%)	2 (1.9%)
Proton pump inhibitors	5 (4.8%)	8 (7.7%)	5 (4.8%)
Selective serotonin reuptake inhibitors	8 (7.6%)	5 (4.8%)	6 (5.7%)
Thiazides, plain	4 (3.8%)	8 (7.7%)	7 (6.7%)
Thyroid hormones	2 (1.9%)	6 (5.8%)	3 (2.9%)

ATC=Anatomical, Therapeutic, Chemical (classification)
a. Taken in the 30 days before screening
Source: Section 11.1, Table 1.9; Appendix 12.2, Listing 1.13

Number analysed

In both studies, no patient was reported to have failed screening because of an inability or unwillingness to use the Staccato system, the most commonly reason patients failed screening was because they did not meet the enrolment criteria. Number of patients that were screened but not enrolled was 30 and 42, for studies 004-301 and 004-302, respectively.

Number of patients analysed are presented in Tables 7 and 8.

Study 004-301

Table 7. Study Populations

Study Population	*Staccato* Placebo (N=115)	*Staccato* Loxapine 5 mg	*Staccato* Loxapine 10 mg (N=113)	Total (N=344)

Safety population, n (%)	115 (100%)	116 (100%)	113 (100%)	344 (100%)
ITT population with LOCF, n (%)	115 (100%)	116 (100%)	112 (99.1%)	343 (99.7%)

ITT=intent to treat, LOCF=last observation carried forward
Source: Section 11.1, Table 1.1; Appendix 12.2, Listings 1.4, 1.6

Study 004-302

Table 8. Study Populations

Study Population	***Staccato* Placebo** (N=105)	***Staccato* Loxapine 5 mg** (N=104)	***Staccato* Loxapine 10 mg** (N=105)	**Total** (N=314)
Safety population, n (%)	105 (100%)	104 (100%)	105 (100%)	314 (100%)
ITT population with LOCF, n (%)	105 (100%)	104 (100%)	105 (100%)	314 (100%)

ITT=intent to treat, LOCF=last observation carried forward
Source: Section 11.1, Table 1.1; Appendix 12.2, Listings 1.4 and 1.6

Outcomes and estimation

Results on the primary outcome measures are presented in Tables 9-10 and Figures 9-10.

Study 004-301

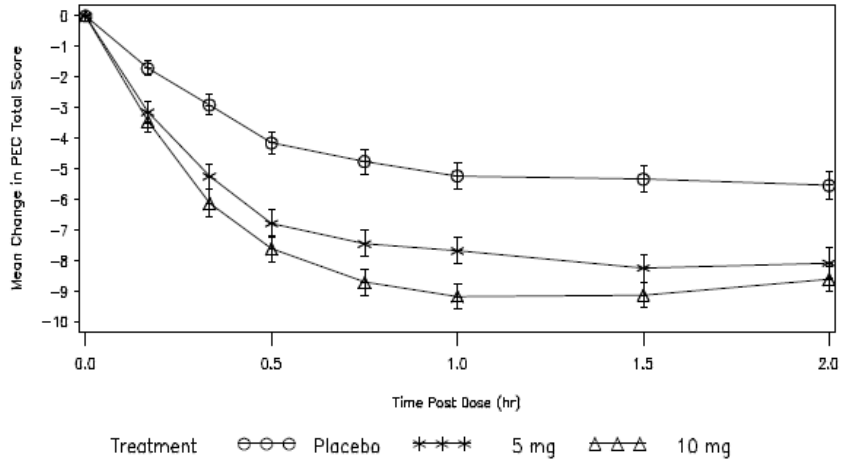
Table 9. Primary Efficacy Endpoint: Change in the PEC Score 2 Hours after Dose 1 (ITT Population with LOCF)

PEC Score	***Staccato* Placebo** (N=115)	***Staccato* Loxapine 5 mg** (N=116)	***Staccato* Loxapine 10 mg** (N=112)
Baseline PEC score			
Mean (SD)	17.4 (1.80)	17.8 (2.34)	17.6 (2.06)
Median	17	18	17
Min, max	14, 24	14, 28	14, 27
Change in PEC score from baseline to 2 hours after Dose 1			
LS mean[a]	-5.8	-8.0	-8.7
Mean (SD)	-5.5 (4.92)	-8.1 (5.17)	-8.6 (4.37)
Median	-5	-9	-10
Min, max	-18, 10	-19, 7	-16, 2
p-value for overall treatment effect[b]	p<0.0001	—	—
p-values for active/placebo comparisons[c]	—	p=0.0004	p<0.0001

ITT=intent to treat; LOCF=last observation carried forward; LS mean=least squares mean; PEC=Positive and Negative Symptom Scale, Excited Component
a. LS mean was used in the primary efficacy analysis
b. ANCOVA model with terms for baseline PEC total score, pseudocenter, and treatment
c. Dunnett's t-test; Source: Section 11.1, Tables 2.1, 2.7; Appendix 12.2, Listing 2.1.2

Figure 9

Figure 3. Mean (SEM) Change in PEC Score from Baseline to 2 Hours — Study 004-301 — Schizophrenia (ITT Population with LOCF)



Mean (SEM)	10 minutes	20 minutes	30 minutes	45 minutes	1 hour	1.5 hours	2 hours
Placebo:	-1.7 (0.23)	-2.9 (0.33)	-4.1 (0.38)	-4.8 (0.41)	-5.2 (0.45)	-5.3 (0.43)	-5.5 (0.46)
5 mg:	-3.1 (0.36)	-5.2 (0.42)	-6.8 (0.44)	-7.4 (0.44)	-7.7 (0.44)	-8.2 (0.45)	-8.1 (0.48)
10 mg:	-3.4 (0.34)	-6.1 (0.45)	-7.6 (0.45)	-8.7 (0.42)	-9.2 (0.42)	-9.1 (0.4)	-8.6 (0.41)

SEM=standard error of the mean

Source: m5.3.5.1, CSR 004-301, Section 11.1, Tables 2.1, 2.7, 2.15

Study 004-302

Table 10. Primary Efficacy Endpoint: Change in the PEC Score 2 Hours after Dose 1 (ITT Population with LOCF)

PEC Score	***Staccato*** **Placebo** (N=105)	***Staccato*** **Loxapine 5 mg** (N=104)	***Staccato*** **Loxapine 10 mg** (N=105)
Baseline PEC score			
Mean (SD)	17.7 (2.80)	17.4 (2.23)	17.3 (2.25)
Median	17	17	17
Min, max	14, 31	14, 26	14, 25
Change in PEC score from baseline to 2 hours after Dose 1			
LS mean[a]	-4.7	-8.2	-9.2
Mean (SD)	-4.9 (4.77)	-8.1 (4.90)	-9.0 (4.67)
Median	-3	-9	-10
Min, max	-19, 5	-21, 2	-20, 4
p-value for overall treatment effect[b]	p<0.0001	—	—
p-values for active/placebo comparisons[c]	—	p<0.0001	p<0.0001

ITT=intent to treat; LOCF=last observation carried forward; LS mean=least squares mean; PEC=Positive and Negative Symptom Scale, Excited Component

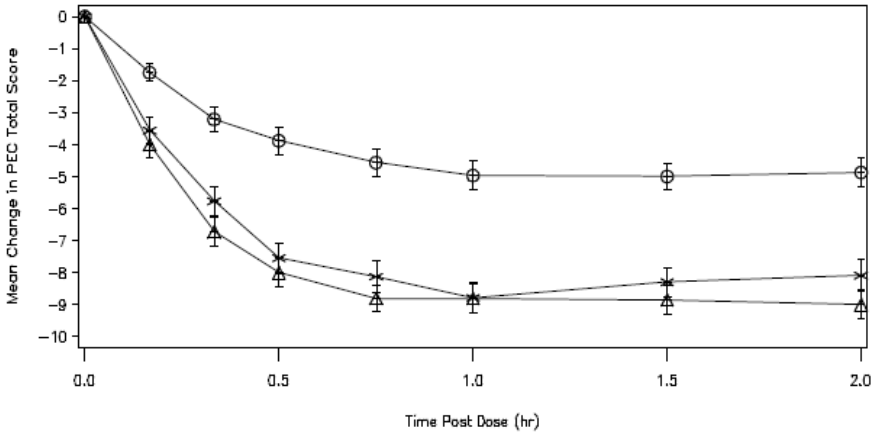
a. LS mean was used in the primary efficacy analysis

b. ANCOVA model with terms for baseline PEC total score, pseudocenter, and treatment

c. Dunnett's t-test; Source: Section 11.1, Tables 2.1 and 2.7; Appendix 12.2, Listing 2.1.2

Figure 10

Figure 4. Mean (SEM) Change in PEC Score from Baseline to 2 Hours — Study 004-302 — Bipolar Disorder (ITT Population with LOCF)



Mean (SEM)	10 minutes	20 minutes	30 minutes	45 minutes	1 hour	1.5 hours	2 hours
Placebo:	-1.8 (0.29)	-3.2 (0.39)	-3.9 (0.43)	-4.6 (0.43)	-5.0 (0.45)	-5.0 (0.42)	-4.9 (0.47)
5 mg:	-3.6 (0.4)	-5.8 (0.46)	-7.5 (0.47)	-8.1 (0.47)	-8.8 (0.46)	-8.3 (0.46)	-8.1 (0.48)
10 mg:	-4.0 (0.4)	-6.7 (0.45)	-8.0 (0.46)	-8.8 (0.43)	-8.8 (0.44)	-8.8 (0.46)	-9.0 (0.46)

Source: m5.3.5.1, CSR 004-302, Section 11.1, Tables 2.1, 2.7, 2.15

Results of main secondary outcome measure are presented in Tables 11 and 12.

Study 004-301

Table 11. Key Secondary Efficacy Endpoint: CGI-I Score 2 Hours after Dose 1 (ITT Population with LOCF)

CGI-S or CGI-I Score	***Staccato*** **Placebo** (N=115)	***Staccato*** **Loxapine 5 mg**[e] (N=116)	***Staccato*** **Loxapine 10 mg** (N=112)
Baseline (CGI-S score [a])			
Mean (SD)	3.9 (0.53)	4.0 (0.55)	4.1 (0.60)
Median	4	4	4
Min, max	2, 5	3, 6	2, 6
2 hours (CGI-I score [b])			
Mean (SD)	2.8 (1.11)	2.3 (1.24)	2.1 (1.00)
Median	3	2	2
Min, max	1, 5	1, 7	1. 4
p-value for overall treatment effect[c]	p<0.0001	—	—
p-values for active/placebo comparisons[d]	—	p=0.0015	p<0.0001

CGI-I=Clinical Global Impression - Improvement Scale; CGI-S=Clinical Global Impression - Severity Scale; ITT=intent to treat; LOCF=last observation carried forward; a. CGI-S scale was used for baseline assessment (0=not assessed, 1=normal, not at all agitated, 2=borderline agitated, 3=mildly agitated, 4=moderately agitated, 5=markedly agitated, 6=severely agitated, 7=among the most extremely agitated patients); b. CGI-I scale was used for assessment after treatment (0=not assessed, 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, 7=very much worse); c. ANOVA with terms for pseudocenter and treatment d. Dunnett's t-test; e. Patient 19-408 was excluded from this analysis because she discontinued before the 2-hour CGI-Iassessment. Source: Section 11.1, Tables 2.4, 2.5; Appendix 12.2, Listing 2.2

Study 004-302

Table 12. Key Secondary Efficacy Endpoint: CGI-I Score 2 Hours after Dose 1 (ITT Population with LOCF)

CGI-S or CGI-I Score	***Staccato* Placebo** (N=105)	***Staccato* Loxapine 5 mg** (N=104)	***Staccato* Loxapine 10 mg** (N=105)
Baseline (CGI-S score [a])			
Mean (SD)	4.1 (0.57)	4.0 (0.53)	4.0 (0.49)
Median	4	4	4
Min, max	2, 6	3, 6	3, 5
2 hours (CGI-I score [b])			
Mean (SD)	3.0 (0.99)	2.1 (1.10)	1.9 (1.14)
Median	3	2	2
Min, max	1, 5	1, 4	1. 6
p-value for overall treatment effect[c]	p<0.0001	—	—
p-values for active/placebo comparisons[d]	—	p<0.0001	p<0.0001

CGI-I=Clinical Global Impression - Improvement Scale; CGI-S=Clinical Global Impression - Severity Scale; ITT=intent to treat; LOCF=last observation carried forward; a. CGI-S scale was used for baseline assessment (0=not assessed, 1=normal, not at all agitated, 2=borderline agitated, 3=mildly agitated, 4=moderately agitated, 5=markedly agitated, 6=severely agitated, 7=among the most extremely agitated patients); b. CGI-I scale was used for assessment after treatment (0=not assessed, 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, 7=very much worse); c. ANOVA with terms for pseudocenter and treatment d. Dunnett's t-test; e. Patient 19-408 was excluded from this analysis because she discontinued before the 2-hour CGI-Iassessment. Source: Section 11.1, Tables 2.4, 2.5; Appendix 12.2, Listing 2.2

Other secondary efficacy results are presented in Tables 13 and 14.

Study 004-301

Table 13. Change in the PEC Score at Assessments through 24 Hours after Dose 1 (ITT Population with LOCF)

PEC Score	***Staccato* Placebo** (N=115)	***Staccato* Loxapine 5 mg** (N=116)	***Staccato* Loxapine 10 mg** (N=112)
Baseline (mean)	**17.4**	**17.8**	**17.6**
+10 minutes (mean change) p-value	-1.7	-3.1 NA[b]	-3.4 p<0.0001[c]
+20 minutes (mean change) p-value	-2.9	-5.2 NA[b]	-6.1 p<0.0001[c]
+30 minutes (mean change) p-value	-4.1	-6.8 NA[b]	-7.6 p<0.0001[c]
+45 minutes (mean change) p-value	-4.8	-7.4 NA[b]	-8.7 p<0.0001[c]
+1 hour (mean change) p-value	-5.2	-7.7 NA[b]	-9.2 p<0.0001[c]
+1.5 hours (mean change) p-value	-5.3	-8.2 NA[b]	-9.1 p<0.0001[c]

+2 hours; primary endpoint (LS mean change)[a] p-value	**-5.8**	**-8.0 p=0.0004**	**-8.7 p<0.0001**
+4 hours (mean change) p-value	-6.3	-8.2 NA[b]	-9.5 p<0.0001[c]
+24 hours (mean change) p-value	-4.4	-6.2 NA[b]	-6.9 p<0.0001[c]

ANCOVA=analysis of covariance; ITT=intent to treat; LOCF=last observation carried forward; LS mean=least squares mean; PEC=Positive and Negative Symptom Scale, Excited Component; a. Primary endpoint analyzed by ANCOVA with Dunnett's t-test, with terms for baseline PEC score, pseudocenter, and treatment; the arithmetic mean changes from baseline to 2 hours are as follows: -5.5 for placebo; -8.1 for 5 mg; -8.6 for 10 mg; b. 5 mg versus placebo was not analyzed statistically for this assessment, per the statistical analysis plan; c. Changes from baseline to 10, 20, 30, and 45 minutes after Dose 1 (10-mg/placebo) are secondary endpoints; changes from baseline to 1, 1.5, 4, and 24 hours after Dose 1 (10-mg/placebo) are tertiary endpoints; analyzed by ANCOVA, with terms for baseline PEC score, pseudocenter, and treatment. Source: Section 11.1, Tables 2.1, 2.7, 2.15; Appendix 12.2, Listing 2.1.2

Study 004-302

Table 14. Change in the PEC Score at Assessments through 24 Hours after Dose 1 (ITT Population with LOCF)

PEC Score	***Staccato* Placebo** (N=105)	***Staccato* Loxapine 5 mg** (N=104)	***Staccato* Loxapine 10 mg** (N=105)
Baseline (mean)	**17.7**	**17.4**	**17.3**
+10 minutes (mean change) p-value	-1.8	-3.6 NA[b]	-4.0 p<0.0001[c]
+20 minutes (mean change) p-value	-3.2	-5.8 NA[b]	-6.7 p<0.0001[c]
+30 minutes (mean change) p-value	-3.9	-7.5 NA[b]	-8.0 p<0.0001[c]
+45 minutes (mean change) p-value	-4.6	-8.1 NA[b]	-8.8 p<0.0001[c]
+1 hour (mean change) p-value	-5.0	-8.8 NA[b]	-8.8 p<0.0001[c]
+1.5 hours (mean change) p-value	-5.0	-8.3 NA[b]	-8.8 p<0.0001[c]
+2 hours; primary endpoint (LS mean change)[a], p-value	**-4.7**	**-8.2 p<0.0001**	**-9.2 p<0.0001**
+4 hours (mean change) p-value	-6.1	-8.3 NA[b]	-9.3 p<0.0001[c]
+24 hours (mean change) p-value	-4.5	-6.1 NA[b]	-6.0 p=0.0011[c]

ANCOVA=analysis of covariance; ITT=intent to treat; LOCF=last observation carried forward; LS mean=least squares mean; PEC=Positive and Negative Symptom Scale, Excited Component;a. Primary endpoint analyzed by ANCOVA with Dunnett's t-test, with terms for baseline PEC score, pseudocenter, and treatment; the arithmetic mean changes from baseline to 2 hours are as follows: -5.5 for placebo; -8.1 for 5 mg; -8.6 for 10 mg; b. 5 mg versus placebo was not analyzed statistically for this assessment, per the statistical analysis plan; c. Changes from baseline to 10, 20, 30, and 45 minutes after Dose 1 (10-mg/placebo) are secondary endpoints; changes from baseline to 1, 1.5, 4, and 24 hours after Dose 1 (10-mg/placebo) are tertiary endpoints; analyzed by ANCOVA, with terms for baseline PEC score, pseudocenter, and treatment. Source: Section 11.1, Tables 2.1, 2.7, 2.15; Appendix 12.2, Listing 2.1.2

Results of the CGI-I responder analysis, Agitation-Calmness Evaluation Scale (ACES) score 2 hours after Dose 1 and total number of patients per group who received 1, 2, or 3 doses of study medication with and without rescue medication by 4 hours and 24 hours after Dose 1 are summarised in Tables 15-22.

Study 004-301

Table 15. Distribution of CGI-I Scores 2 Hours after Dose 1 (ITT Population with LOCF)

CGI-I Score[a] (Description), n (%)	***Staccato* Placebo** (N=115)	***Staccato* Loxapine 5 mg[b]** (N=116)	***Staccato* Loxapine 10 mg** (N=112)
1 (very much improved)	20 (17.4%)	38 (33.0%)	41 (36.6%)
2 (much improved)	21 (18.3%)	28 (24.3%)	34 (30.4%)
3 (minimally improved)	34 (29.6%)	28 (24.3%)	26 (23.2%)
4 (no change)	39 (33.9%)	18 (15.7%)	11 (9.8%)
5 (minimally worse)	1 (0.9%)	1 (0.9%)	0
6 (much worse)	0	1 (0.9%)	0
7 (very much worse)	0	1 (0.9%)	0

CGI-I=Clinical Global Impression - Improvement Scale; ITT=intent to treat; LOCF=last observation carried forward; a. CGI-I scale was used for assessment after treatment; b. One was excluded from this analysis because she discontinued before the 2-hour CGI-I assessment. Source: Section 11.1, Table 2.4; Appendix 12.2, Listing 2.2

Table 16. ACES Score 2 Hours after Dose 1 (ITT Population with LOCF)

ACES Score[a]	***Staccato* Placebo** (N=115)	***Staccato* Loxapine 5 mg[b]** (N=116)	***Staccato* Loxapine 10 mg** (N=112)
Baseline			
Mean (SD)	2.3 (0.51)	2.2 (0.63)	2.2 (0.51)
Median	2	2	2
Min, max	1, 4	1, 5	1, 4
+2 hours (observed value)			
Mean (SD)	3.9 (1.76)	4.7 (2.09)	4.9 (2.03)
Median	3	5	5
Min, max	1, 8	1, 8	2, 8

ACES=Agitation-Calmness Evaluation Scale; ITT=intent to treat; LOCF=last observation carried forward; a. 1=marked agitation, 2=moderate agitation, 3=mild agitation, 4=normal, 5=mild calmness, 6=moderate calmness, 7=marked calmness, 8=deep sleep, 9=unarousable; b. Patient 19-408 was excluded from this analysis because she discontinued before the 2-hour ACES assessment. Source: Section 11.1, Table 2.20; Appendix 12.2, Listing 2.3

Table 17. Doses of Study and Rescue Medication by 4 Hours after Dose 1 (ITT Population with LOCF)

Treatment Received, n (%)	***Staccato* Placebo** (N=115)	***Staccato* Loxapine 5 mg[a]** (N=116)	***Staccato* Loxapine 10 mg** (N=112)

1 dose study medication/no rescue medication	64 (55.7%)	78 (68.4%)	84 (75.0%)
2 doses study medication/no rescue medication	50 (43.5%)	35 (30.7%)	27 (24.1%)
2 doses study medication/with rescue medication	1 (0.9%)	1 (0.9%)	1 (0.9%)
p-value (active vs placebo, Fisher's Exact Test)	__	p=0.0850	p=0.0039

ITT=intent to treat; LOCF=last observation carried forward; vs=versus. Note: For the purpose of this analysis, "rescue medication" included the protocol-specified i.m. lorazepam, as well as any other medication used for that purpose; a. Two 5-mg patients (12-386 and 19-408) were excluded from this analysis because they discontinued before the 4-hour PEC assessment. Source: Section 11.1, Table 2.16; Appendix 12.2, Listings 1.17, 2.4

Table 18. Doses of Study and Rescue Medication by 24 Hours after Dose 1 (ITT Population with LOCF)

Treatment Received, n (%)	***Staccato* Placebo** (N=115)	***Staccato* Loxapine 5 mg[b]** (N=116)	***Staccato* Loxapine 10 mg[b]** (N=112)
1 dose study medication/no rescue medication	53 (46.1%)	62 (54.4%)	67 (60.9%)
2 doses study medication/no rescue medication	34 (29.6%)	35 (30.7%)	29 (26.4%)
3 doses study medication/no rescue medication	10 (8.7%)	10 (8.8%)	8 (7.3%)
1 dose study medication/with rescue medication[a]	0	1 (0.9%)	1 (0.9%)
2 doses study medication/with rescue medication	12 (10.4%)	4 (3.5%)	3 (2.7%)
3 doses study medication/with rescue medication	6 (5.2%)	2 (1.8%)	2 (1.8%)
p-value (active vs placebo, Fisher's Exact Test)	__	p=0.1548	p=0.0485

ITT=intent to treat; LOCF=last observation carried forward; vs=versus. Note: For the purpose of this analysis, "rescue medication" included the protocol-specified i.m. lorazepam, as well as any other medication used for that purpose; a. Two 5-mg patients (12-386 and 19-408) were excluded from this analysis because they discontinued before the 4-hour PEC assessment. Source: Section 11.1, Table 2.16; Appendix 12.2, Listings 1.17, 2.4

Study 004-302

Table 19. Distribution of CGI-I Scores 2 Hours after Dose 1 (ITT Population with LOCF)

CGI-I Score[a] (Description), n (%)	***Staccato* Placebo** (N=105)	***Staccato* Loxapine 5 mg** (N=104)	***Staccato* Loxapine 10 mg** (N=105)
1 (very much improved)	9 (8.6%)	38 (36.5%)	52 (49.5%)
2 (much improved)	20 (19.0%)	31 (29.8%)	26 (24.8%)
3 (minimally improved)	37 (35.2%)	17 (16.3%)	12 (11.4%)
4 (no change)	37 (35.2%)	18 (17.3%)	14 (13.3%)
5 (minimally worse)	2 (1.9%)	0	0
6 (much worse)	0	0	1 (1.0%)
7 (very much worse)	0	0	0

CGI-I=Clinical Global Impression - Improvement Scale; ITT=intent to treat; LOCF=last observation carried forward; a. CGI-I scale was used for assessment after treatment. Source: Section 11.1, Table 2.4; Appendix 12.2, Listing 2.2

Table 20. ACES Score 2 Hours after Dose 1 (ITT Population with LOCF)

ACES Score[a]	*Staccato* Placebo (N=105)	*Staccato* Loxapine 5 mg (N=104)	*Staccato* Loxapine 10 mg (N=105)
Baseline			
Mean (SD)	2.0 (0.40)	2.1 (0.44)	2.1 (0.42)
Median	2	2	2
Min, max	1, 3	1, 3	1, 4
+2 hours (observed value)			
Mean (SD)	3.3 (1.68)	4.7 (1.98)	5.1 (2.06)
Median	3	5	6
Min, max	1, 8	2, 8	1, 8

ACES=Agitation-Calmness Evaluation Scale; ITT=intent to treat; LOCF=last observation carried forward; a. 1=marked agitation, 2=moderate agitation, 3=mild agitation, 4=normal, 5=mild calmness, 6=moderate calmness, 7=marked calmness, 8=deep sleep, 9=unarousable. Source: Section 11.1, Table 2.20; Appendix 12.2, Listing 2.3

Table 21. Doses of Study and Rescue Medication by 4 Hours after Dose 1 (ITT Population with LOCF)

Treatment Received, n (%)	*Staccato* Placebo (N=105)	*Staccato* Loxapine 5 mg (N=104)	*Staccato* Loxapine 10 mg[a] (N=105)
1 dose study medication/no rescue medication	38 (36.2%)	62 (59.6%)	79 (76.0%)
2 doses study medication/no rescue medication	61 (58.1%)	40 (38.5%)	23 (22.1%)
2 doses study medication/with rescue medication	6 (5.7%)	2 (1.9%)	2 (1.9%)
p-value (active vs placebo, Fisher's Exact Test)	—	p=0.0019	p<0.0001

ITT=intent to treat; LOCF=last observation carried forward; vs=versus. Note: For the purpose of this analysis, "rescue medication" included the protocol-specified i.m. lorazepam, as well as any other medication used for that purpose; a. One patient on 10 mg was excluded from the analysis because she discontinued before Hour 4. Source: Section 11.1, Table 2.16; Appendix 12.2, Listings 1.16 and 2.4

Table 22. Doses of Study and Rescue Medication by 24 Hours after Dose 1 (ITT Population with LOCF)

Treatment Received, n (%)	*Staccato* Placebo (N=105)	*Staccato* Loxapine 5 mg (N=104)	*Staccato* Loxapine 10 mg[b] (N=105)
1 dose study medication/no rescue medication	28 (26.7%)	43 (41.3%)	64 (61.5%)
2 doses study medication/no rescue medication	43 (41.0%)	46 (44.2%)	27 (26.0%)
3 doses study medication/no rescue medication	12 (11.4%)	6 (5.8%)	4 (3.8%)
1 dose study medication/with rescue medication[a]	0	0	0
2 doses study medication/with rescue medication	15 (14.3%)	7 (6.7%)	7 (6.7%)
3 doses study medication/with rescue medication	7 (6.7%)	2 (1.9%)	2 (1.9%)
p-value (active vs placebo, Fisher's Exact Test)	—	p=0.0280	p<0.0001

ITT=intent to treat; LOCF=last observation carried forward; vs=versus. Note: For the purpose of this analysis, "rescue medication" included the protocol-specified i.m. lorazepam, as well as any other medication used for that purpose; a. Use of

rescue medication before Dose 2 would have been a protocol deviation; b. One patient on 10 mg was excluded from the analysis because she discontinued before Hour 24. Source: Section 11.1, Table 2.17; Appendix 12.2, Listings 1.16, 2.4

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of efficacy for trial 004-301

Title: A Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Multi-Dose Efficacy and Safety Study of Staccato Loxapine for Inhalation in Schizophrenic Patients with Agitation				
Study identifier	AMDC-004-301			
Design	Phase III efficacy and safety study			
	Pre-treatment Duration of screening phase: Duration of baseline assessment: **Post treatment** Primary efficacy evaluation phase: Extended evaluation phase:	2 weeks one hour prior to study drug administration 2 h >2 hours through 24 hours after Dose 1		
Hypothesis	Superiority			
Treatments groups	*Staccato* Placebo	Placebo. 115 randomized. 1 to 3 doses during a 24-hour. Doses 2 and 3 administered only if needed: Dose 2 >2 hours after Dose 1, and Dose 3 ≥4 hours after Dose 2.		
	Staccato Loxapine 5 mg	Loxapine 5 mg. 116 randomized. 1 to 3 doses during a 24-hour. Doses 2 and 3 administered only if needed: Dose 2 >2 hours after Dose 1, and Dose 3 ≥4 hours after Dose 2.		
	Staccato Loxapine 10 mg	Loxapine 10 mg. 113 randomized. 1 to 3 doses during a 24-hour. Doses 2 and 3 administered only if needed: Dose 2 >2 hours after Dose 1, and Dose 3 ≥4 hours after Dose 2.		
Endpoints and definitions	Primary endpoint		The absolute change in Positive and Negative Symptom Scale, Excited Component (**PEC**) scale score from baseline to 2 hours following Dose 1 of *Staccato* Loxapine, compared with placebo	
	Additional Secondary endpoint		For the 10 mg *Staccato* Loxapine - placebo comparison (only), the changes from baseline in **PEC** scores through 24 hours after dose 1	
	Key Secondary endpoint		The value of the Clinical Global Impression – Improvement Scale (**CGI-I**) score 2 hours following Dose 1 of *Staccato* Loxapine, compared with placebo	
Database lock (End of Protocol-Mandated AE Reporting Period):	27 June 2008			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Screened: 374 Per protocol: 344 (Safety Population) Intention To Treat: 343			
Descriptive statistics and estimate variability - Analysis of covariance (ANCOVA) with Dunnett's tests		Staccato Placebo Number of subjects 115 (ITT)	Staccato Loxapine 5 mg Number of subjects 116 (ITT)	Staccato Loxapine 10 mg Number of subjects 112 (ITT)
	PEC baseline score (SD)	17.4 (1.8)	17.8 (2.34)	17.6 (2.06)

	primary endpoint: Change in the PEC score from baseline to 2 hours after Dose 1	**Least Square LS - mean -5.8** **Mean (±SD) -5.5 (4.92)**	**Least Square LS - mean - 8.0** **Mean (±SD) -8.1 (5.17)**	**Least Square LS - mean -8.7** **Mean (±SD) -8.6 (4.37)**
	+ 10 minutes (mean change) p-value	-1.7	-3.1 NA	-3.4 p<0.0001
	+ 20 minutes (mean change) p-value	-2.9	-5.2 NA	-6.1 p<0.0001
	+30 minutes (mean change) p-value	-4.1	-6.8 NA	-7.6 p<0.0001
	+45 minutes (mean change) P-value	-4.8	-7.4 NA	-8.7 p<0.0001
	+ 1 hour (mean change) p-value	-5.2	-7.7 NA	-9.2 p<0.0001
	+ 1.5 hours (mean change) p-value	-5.3	-8.2 NA	-9.1 p<0.0001
	+ 2 hours (LS mean change) p-value	-5.8	-8.0 p=0.0004	-8.7 p<0.0001
	+ 4 hours (mean change) p-value	-6.3	-8.2 NA	-9.5 p<0.0001
	additional secondary endpoint: + 24 hours (mean change) p-value	**-4.4**	**-6.2 NA**	**-6.9 p<0.0001**
	key secondary endpoint: CGI-I score baseline (mean ±SD)	3.9 (0.53)	4.0 (0.55)	4.1 (0.60)
	+ 2 hours (mean ±SD) p-value	2.8 (1.11)	2.3 (1.24) p=0.0015	2.1 (1.00) p<0.0001
Notes	NA			
Analysis description	**Additional analysis**			
CGI-I Responders: those patients judged by the investigator to be "very much improved" (CGI-I score of 1) or "much improved" (CGI-I score of 2) 2 hours after the first dose of study medication.	placebo CGI-I responders (score 1 and 2) = 35.7% 5 mg CGI-I responders (score 1 and 2) = 57.3% p-value 5-mg/placebo p=0.0015 Fisher's Exact Test 10 mg CGI-I responders (score 1 and 2) = 67.0% p-value 10-mg/placebo p<0.0001 Fisher's Exact Test			

Agitation-Calmness Evaluation Scale (**ACES**) Score 2 Hours after Dose 1 Mean (SD)	Staccato Placebo N=115 (ITT)	Staccato Loxapine 5mg N=116 (ITT)	Staccato Loxapine 10 mg N=112 (ITT)
	Baseline 2.3 (0.51)	Baseline 2.2 (0.63)	Baseline 2.2 (0
	+ 2 hours 3.9 (1.76)	+ 2 hours 4.7 (2.09)	+ 2 hours 4.9 (2.03)
Use of rescue medication (beyond Dose 1) by 4	1 (0.9%)	1 (0.9%)	1 (0.9%)
1 dose study medication/with rescue medication by 24 h 24h	0	1 (0.9%)	1 (0.9%)
2 dose study medication/with rescue medication by 24 h	12 (10.4%)	4 (3.5%)	3 (2.7%)
3 dose study medication/with rescue medication by 24 h	6 (5.2%)	2 (1.8%)	2 (1.8%)

Summary of efficacy for trial 004-302

Title: A Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Multi-Dose Efficacy and Safety Study of Staccato Loxapine for Inhalation in Patients with Bipolar I Disorder and Acute Agitation			
Study identifier	AMDC-004-302		
Design	Phase III efficacy and safety study		
	Pre-treatment Duration of screening phase: Duration of baseline assessment: **Post treatment** Primary efficacy evaluation phase: Extended evaluation phase:	2 weeks one hour prior to study drug administration 2 h >2 hours through 24 hours after Dose 1	
Hypothesis	Superiority		
Treatments groups	*Staccato* Placebo		Placebo. 115 randomized. 1 to 3 doses during a 24-hour. Doses 2 and 3 administered only if needed: Dose 2 >2 hours after Dose 1, and Dose 3 ≥4 hours after Dose 2.
	Staccato Loxapine 5 mg		Loxapine 5 mg. 116 randomized. 1 to 3 doses during a 24-hour. Doses 2 and 3 administered only if needed: Dose 2 >2 hours after Dose 1, and Dose 3 ≥4 hours after Dose 2.
	Staccato Loxapine 10 mg		Loxapine 10 mg. 113 randomized. 1 to 3 doses during a 24-hour. Doses 2 and 3 administered only if needed: Dose 2 >2 hours after Dose 1, and Dose 3 ≥4 hours after Dose 2.
Endpoints and definitions	Primary endpoint		The absolute change in Positive and Negative Symptom Scale, Excited Component (PEC) scale score from baseline to 2 hours following Dose 1 of *Staccato* Loxapine, compared with placebo
	Key Secondary endpoint		The value of the Clinical Global Impression – Improvement Scale (CGI-I) score 2 hours following Dose 1 of *Staccato* Loxapine, compared with placebo

	Additional Secondary endpoint		For the 10 mg *Staccato* Loxapine - placebo comparison (only), the changes from baseline in PEC scores at 10, 20, 30, and 45 minutes
Database lock (End of Protocol-Mandated AE Reporting Period):	2nd November 2008		
Results and Analysis			

Analysis description	**Primary Analysis**			
Analysis population and time point description	Screened: 356 Per protocol: 314 (Safety Population) ITT: 314			
Descriptive statistics and estimate variability		Staccato Placebo Number of subjects 105	Staccato Loxapine 5 mg Number of subjects 104	Staccato Loxapine 10 mg Number of subjects 105
	PEC baseline score	17.7 (2.8)	17.4 (2.23)	17.3 (2.25)
	Change in the PEC score from baseline to 2 hours after Dose 1 (primary endpoint)	**LS mean -4.7 Mean (SD) -4.9 (4.77)**	**LS mean - 8.2 Mean (SD) -8.1 (4.90)**	**LS mean -9.2 Mean (SD) -9.0 (4.67)**
	+ 10 minutes (mean change) p-value	-1.8	-3.6 NA	-4.0 p<0.0001
	+ 20 minutes (mean change) p-value	-3.2	-5.8 NA	-6.7 p<0.0001
	+30 minutes (mean change) p-value	-3.9	-7.5 NA	-8.0 p<0.0001
	+45 minutes (mean change) P-value	-4.6	-8.1 NA	-8.8 p<0.0001
	+ 1 hour (mean change) p-value	-5.0	-8.8 NA	-8.8 p<0.0001
	+ 1.5 hours (mean change) p-value	- 5.0	-8.3 NA	-8.8 p<0.0001
	+ 2 hours (mean change) p-value	**-4.7**	**-8.2 p<0.0001**	**-9.2 p<0.0001**
	+ 4 hours (mean change) p-value	-6.1	-8.3 NA	-9.3 p<0.0001
	+ 24 hours (mean change) p-value (additional secondary endpoint)	**-4.5**	**-6.1 NA**	**-6.0 P=0.0011**

	CGI-I score baseline (Mean ±SD)- key secondary endpoint	4.1 (0.57)	4.0 (0.53)	4.0 (0.49)
	+ 2 hours	3.0 (0.99)	2.1 (1.10)	1.9 (1.14)
	p-value for active/placebo comparison	-	p<0.0001	p<0.0001
Analysis description	**Additional Analysis**			
CGI-I Responders: those patients judged by the investigator to be "very much improved" (CGI-I score of 1) or "much improved" (CGI-I score of 2) 2 hours after the first dose of study medication.	placebo CGI-I responders (score 1 and 2) = 27.6% 5 mg CGI-I responders (score 1 and 2) = 66.3% p-value 5-mg/placebo p<0.0001Fisher's Exact Test 10 mg CGI-I responders (score 1 and 2) = 74.3% p-value 10-mg/placebo p<0.0001 Fisher's Exact Test			
Agitation-Calmness Evaluation Scale (**ACES**) Score 2 Hours after Dose 1 Mean (SD)	Staccato Placebo (N=105)	Staccato loxapine 5mg (N=104)	Staccato loxapine 10mg (N=105)	
	Baseline 2.0 (0.40)	Baseline 2.1 (0.44)	Baseline 2.1 (0.42)	
	+2 hours 3.3 (1.68)	+2 hours 4.7 (1.98)	+2 hours 5.1 (2.06)	
Use of rescue medication (beyond Dose 1) by 4	6 (5.7%)	2 (1.9%)	2 (1.9%)	
1 dose study medication/with rescue medication by 24 h	0	0	0	
2 dose study medication/with rescue medication by 24 h	15 (14.3%)	7 (6.7%)	7 (6.7%)	
3 dose study medication/with rescue medication by 24 h	7 (6.7%)	2 (1.9%)	2 (1.9%)	
Notes				

2.5.3. Ancillary analyses

Changes in PEC-score remained significantly greater in loxapine-treated patients as compared to placebo at 4 and 24 hours post administration. Analyses of comparisons between loxapine versus placebo-treated groups (PEC-score change from baseline) in subgroups defined by age, sex, and race revealed no substantial divergence from overall results. Also, treatment results did not separate from placebo differently in comparisons between schizophrenia versus schizoaffective disorder and schizophreniform disorder in study 004-301, and in comparison between manic episodes versus mixed episodes of bipolar disorder in study 004-302. In both the placebo-treated and the loxapine treated

patient-groups there was a tendency towards a slightly greater decrease of PEC scores in subgroups defined by a higher PEC-scores at baseline in studies 004-301 and 004-302, in a similar order of magnitude.

At the CHMP request, post-hoc subgroup analyses were performed evaluating the efficacy in patients that stopped excluded medications (e.g antipsychotics) and those who were not taking excluded medications. Among the excluded medications, the most common CNS active medications were: quetiapine (13.9%), zolpidem (6.4%), risperidone (5.8%), olanzapine (4.3%), aripiprazole (2.5%), clonazepam (2.2%). Results are presented in Tables 23-25.

Tables 23-24

Table 42. Subgroup Analyses for Excluded Medication Study 004-301

Parameter	Comparison	Stopped Excluded Med (N=168)		Not Taking Excluded Med (N=175)	
		Trt Effect	P-value	Trt Effect	P-value
Primary PEC@2hrs	10mg/Pbo	2.6	0.0103	3.2	0.0001
	5mg/Pbo	2.5	0.0141	2.2	0.0135
Key 2nd CGI-I	10mg/Pbo	-0.7	0.0065	-0.8	<.0001
	5mg/Pbo	-0.5	0.0617	-0.5	0.0124

[Trt effect = Δ LSMeans; P-values for 2 pairwise contrasts = Adjusted p-values based on Dunnett's t-test in ANCOVA(1°)/ANOVA(Key 2nd) main effects models with the term for center removed]

Table 43. Subgroup Analyses for Excluded Medication Study 004-302

Parameter	Comparison	Stopped Excluded Med (N=88)		Not Taking Excluded Med (N=226)	
		Trt Effect	P-value	Trt Effect	P-value
Primary PEC@2hrs	10mg/Pbo	1.9	0.3559	4.9	<.0001
	5mg/Pbo	3.1	0.0412	3.5	<.0001
Key 2nd CGI-I	10mg/Pbo	-0.4	0.3637	-1.3	<.0001
	5mg/Pbo	-0.7	0.0507	-1.0	<.0001

[Trt effect = Δ LSMeans; P-values for 2 pairwise contrasts = Adjusted p-values based on Dunnett's t-test in ANCOVA(1°)/ANOVA(Key 2nd) main effects models with the term for center removed]

Table 25

Table 44. Subgroup Analyses for Excluded Medication Studies 004-301 and 004-302 Combined

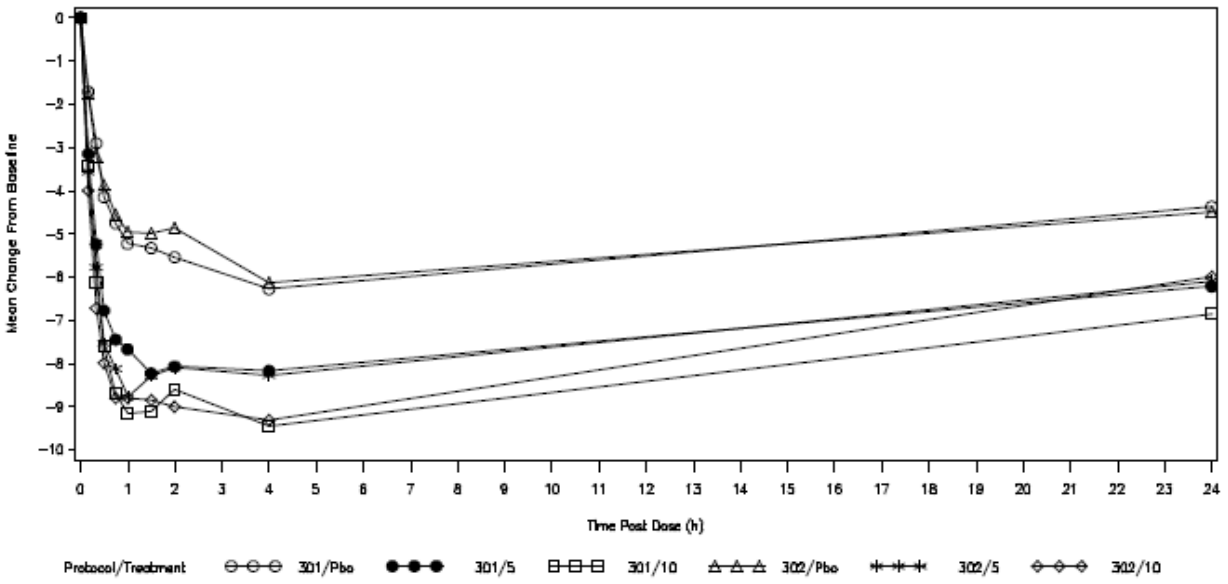
Parameter	Comparison	Stopped Excluded Med (N=256)		Not Taking Excluded Med (N=401)	
		Trt Effect	P-value	Trt Effect	P-value
Primary PEC@2hrs	10mg/Pbo	2.4	0.0044	4.2	<.0001
	5mg/Pbo	2.7	0.0008	2.9	<.0001
Key 2nd CGI-I	10mg/Pbo	-0.6	0.0029	-1.1	<.0001
	5mg/Pbo	-0.5	0.0048	-0.8	<.0001

[Trt effect = Δ LSMeans; P-values for 2 pairwise contrasts = Adjusted p-values based on Dunnett's t-test in ANCOVA(1°)/ANOVA(Key 2nd) main effects models with the term for center removed and a term for Study added]

Following the CHMP findings that in study 004-301, a higher number of patients were on active treatment (including rescue medication) in the loxapine 5 mg and 10 mg groups (33-39% on 2 or 3 doses, 4.5-5.3% on rescue medication) as compared to the placebo (15.6% on rescue medication) while similar decline of the control of agitation over time was observed across groups, the applicant provided results of the PEC score changes over 24 hours in both pivotal studies. These are presented in Figure 11.

Figure 11

Figure 33. Change in PEC Score over 24 Hours in Studies 004-301 and 004-302 (ITT Population with LOCF)



Program Name:f-4-meanpec.sas Date:21OCT2009:15:31:18

ITT=intent to treat; LOCF=last observation carried forward; PEC=Positive and Negative Symptom Scale, Excited Component

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

No pooled analyses or meta-analysis were performed.

2.5.5. Clinical studies in special populations

No studies in special patient-groups were performed regarding efficacy in reduction of acute agitation. The applicant did submit an efficacy study in migraine patients. In study 104-201 Staccato loxapine 5 mg was compared with placebo in migraine patients (loxapine 5 mg: n=43; placebo: n=39), demonstrating superiority of loxapine in percentage of 2-hour pain relief responders (76.7% versus 51.3%, p=0.0212).

2.5.6. Supportive studies

2.5.6.1. *Introduction*

Due to the lack of active comparator in the presented clinical programme, the applicant provided an indirect comparison of the efficacy results of loxapine versus i.m. aripiprazole and i.m. olanzapine. The objective of this analysis was to put the observed effects into clinical context via historical comparisons of data from the confirmatory trials to the trials of an appropriate reference treatment.

In addition, the applicant provided a comparative analysis regarding medications used in the treatment of schizophrenia in EU and US to support the extrapolation of the results from pivotal studies that were only performed in the US.

2.5.6.2. *Comparative efficacy with intramuscular aripiprazole and olanzapine*

Methodology

On the basis of similar methodology used, data sources from the following studies were analysed (see Tables 26-28.

Table 26

Table 1. Approval Documents, Pivotal Studies, and Key Publications for IM Zyprexa and IM Abilify

	IM Zyprexa (olanzapine)		IM Abilify (aripiprazole)	
Patient Type:	**Schizophrenia***	**Bipolar Disorder**	**Schizophrenia***	**Bipolar Disorder**
US Approval Documents:	NDA 21-253 Statistical and Medical Reviews	NDA 21-253 Statistical and Medical Reviews	NDA 21-866 Statistical and Medical Reviews	NDA 21-866 Statistical and Medical Reviews
Approval Date:	2001	2001	2006	2006
Pivotal Study Cited:	F1D-MC-HGHB; F1D-MC-HGHV	F1D-MC-HGHW	CN138050; CN138012	CN138013
EU Approval Document:	Scientific Review: CPMP/0646/96	Scientific Review: CPMP/0646/96	Scientific Review: EMEA/H/C/471/II/0015	Scientific Review: EMEA/H/C/000471/II/0041
Approval Date:	18 October 2002	18 October 2002	4 October 2006	20 June 2008
Pivotal Study Cited:	F1D-MC-HGHB; F1D-MC-HGHV	F1D-MC-HGHW	CN138050; CN138012	CN138013
Pivotal Study Publication:	**HGHB**: Wright et al, 2001 **HGHV**: Breier et al, 2002	**HGHW**: Meehan et al, 2001	**138050**: Tran-Johnson et al, 2007 **138012**: Andrezina et al, 2006	**138013**: Zimbroff et al, 2007

* includes patients with schizoaffective and/or schizophreniform disorder

Table 27

Table 2. Pivotal Study Design Characteristics for Patients with Schizophrenia

Treatment	*Staccato* Loxapine	IM Zyprexa		IM Abilify	
Pivotal Study #	004-301	F1D-MC-HGHB	F1D-MC-HGHV	CN138050	CN138012
Study Design	DB, R, repeat-dose (as needed), placebo-controlled, parallel group	DB, R, repeat-dose (as needed), placebo and active-controlled, parallel group	DB, R, repeat-dose (as needed), placebo and active -controlled, parallel group	DB, R, repeat-dose (as needed), placebo and active -controlled, parallel group	DB, R, repeat-dose (as needed), placebo and active -controlled, parallel group
Study Duration	24 hours	24 hours	24 hours	24 hours	24 hours
Patients Randomized	344	311	270	357	448
Active Doses	5, 10 mg	10 mg	2.5, 5, 7.5, 10 mg	1, 5.25, 9.75, 15 mg	9.75 mg
Dosing Schedule	Up to 3 doses within the first 20 h post Dose 1; if needed, Dose 2 given > 2h after Dose 1; Dose 3 ≥ 4h after Dose 2	Up to 3 doses within the first 20 h post Dose 1; if needed, Dose 2 given > 2h after Dose 1; Dose 3 ≥ 4h after Dose 2	Up to 3 doses within the first 20 h post Dose 1; if needed, Dose 2 given > 2h after Dose 1; Dose 3 ≥ 4h after Dose 2	Up to 3 doses within the first 20 h post Dose 1; if needed, Dose 2 or Dose 3 ≥ 2h after previous dose	Up to 3 doses within the first 20 h post Dose 1; if needed, Dose 2 or Dose 3 ≥ 2h after previous dose
Control Group	*Staccato* Placebo	IM Placebo	IM Placebo	IM Placebo	IM Placebo
Active Comparator	None	Haloperidol 7.5 mg IM	Haloperidol 7.5 mg IM	Haloperidol 7.5 mg IM	Haloperidol 6.5 mg IM
Rescue Medication	Lorazepam Allowed ≥ 20 min after Dose 2 unless medically required	Lorazepam (or other BZ) Allowed ≥ 60 min after Dose 2 unless medically required	Lorazepam (or other BZ) Allowed ≥ 60 min after Dose 2 unless medically required	Lorazepam (or other BZ) Allowed ≥ 60 min after Dose 2 unless medically required	Lorazepam (or other BZ) Allowed ≥ 60 min after Dose 2 unless medically required
# Study Sites					
US:	24	15	0	30	40
Europe:	0	27	8	17	26
Other:	0	9	6	3	2
Primary Source	CSR 004-301 (m5.3.5.1)	NDA 21-253, Medical Review	NDA 21-253, Medical Review	NDA 21-866, Medical Review	NDA 21-866, Medical Review

Schizophrenia includes patients with schizoaffective and/or schizophreniform disorder; DB = Double-Blind; R = Randomized

Table 28

Table 3. Pivotal Study Design Characteristics for Patients with Bipolar Disorder

Treatment	*Staccato* Loxapine	IM Zyprexa	IM Abilify
Pivotal Study #	004-302	F1D-MC-HGHW	CN138013
Study Design	DB, R, repeat-dose (as needed), placebo-controlled, parallel group,	DB, R, repeat-dose (as needed), placebo and active-controlled, parallel group,	DB, R, repeat-dose (as needed), placebo and active -controlled, parallel group,
Study Duration	24 hours	24 hours	24 hours
Patients Randomized	314	201	301
Active Doses	5, 10 mg	10 mg	9.75, 15 mg
Dosing Schedule	Up to 3 doses within the first 20 h post Dose 1; if needed, Dose 2 given > 2h after Dose 1; Dose 3 ≥ 4h after Dose 2	Up to 3 doses within the first 20 h post Dose 1; if needed, Dose 2 given > 2h after Dose 1; Dose 3 ≥ 4h after Dose 2	Up to 3 doses within the first 20 h post Dose 1; if needed, Dose 2 or Dose 3 ≥ 2h after previous dose
Control Group	*Staccato* Placebo	IM Placebo	IM Placebo
Active Comparator	None	Lorazepam 2 mg IM	Lorazepam 2 mg IM
Rescue Medication	Lorazepam Allowed ≥ 20 min after Dose 2 unless medically required	unknown	unknown
# Study Sites			
US:	17	26	35
Europe:	0	3	2
Other:	0	0	0
Primary Source	CSR 004-302 (m5.3.5.1)	NDA 21-253, Medical Review	NDA 21-866, Medical Review

Table 29

Table 7. Efficacy and Safety Endpoints for Patients with Bipolar Disorder

Treatment	*Staccato* Loxapine	IM Zyprexa	IM Abilify
Pivotal Study #	004-302	F1D-MC-HGHW	CN138013
Primary Endpoint	PEC: Change from Baseline at 2 h	PEC: Change from Baseline at 2 h	PEC: Change from Baseline at 2 h
PEC Assessment Times	BL, and 10, 20, 30, 45, 60, 90 min & 2, 4, 24 h post Dose 1	BL and 30, 60, 90 min & 2 h post Dose 1	BL and 30, 45, 60, 90 min & 2, 4, 6, 12, 24 h post Dose 1[+]
Key Secondary Endpoint	CGI-I at 2 h post Dose 1	None	CGI-I at 2 h post Dose 1
Other Rating Scales	ACES, CGI-S	ACES, BPRS, CABS, CGI-S, YMRS	ACES, CABS, CGI-S, YMRS[+]
Safety Assessments	Adverse events, vital signs, clinical labs, physical exam, ACES	Adverse events, vital signs, clinical labs[+], ECG, EPS	Adverse events, vital signs, clinical labs[+], ECG, EPS
Primary Source	004-302 CSR (m5.3.5.1)	NDA 21-253, Medical Review and Statistical Review	NDA 21-866, Medical Review and Statistical Review
Additional Source	N/A	Meehan et al, 2001	Zimbroff et al, 2007

[+] Information obtained from Additional Source
N/A: not applicable

Results

Baseline data

Many of the key demographic characteristics, including age, gender, and race were comparable across the 3 programs. However, in the trials of patients with schizophrenia, the majority of patients were males; and this preponderance was less pronounced in the studies with bipolar disorder patients. There were more black patients in the Staccato loxapine trials than in the i.m. Abilify or i.m. Zyprexa studies, especially in patients with schizophrenia.

Baseline agitation scores are presented in Table 30.

Table 30

Table 11. Baseline Agitation Scores for Patients with Bipolar Disorder

Study	Treatment	N	Mean PEC	Mean CGI-S	Mean ACES
Staccato Loxapine 004-302	Placebo	105	17.7	4.1	2.0
	5 mg	104	17.4	4.0	2.1
	10 mg	105	17.3	4.0	2.1
IM Zyprexa F1D-MC-HGHW	Placebo	50	12.7*	NR	2.3
	10 mg	98	13.0*	NR	2.2
	Lorazepam	51	12.4*	NR	2.3
IM Abilify CN 138013	Placebo	73	18.0	4.1	2.4
	9.75 mg	75	18.8	4.2	2.3
	15 mg	75	18.3	4.1	2.4
	Lorazepam	68	18.5	4.2	2.4

Change from Baseline in PEC score

In the pivotal studies conducted for Staccato loxapine, as well as those for i.m. Abilify and i.m. Zyprexa, the primary efficacy endpoint was the change from baseline in PEC score at 2 hours after the first administration of study medication. Table 31 presents the primary efficacy endpoint data from the pivotal studies. The mean changes from baseline to 2 hours in PEC scores were similar for Staccato loxapine compared with the other two drugs. This confirms the relative effectiveness of Staccato loxapine at both dose levels, based on comparison to the historical data for i.m. Abilify and i.m.

Zyprexa from studies with designs and endpoints similar to those in the pivotal trials of Staccato loxapine.

Table 31

Table 12. Mean Change in PEC Score from Baseline to 2 Hours in *Staccato* Loxapine Phase 3 Studies and Comparator Studies

Staccato Loxapine Studies				
Study	Population	Placebo	Loxapine Dose (Inhaled)	
			5 mg	10 mg
004-301	Schizophrenia	-5.5	-8.1	-8.6
004-302	Bipolar Disorder	-4.7	-8.2	-9.2

IM Abilify Studies							
Study	Population	Placebo	Active Comparator	Abilify Dose (IM)			
				1 mg	5 mg	10 mg	15 mg
CN138012	Schizophrenia, Schizoaffective	-5.68	-8.25 (Haloperidol)	NT	NT	-7.99	NT
CN138050	Schizophrenia, Schizoaffective, Schizophreniform	-4.78	-7.32 (Haloperidol)	-4.87	-6.94	-7.82	-6.94
CN138013	Bipolar Disorder	-5.76	-9.57 (Lorazepam)	NT	NT	-8.74	-8.67

IM Zyprexa Studies							
Study	Population	Placebo	Active Comparator	Zyprexa Dose (IM)			
				2.5 mg	5 mg	7.5 mg	10 mg
MC-HGHB	Schizophrenia	-3.55	-7.63 (Haloperidol)	NT	NT	NT	-7.74
MC-HGHV	Schizophrenia	-2.59	-7.29 (Haloperidol)	-5.20	-7.80	-8.42	-8.95
MC-HGHW	Bipolar Disorder	-4.20	-6.08 (Lorazepam)	NT	NT	NT	-8.98

NT: not tested in study

Onset of Effect on PEC score

The approved i.m. drugs were shown in their pivotal trials to have variable onset of anti-agitation effect. Table 32 presents the time points of the first statistically significant changes from baseline in PEC scores relative to placebo in the Staccato loxapine, i.m. Abilify, and i.m. Zyprexa Phase 3 studies. For i.m. Abilify and i.m. Zyprexa, there was variability in the onset of effect based on both the treatment population and the dose of the drug. By contrast, Staccato loxapine showed a rapid and consistent onset of anti-agitation effect at 10 minutes in both populations and at both doses (5-mg onset data analysis was post hoc). This difference in time to producing a significant reduction in agitation may be more evident in patients with bipolar disorder in whom Staccato loxapine had effects in 10 minutes, compared with 30 minutes and 60 minutes for the prescribed doses of i.m. Zyprexa and i.m. Abilify, respectively.

Table 32

Table 13. Time to First Statistically Significant Change from Baseline PEC Score in *Staccato* Loxapine Phase 3 Studies and Comparator Studies

Staccato Loxapine Studies			
Study	**Population**	**Loxapine Dose (Inhaled)**	
		5 mg	**10 mg**
004-301	Schizophrenia	10 min	10 min
004-302	Bipolar Disorder	10 min	10 min

IM Abilify Studies					
Study	**Population**	**Abilify Dose (IM)**			
		1 mg	**5 mg**	**10 mg**	**15 mg**
CN138012	Schizophrenia, Schizoaffective	NT	NT	120 min	NT
CN138050	Schizophrenia, Schizoaffective, Schizophreniform	ns	120 min	45 min	120 min
CN138013	Bipolar Disorder	NT	NT	90 min	60 min

IM Zyprexa Studies					
Study	**Population**	**Zyprexa Dose (IM)**			
		2.5 mg	**5 mg**	**7.5 mg**	**10 mg**
MC-HGHB	Schizophrenia	NT	NT	NT	15 min
MC-HGHV	Schizophrenia	60 min	30 min	30 min	30 min
MC-HGHW	Bipolar Disorder	NT	NT	NT	30 min

NT: not tested in study

Responder Analysis on PEC score

In the pivotal studies for i.m. Abilify and i.m. Zyprexa, responder analyses assessed the percentage of patients with a ≥40% decrease from baseline in the total PEC score at selected time points. The same responder analyses were performed for the pivotal Staccato loxapine studies at all assessment times from 10 minutes through 2 hours after administration of Dose 1 (post-hoc analyses). The results of these Staccato loxapine responder analyses, along with available data for i.m. Abilify and i.m. Zyprexa, are summarized in Table 33 (schizophrenia) and Table 34 (bipolar disorder) and Figure 12.

Table 33

Table 14. PEC Scale Responder Analysis in *Staccato* Loxapine Phase 3 Study and Comparator Studies: Schizophrenia Studies

***Staccato* Loxapine Study**

(Percentage 40% Responders)

Study	Minutes after Dose 1	Placebo	Loxapine Dose (Inhaled)	
			5 mg	10 mg
004-301	10	6.1%	17.2% (p=0.0056)	18.8% (p=0.0012)
	20	15.7%	29.3% (p=0.0088)	42.9% (p<0.0001)
	30	27.8%	46.6% (p=0.0016)	57.1% (p<0.0001)
	45	32.2%	50.0% (p=0.0045)	70.5% (p<0.0001)
	60	38.3%	57.8% (p=0.0026)	71.4% (p<0.0001)
	90	38.3%	61.2% (p=0.0004)	74.1% (p<0.0001)
	120	38.3%	62.9% (p=0.0002)	69.6% (p<0.0001)

IM Abilify Studies

(Percentage 40% Responders)

Study	Minutes after Dose 1	Placebo	Abilify Dose (IM)			
			1 mg	5 mg	10 mg	15 mg
CN138012	120	42%	NT	NT	57% (p=0.045)	NT
CN138050[a]	60	25%	20% (ns)	30% (ns)	45% (p<0.05)	45% (p<0.05)
	120	36%	38% (ns)	50% (ns)	54% (p<0.05)	55% (ns)

IM Zyprexa Studies

(Percentage 40% Responders)

Study	Minutes after Dose 1	Placebo	Zyprexa Dose (IM)			
			2.5 mg	5 mg	7.5 mg	10 mg
MC-HGHB[b]	120	33.3%	NT	NT	NT	73% (p<0.01)
MC-HGHV[c]	120	20.0%	50.0% (p=0.003)	62.6% (p<0.001)	73.9% (p<0.001)	80.4% (p<0.001)

NT: not tested in study

Table 34

Table 15. PEC Scale Responder Analysis in *Staccato* Loxapine Phase 3 Study and Comparator Studies: Bipolar Disorder Studies

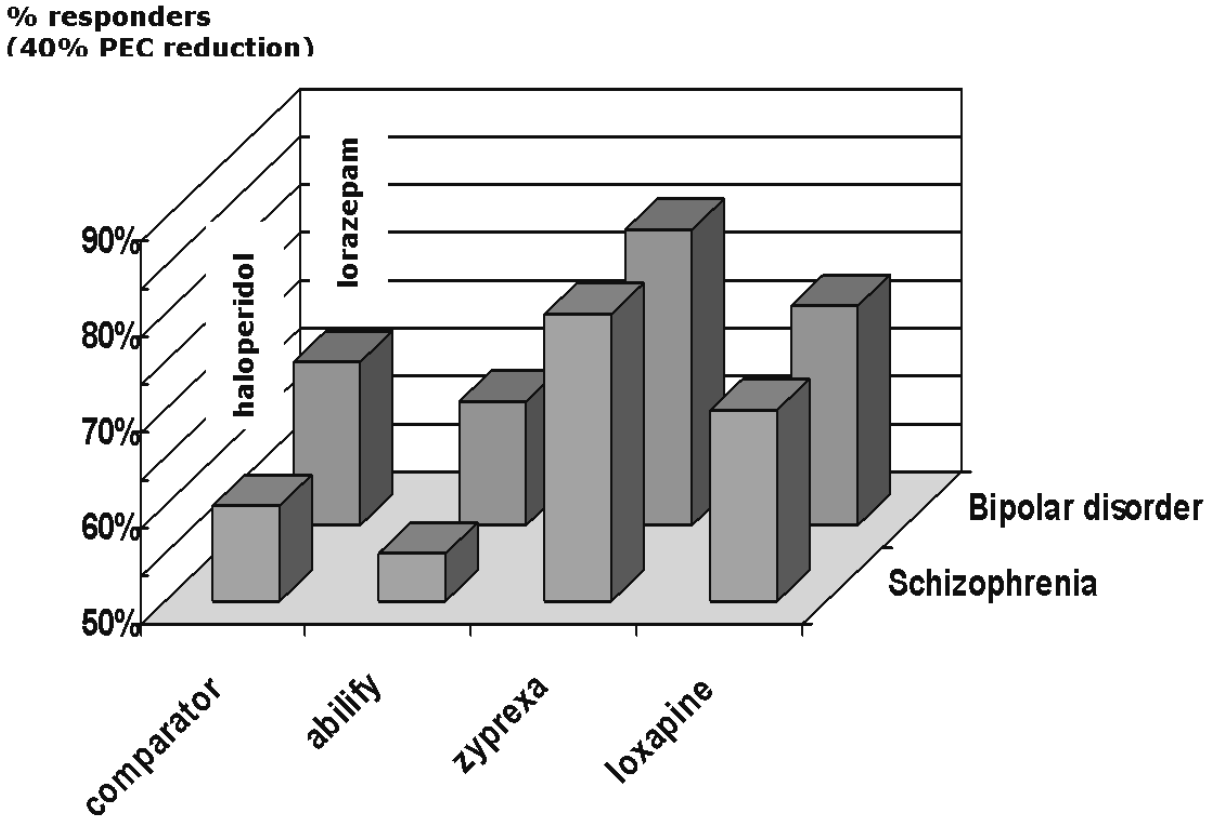
Staccato Loxapine Study (Percentage 40% Responders)				
Study	**Minutes after Dose 1**	**Placebo**	**Loxapine Dose (Inhaled)**	
			5 mg	**10 mg**
004-302	10	7.6%	18.3% (p=0.0059)	21.9% (p=0.0017)
	20	15.2%	36.5% (p<0.0001)	49.5% (p<0.0001)
	30	23.8%	59.6% (p<0.0001)	61.9% (p<0.0001)
	45	29.5%	64.4% (p<0.0001)	70.5% (p<0.0001)
	60	28.6%	69.2% (p<0.0001)	72.4% (p<0.0001)
	90	27.6%	62.5% (p<0.0001)	72.4% (p<0.0001)
	120	27.6%	62.5% (p<0.0001)	73.3% (p<0.0001)

IM Abilify Study (Percentage 40% Responders)						
Study	**Minutes after Dose 1**	**Placebo**	**Abilify Dose (IM)**			
			1 mg	**5 mg**	**10 mg**	**15 mg**
CN138013	30	18%	NT	NT	12% (ns)	13% (ns)
	45	26%	NT	NT	37% (ns)	35% (ns)
	60	37%	NT	NT	43% (ns)	48% (ns)
	90	41%	NT	NT	57% (p=0.046)	52% (ns)
	120	37%	NT	NT	69% (p<0.001)	63% (p=0.002)

IM Zyprexa Study (Percentage 40% Responders)						
Study	**Minutes after Dose 1**	**Placebo**	**Zyprexa Dose (IM)**			
			2.5 mg	**5 mg**	**7.5 mg**	**10 mg**
HGHW	30	28.0%	NT	NT	NT	50.0%
	120	44.0%	NT	NT	NT	80.6% (p<0.001)

NT: not tested in study

Figure 12



2.5.6.3. *Comparative on medications used in the treatment of schizophrenia in EU and the US*

The analysis showed that no major differences exist in the treatment of antipsychotic patients between US and EU and that the medications most commonly used both in US as well as in EU are those that were received in the highest percentage by the study patients (namely diazapines, oxazepines, and thiazepines).

2.5.7. Discussion on clinical efficacy

The clinical development program consisted of one dose ranging study (004-201) and 2 pivotal phase III studies, respectively performed in population with schizophrenia (004-301) and Bipolar I disorder (004-302). An indirect comparison versus historical data was performed in the absence of confirmatory trials including an active comparator.

Design and conduct of clinical studies

In study 004-201, the design was limited to only two doses tested (5 mg and 10mg) questioning if the minimum effective dose was achieved. No pair-wise comparison was performed between loxapine 5 mg and 10 mg.

In both pivotal studies (004-301,004-302), the 24 hour duration was considered in principle adequate to assess efficacy given the intended short term treatment in acute agitation. However, no data were available on repeated use over several days in case the agitation showed a fluctuating pattern.

The CHMP also considered that the inclusion criteria reflected the target population. In addition, the informed consent procedure appeared to include the possibility of consent by legal representative or impartial witness, thus allowing for enrolment of severely agitated patients who are unable to give a personal informed consent.

The CHMP was however concerned about the exclusion criteria that may have limited the generalisability of the results. In clinical practice, most of the determinants that excluded patients from the pivotal studies characterised a considerable proportion of patients in need of treatment of acute agitation e.g agitation due to drug intoxication or agitation due to physical disease (delirium), patients with suicidal thought, and patients who use injectable depot neuroleptics or psychostimulants. The instruction of patients on the use of the device also suggested that moderately agitated patients only could be enrolled, this being further supported by selecting “uncooperativeness” as one of the five symptoms used in the definition of the agitation for the studied population.

Although the study criteria were similar to the studies performed for other approved drugs in this indication and used as intramuscular injection, the extrapolation of the results from clinical trials to actual clinical setting was questionable for Adasuve since the product is used as an oral inhaler and a certain level of cooperativeness from the patient is required under such administration. In addition, patients were evaluated for their ability to perform the inhalation manoeuvre required to use the Staccato device in the clinical studies raising again doubts on the generalisability of the study results, considering the use of educational measures may not be feasible in the intended clinical setting. In addition, an enrolment of moderately agitated patients could impact on the representativeness of the studied population as patients truly in need of fast onset of effect in the treatment of agitation, will generally be suffering from severe, and not moderate agitation.

Patients over 65 years of age were excluded from both pivotal studies and therefore data in the elderly population are lacking. In addition, the vast majority of the patients were not naïve to antipsychotics and a large proportion of patients were receiving concomitant medication including benzodiapezines and other sedatives (see Tables 4 and 6).

PEC and CGI-I scales are used in clinical practice and their validity have been confirmed in the assessment of agitation: the PEC score is a summation of individual scores (from 1-7) across five items: poor impulse control, tension, hostility, uncooperativeness, and excitement. The range of possible PEC scores is 5 through 35; CGI-I is a 7 point scale that rates:1. very much improved; 2. much improved; 3. minimally improved;4. no change; 5. Minimally worse;6. much worse; or 7.very much worse.

The PEC scale shows highly sensitivity, and does not present ceiling or floor effect; CGI is known to assess the severity of agitation and post-treatment changes in clinical condition. Nevertheless, the clinical relevance of the primary outcome measure with respect to the chosen interval, the absolute change from baseline to 2 hours after the first dose on the PEC score and claimed use as faster onset of efficacy as compared to other available oral treatment (e.g. haloperidol, lorazepam tablets) was questioned. Furthermore the applicant had chosen to statistically analyse the PEC score results at early time points only for the 10 mg group, on the basis of study 004-201 results showing a statistical clinical effect after 2 hours for the 10 mg dose, but not for the 5 mg dose. Considering the design of study 004-201 and possible high variability that may be observed in dose-response trials, the exclusion of the 5 mg group for the secondary analysis was questioned by the CHMP, especially given that both the primary and the key secondary endpoint were reached for the 5 mg dose in the pivotal studies (see below).

In the post-hoc analysis, the responders were defined as patients having PEC-scale decrease of ≥40%. The CHMP noted this definition was used to support the approval of products in this indication and could therefore be accepted for the analysis.

In study 004-201, 6 out of 149 patients refused to participate. In studies 004-301 and 004-302 no patient refused to use the Staccato system suggesting apparent cooperativeness from the patients enrolled and questioning the severity of agitation, as the target population is generally known for low treatment compliance inherent to the nature of disorders, which is mostly enhanced during agitated episodes.

Baseline PEC-scores were below 18 in both pivotal studies, which confirmed that the studied population had moderate agitation (Tables 3 and 5, Figures 7 and 8). This is also reflected by the protracted mean duration of agitation that could last more than 1 week time (see Tables 3 and 5). This observation could be seen as atypical for acute agitation and could reflect unstable disease. The CHMP noted that the studied population contrasted with available published study conducted by Currier et al (2001). This study included patients with an average baseline PEC-score of 27.5 and used both oral treatment and injections. From the CHMP view point, it is unclear whether results in patients with moderate agitation can be extrapolated to severe agitation, which may be more treatment resistant.

Efficacy data and additional analyses.

In study 004-201, 10 mg dose of Adasuve demonstrated statistically significant improvements compared with placebo for the primary endpoint (PEC score at 2 hrs: -8.56, p=0.0002). The 5 mg dose of Adasuve also produced positive results but these did not reach statistical significance (PEC score at 2 hrs: -6.71, p=0.088). The CHMP noted that the dose finding results were not reproduced in the two pivotal studies where the efficacy of 5 mg loxapine did not significantly differ from 10 mg in the primary analysis (see below). Although only 2 doses were tested and no pair-wise comparison was performed between loxapine 5 mg and 10 mg, post-hoc PEC scale responder analysis at early time points showed a trend towards a large percentage of responders for the 10 mg dose as compared to the 5 mg dose (Tables 33 and 34), and results on the overall use of additional study medication and/or rescue medication by 4 and 24 hours after Dose 1 favoured the 10 mg dose (see Tables 17-18 and 21-22). The CHMP therefore considered acceptable to recommend an initial dose of 10 mg, also taking into account that subgroup analyses revealed that 5 mg was not effective in male patients (PEC score at 2 hrs: 1.4, p= 0.0996; CGI-I score at 2 hrs: -0.3, p=0.1284).

In both pivotal studies, treatment groups were generally well matched for demographic characteristics. The mean age of randomized patients was 43.1 years in study 004-301 and 40.8 years in study 004-302: young adults (18-25 years old) were scarcely (7.3%) represented in either trial. Women in the schizophrenia trial were scarcely represented (26.5%), and about half of the patients were male (49.7%) in study 004-302. Most patients were either black or Caucasian: 57.6% vs 33.7% and 44.3% vs 43.9%, in studies 004-301 and 004-302, respectively. About 35% of the patients with schizophrenia were taking concomitant antipsychotics at the time of dosing while approximately 13% of the patients with bipolar disorder were taking these drugs reflecting that a considerable proportion of patients were not naive to antipsychotics. A majority of the patients in both Phase 3 studies were smokers with about 82% of the patients with schizophrenia and 74% of the patients with bipolar disorder currently smoking.

In study 004-301, efficacy of Adasuve was demonstrated over placebo, on the primary endpoint and secondary endpoints defined as PEC score at 2 hours and at 10 minutes timepoint, respectively for the tested doses. For 5 mg dose, PEC scores were: -8.0 at 2hrs (p=0.0004) and -3.1 at 10 minutes (p=n/a). For 10 mg dose, PEC scores were: -8.7 at 2hrs (p=<0.0001) and -3.4 at 10 minutes

(p<0.0001). Adasuve 5 mg dose appeared as efficacious as the 10 mg dose in decreasing PEC score. Results in the PEC score are confirmed by the effects observed on the key secondary endpoints, CGI-I score at 2 hours (for 5 mg: 2.3, p=0.0015 and for 10 mg: 2.1, p<0.0001), and in the additional secondary endpoints, with no major difference observed between 5mg and 10 mg doses (see Tables 13, 15-18).

Similar efficacy results were observed in study 004-302, conducted in acutely agitated bipolar type I patients. Efficacy of Adasuve was demonstrated over placebo at 2 hours and after 10 minutes for the tested doses. For 5 mg dose, PEC scores were: -8.2 at 2hrs (p=<0.0001) and -3.6 at 10 minutes (p=n/a). For 10 mg dose, PEC scores were: -9.2 at 2hrs (p=<0.0001) and -4 at 10 minutes (p<0.0001). No major difference was observed between 5mg and 10 mg doses in decreasing PEC score, as well as on the other main efficacy endpoints (see Tables 14, 19-22).

In both studies, a significant proportion of the patients (approximately 25 to 45%) were administered a second dose after the 2 hours to reach an adequate control of the agitation.

In both pivotal studies, from 30 minutes post dose onwards the 10 mg dose resulted in a 40% or higher decrease of agitation rating levels in about 60% of patients, as compared to 26% of patients who were given placebo. However, the CHMP noted that there was a 1.6-2.0 point decrease in the PEC score over time, from 4h to 24h across all groups (see Figure 11). According to the applicant, this may have reflected some early re-emergence of symptoms across all groups, the investigators were not yet being allowed to start or resume a maintenance regimen. In fact, during this time, the placebo subjects received more dose 2, dose 3 and rescue medication combined compared to the active treatments (see Tables 18 and 22). In addition, additional analyses performed at the CHMP request indicated that the efficacy of Adasuve 10 mg on acute agitation in bipolar I disorder was not significant among patients that were using stable antipsychotic medication on the primary and key secondary endpoints for 10 mg dose (PEC at 2 hours: 1.9, p=0.3559; CGI-I at 2 hours: -0.4, p=0.3637). From the CHMP viewpoint, a possible saturation of dopamine-receptors could not be excluded in those patients.

The indirect comparison between Adasuve and i.m. aripiprazole and i.m. olanzapine showed similar order of magnitude of efficacy in the intended population (see Figure 12). However, the CHMP could not conclude on added clinical benefit versus existing available therapy due to the lack of active comparator.

Overall, the CHMP considered that the presented efficacy data did not support a broad indication for “for the rapid agitation in adult patients with schizophrenia or bipolar disorder” as claimed by the applicant. In addition, the pharmacological profile of Adasuve raised efficacy and safety concerns in patients on stable, chronic antipsychotics regimens and in patients with asthma and COPD patients (see 2.4.4). The CHMP consequently agreed to convene the Psychiatry Scientific Advisory Group (SAG-Psychiatry) to ask the view of the experts in the field on whether in clinical practice there will be a patient population in which the product can be safely used.

Prior the SAG Psychiatry meeting, the applicant revised the indication as follows: “ADASUVE is indicated for the rapid control of mild-to-moderate agitation in adult patients with schizophrenia or bipolar disorder.”

The SAG Psychiatry was held on 6 November 2012 and the main conclusions were as follows:

- The group considered that there was a need for alternative options in the rapid control of agitation in adult patients with schizophrenia or bipolar disorder. In this respect, ADASUVE may represent a non invasive alternative to the more coercive intramuscular injections.

- ADASUVE administration required some level of cooperation from the patient who has to accept to breathe into the device. Severely agitated patients were not investigated and patients who are not cooperative would not be eligible for this treatment.
- Based on the provided data, the group was of the opinion that there may be a place for Adasuve in the management of mild to moderately agitated patients. Severity is meant to be a clinical judgement.

While there may be a patient population in which the product can be used in clinical practice, the group noted that the use of ADASUVE raises some safety concerns that make the assessment of the benefit/risk of the product difficult due to :

- The risk of severe bronchospasm requiring a treatment in half of the patients presenting with asthma/COPD. Although this risk is considered manageable in a clinical setting, appropriate contraindications are needed for patients at higher risk. Whereas this risk seems to be confined to patients with certain pulmonary conditions (irritation e.g asthma) , emphasis is put on the fact that psychiatric patients do present quite often with medical comorbidities, quite often poorly stabilised, and therefore may also be at risk.
- Safety concerns in case of co-administration with other antipsychotics, particularly with regard to the potential increased risk of QT prolongation.
- The need to have a second dose at 2 hours interval to achieve a satisfactory level of sedation may increase the drug exposure. However, the group considered that administration of up to 2 doses at 2 hours interval was reasonable.

Taking into account the above and the CHMP question, the SAG Psychiatry agreed that there would be a patient population in which Adasuve can be used in clinical practice, provided that its use is limited to patients with mild to moderate acute agitation, without evidence of active airways disease and that only a maximum of 2 doses is administered to the patients.

Following the SAG Psychiatry conclusions, the CHMP considered that the presented data could support the indication, as revised by the applicant. The CHMP also noted that the contraindication in patients with active airways disease was already proposed by the applicant. However the CHMP recommended further restrictions including the use in hospital setting only and a limitation of the posology to “no more than 2 doses”. In addition, the following warnings were recommended by the CHMP:

- Correct use of ADASUVE inhaler is important for administration of the full dose of loxapine. Healthcare professionals should ensure the patient will use the inhaler properly.
- ADASUVE may have limited effectiveness when patients are on concomitant medicinal products, predominantly other antipsychotics.

2.5.8. Conclusions on the clinical efficacy

The CHMP concluded that the efficacy in the rapid control of mild-to-moderate agitation in adult patients with schizophrenia or bipolar disorder was demonstrated for Adasuve in the proposed dosing regimen of “no more than 2 doses”.

2.6. Clinical safety

The safety database presented in this dossier included the following datasets: 1) agitated patients in controlled studies (studies 004-201,301 and 302) or pool 1; 2) healthy volunteers (004-101,103,104,106,107) or pool 2; 3) subjects on stable antipsychotic regimens (004-102); 4) subjects

with asthma (004-108); 5) subjects with COPD (004-105);6) in patients with migraine/headache (104-201);7) outpatient subject with migraine/headache (104-202).

In addition to these studies, literature data on safety experience with loxapine marketed as oral or parenteral formulations were summarised.

2.6.1. Patient exposure

The overall safety population included a total of 1653 subjects: 578 receiving placebo; 348 receiving less than 5mg of loxapine and 347 and 452 receiving loxapine 5 mg and 10 mg respectively. A limited number of subjects were exposed to more than one dose (see Table 35).

Table 35

Doses of Study Medication, n (%)	Placebo (N=578)	*Staccato* Loxapine Dose-Level			All *Staccato* Loxapine (N=1147)
		<5 mg [a] (N=348)	5 mg (N=347)	10 mg (N=452)	
1 dose	351 (60.7%)	348 (100.0%)	203 (58.5%)	283 (62.6%)	834 (72.7%)
2 doses	184 (31.8%)	0	94 (27.1%)	130 (28.8%)	224 (19.5%)
3 doses	43 (7.4%)	0	37 (10.7%)	25 (5.5%)	62 (5.4%)
4 doses	0	0	13 (3.7%)	14 (3.1%)	27 (2.4%)

2.6.2. Adverse events

The AE profile of the agitated patients and healthy volunteers are presented in Tables 36 and 37.

Table 36

MedDRA System Organ Class Preferred Term, n (%)	Placebo (N=263)	*Staccato* Loxapine Total Daily Dose				
		5 mg (N=152)	10 mg (N=269)	15 mg (N=20)	20 mg (N=67)	30 mg (N=16)
Patients with at least 1 AE	98 (37.3%)	54 (35.5%)	97 (36.1%)	11 (55.0%)	21 (31.3%)	8 (50.0%)
Nervous system disorders	58 (22.1%)	39 (25.7%)	50 (18.6%)	6 (30.0%)	7 (10.4%)	4 (25.0%)
Dizziness	23 (8.7%)	12 (7.9%)	14 (5.2%)	2 (10.0%)	5 (7.5%)	3 (18.8%)
Sedation	20 (7.6%)	23 (15.1%)	25 (9.3%)	2 (10.0%)	4 (6.0%)	1 (6.3%)
Akathisia	0	0	1 (0.4%)	0	0	1 (6.3%)
Headache	26 (9.9%)	6 (3.9%)	10 (3.7%)	1 (5.0%)	0	0
Migraine	0	0	0	1 (5.0%)	0	0
Somnolence	5 (1.9%)	3 (2.0%)	4 (1.5%)	1 (5.0%)	0	0
Gastrointestinal disorders	35 (13.3%)	16 (10.5%)	48 (17.8%)	8 (40.0%)	14 (20.9%)	4 (25.0%)
Dysgeusia	13 (4.9%)	11 (7.2%)	37 (13.8%)	4 (20.0%)	12 (17.9%)	3 (18.8%)
Hypoaesthesia oral	1 (0.4%)	0	3 (1.1%)	1 (5.0%)	1 (1.5%)	1 (6.3%)
Diarrhoea	3 (1.1%)	0	1 (0.4%)	1 (5.0%)	0	0
Dry mouth	4 (1.5%)	2 (1.3%)	4 (1.5%)	1 (5.0%)	0	0
Dyspepsia	3 (1.1%)	1 (0.7%)	0	1 (5.0%)	0	0
Respiratory, thoracic, and mediastinal disorders	3 (1.1%)	5 (3.3%)	7 (2.6%)	0	4 (6.0%)	3 (18.8%)
Throat irritation	1 (0.4%)	2 (1.3%)	3 (1.1%)	0	2 (3.0%)	2 (12.5%)
Hiccups	0	0	0	0	0	1 (6.3%)
Pharyngeal hypoaesthesia	0	1 (0.7%)	1 (0.4%)	0	0	1 (6.3%)
General disorders and administration site conditions	6 (2.3%)	6 (3.9%)	2 (0.7%)	0	2 (3.0%)	0
Fatigue	5 (1.9%)	6 (3.9%)	1 (0.4%)	0	2 (3.0%)	0

Table 37

MedDRA System Organ Class Preferred Term, n (%)	Placebo (N=90)	*Staccato* loxapine Dose-Level			All *Staccato* Loxapine (N=177)
		<5 mg (N=21)	5 mg (N=23)	10 mg (N=133)	
Subjects with at least 1 AE	34 (37.8%)	12 (57.1%)	21 (91.3%)	113 (85.0%)	146 (82.5%)
Nervous system disorders	24 (26.7%)	12 (57.1%)	19 (82.6%)	98 (73.7%)	129 (72.9%)
Somnolence	10 (11.1%)	3 (14.3%)	17 (73.9%)	83 (62.4%)	103 (58.2%)
Dizziness	7 (7.8%)	7 (33.3%)	7 (30.4%)	49 (36.8%)	63 (35.6%)
Headache	10 (11.1%)	2 (9.5%)	7 (30.4%)	12 (9.0%)	21 (11.9%)
Gastrointestinal disorders	4 (4.4%)	7 (33.3%)	5 (21.7%)	44 (33.1%)	56 (31.6%)
Dysgeusia	2 (2.2%)	5 (23.8%)	2 (8.7%)	40 (30.1%)	47 (26.6%)
Respiratory, thoracic, and mediastinal disorders	5 (5.6%)	0	1 (4.3%)	24 (18.0%)	25 (14.1%)
Cough	2 (2.2%)	0	0	13 (9.8%)	13 (7.3%)

In addition, in the thorough QT-study in healthy volunteers the most common treatment-related AEs reported were somnolence (Staccato Loxapine, 61.7%; placebo, 14.9%; moxifloxacin, 4.3%), dizziness (Staccato Loxapine, 36.2%; placebo, 4.3%; moxifloxacin, 8.5%), dysgeusia (Staccato Loxapine, 19.1%; placebo, 2.1%; moxifloxacin, 4.3%), and cough (Staccato Loxapine, 14.9%; placebo, 2.1%; moxifloxacin, 0.0%).

2.6.3. Serious adverse event / deaths / other significant events

Severe sedation was experienced by 2 patients (0.8%) in the 10 mg group. Severe AEs that were experienced by 1 patient each in the loxapine groups were somnolence, schizophrenia (exacerbation), dystonia, oculogyration, gastroenteritis, hypertension, and hyperhidrosis. Severe AEs experienced in the placebo group (1 patient each) were headache, nausea, agitation, schizophrenia (exacerbation), overdose, and pelvic inflammatory disease. There were no deaths in the studies submitted by the applicant within the study periods or related to study treatments.

2.6.4. Laboratory findings

Among loxapine-treated patients in the pivotal efficacy studies, one patient had blood creatine kinase increase, and one patient had hepatic enzyme increase. There were no clinically relevant mean changes in hematology, blood chemistry, and urinalysis.

2.6.5. Safety in special populations

Available data on subjects with active airways and on stable antipsychotic regimen are derived from the phase I studies (see 2.4.3.2) since these patients were not included in the pivotal studies according to their protocols.

Subjects with active airways disease

In subjects with asthma or COPD, bronchospasm (which included reports of wheezing, shortness of breath or cough) was reported in patients following administration of 2 inhaled doses of loxapine with a 8-10 hour interval. Bronchospasm was reported in 14 of 26 subjects (53.8%) with mild-to-moderate persistent asthma, and in 5 of 26 subjects (19.2%) with COPD. These events occurred within 25 minutes of dosing in 12 of the 14 asthma subjects and in 4 of the 5 COPD subjects. The events were rated mild to moderate in severity. Spontaneous recovery did not occur in 13 asthma and 2 COPD subjects so that treatment with an inhaled bronchodilatator was required.

In asthma subjects, 18 (69.2%) loxapine-treated subjects and 3 (11.5%) placebo-treated subjects had notable respiratory signs and/or symptoms, defined as an FEV1 decrease from baseline of ≥20%, an airway AE, or use of rescue medication. In addition, according to the protocol, 10 subjects (9 loxapine, 1 placebo) did not receive the second dose 2 because of an AE of dyspnea, wheezing, or bronchospasm, or a decrease from baseline FEV1 of ≥20%. Two loxapine-treated subjects did not receive the second dose because of an FEV1 decrease of ≥20%, and 2 loxapine-treated subjects did not receive the second dose because of AEs (chest discomfort and cough in one patient and chest discomfort in the other patient). The remaining 5 loxapine-treated subjects did not receive the second dose because of an FEV1 decrease of ≥20% and AEs (wheezing (2); bronchospasm (2); chest discomfort, dyspnea, FEV1 decreased, wheezing, throat tightness (1); bronchospasm. The placebo-treated subject had an AE of chest discomfort. Airway AEs were reported by 14 (53.8%) loxapine-treated subjects and 3 (11.5%) placebo-treated subjects. Airway AEs that occurred in more than a single loxapine-treated subject were bronchospasm (7 subjects), chest discomfort (6 subjects), wheezing (4 subjects), and dyspnea (3 subjects). Airway AEs were also reported for 3 (11.5%) placebo-treated subjects: chest discomfort in 2 subjects; bronchospasm in 1 subject.

In COPD subjects, 15 (57.7%) loxapine-treated subjects and 6 (22.2%) placebo-treated subjects had notable respiratory signs and/or symptoms. In addition, according to the protocol, 8 subjects (7 loxapine, 1 placebo) did not receive the second dose 2 because of an AE of dyspnea, wheezing, or bronchospasm, or a decrease from baseline FEV1 of ≥20%. Five loxapine-treated subjects did not receive the second dose because of an FEV1 decrease of ≥20%, and 2 loxapine-treated subjects did not receive the second dose because of AEs (wheezing in one patient, dyspnea and wheezing in the other patient). The placebo-treated subject had an AE of bronchospasm and an FEV1 decrease of ≥20%. Airway AEs were reported for 5 (19.2%) loxapine-treated subjects. Airway AEs that occurred in more than a single loxapine-treated subject were dyspnea (3 subjects), cough (3 subjects), and wheezing (2 subjects). Airway AEs were also reported for 3 (11.1%) placebo-treated subjects: dyspnea, bronchospasm and productive cough.

Subjects on stable antipsychotic regimen

Among 32 patients 18-65 years of age on chronic, stable antipsychotic regimens, 3 doses of loxapine with a 4-hour interval were administered over an 8-hour period. Mild to moderate AEs were reported in loxapine-treated group, no AEs were reported in the placebo-treated group. The percentage of subjects with AE were 38%, 38% and 50% for the 15, 20 and 30 mg loxapine dose, respectively. The most frequently reported AE's were cough (3), sedation (3) and dysgeusia (2).

2.6.6. Safety related to drug-drug interactions and other interactions

At the CHMP request, the applicant analysed the potential risk of respiratory depression in case of administration of benzodiazepines or other ventilation depressants after loxapine was given. The applicant clarified that by protocol, patients received rescue lorazepam following the second dose of study medication and were not eligible to receive additional loxapine after the rescue medication, hence there was no possible concomitant administration of lorazepam shortly before loxapine was

given. The percentage of patients in the pivotal studies receiving rescue lorazepam following the second dose was 17.2%. According to the applicant, there was no difference in the AE profile between these patients and those who did not receive lorazepam. However, one case of overdose in a patient treated with more than 1 CNS active drug was reported in the literature.

2.6.7. Discontinuation due to adverse events

In the pivotal efficacy studies, discontinuations due to AE's were rare and occurred only in the group treated with Staccato loxapine 10 mg (1.2%, 3/259).

2.6.8. Post marketing experience

Loxapine has been marketed for a number of decades in both Europe and the US as oral tablets and solution for intramuscular injection. A review of 164 clinical studies from published literature on safety experience with these existing formulations was submitted by the applicant. In most publications, dose-dependent sedation effects were noted in 10 to 50% of all treated patients. In comparison with other conventional anti-psychotics, loxapine may have a stronger hypno-sedative effect. Other frequently occurring adverse effects were tachycardia and palpitations in up to 82% of all patients, returning to normal after several days, dose-dependent extra-pyramidal symptoms (~39% of treated patients) including akathisia, dystonia, rigidity and tremor ('hypokinetic-rigidity syndrome'), dose-dependent hypotension (13% of patients at a dose of 200 mg) and parasympaticolytic /anti-cholinergic side effects such as dry mouth, nasal congestion, constipation, blurred vision, urinary retention and paralytic ileus.

Rare but severe adverse effects described in loxapine users were neuroleptic malignant syndrome (1 fatal case has been reported) and rhabdomyolysis was also reported in one patient after intramuscular 'rapid neuroleptization'. Also tardive dyskinesia may develop after chronic use. Hypertension and bradycardia were reported, as well as seizures, predominantly with overdose.

ECG changes were reported in a few studies but in some prospective studies only sinus tachycardia was shown. The hERG channel blockade responsible for QT-interval prolongation was reported to occur only at relatively high concentrations. The halfway hERG channel blocking (IC_{50}) of loxapine is at 1800 nM. (IC_{50} droperidol /risperidone /haloperidol = 167-174 nM; IC_{50} ziprasidone = 3 nM) indicating low pro-arrhythmic potential.

Respiratory effects of loxapine have not been well studied, but cases of hypoventilation were reported when co-administered with benzodiazepines. Other side-effects were liver enzyme elevations, hyperglycemia and rare hematologic abnormalities such as agranulocytosis /leucopenia and neutropenia. Predominantly after chronic administration, hyperprolactinaemia may cause impotence, galactorrhea, gynaecomastia and amenorrhea.

In one report, 3 personality disordered patients were described to abuse loxapine for its soporic and dulling effect ('flush').

Based on the applicant's review, 15 deaths were identified possibly related to loxapine therapy, amongst which were two cases of myocardial infarction /heart disease, one neuroleptic malignant syndrome, and one opioid-induced neuro-toxicity. Other causes of death were suicide, overdose or injury.

2.6.9. Discussion on clinical safety

Loxapine is a dibenzoxazepine, exhibiting antagonism of dopamine D2 receptors, 5-HT2A antagonistic activity and anti-cholinergic, anti-histaminergic and anti-alpha-adrenergic properties. The known side effect profiles of loxapine tablets and loxapine intramuscular injection are similar to other conventional anti-psychotics with a relatively modest influence on cardiac repolarisation and a similar extra-pyramidal effects profile. However tachycardia appeared to be common, possibly related to hypotension due to alpha-1 adrenergic blocking potential of loxapine. Also, neuroleptic malignant syndrome including rhabdomyolysis may occur as a rare but potentially life-threatening complication.

The safety profile of Adasuve appeared to be similar to the other anti-psychotic agents, however, high risk of bronchospasm in lung disease patients has been identified. This risk is most likely due to specific tolerability problem in susceptible individuals, given the novel route of administration of this product, used as an inhaler. The CHMP noted that this patient population were excluded in the pivotal studies and were only investigated in phase I studies.

In subjects with asthma or COPD, bronchospasm (which included reports of wheezing, shortness of breath or cough) was reported in patients following administration of 2 inhaled doses of loxapine with a 8-10 hour interval. Bronchospasm was reported in 14 of 26 subjects (53.8%) with mild-to-moderate persistent asthma, and in 5 of 26 subjects (19.2%) with COPD. These events occurred within 25 minutes of dosing in 12 of the 14 asthma subjects and in 4 of the 5 COPD subjects. The events were rated mild to moderate in severity. Spontaneous recovery did not occur in 13 asthma and 2 COPD subjects so that treatment with an inhaled bronchodilatator was required. After the SAG Psychiatry (see 2.5.7) and PRAC consultations (see 2.7.2), the following risk minimisation measures were considered sufficient to address this risk: 1) restriction to hospital use only, 2) availability of short acting beta agonist in the clinical setting, 3) the need to observe patients during the first hour after each dose for signs and symptoms of bronchospasm, 4) contraindication in patients with asthma, COPD and acute respiratory symptoms, 5) SmPC warnings related to the bronchospasm reflected on the pouch Label. In addition, the CHMP recommended that educational materials should be provided to healthcare professionals to ensure safe and effective use of the product.

In the pivotal efficacy studies, discontinuations due to AE's were rare and occurred only in the group treated with Staccato loxapine 10 mg (1.2%, 3/259).

There is a lack of data regarding patients using concomitantly lorazepam or other ventilation depressants and elderly patients due to the design of the submitted clinical studies. Appropriate warnings have been reflected in the SmPC regarding these patient populations.

A post authorisation study (PASS) to further investigate respiratory safety concern in real world settings, together with a retrospective drug utilisation study to determine the usage of Adasuve have been included as additional pharmacovigilance activities in the risk management plan (RMP). Safety data from the PASS will also be further collected regarding patients on concomitant medicinal products and potential lack of efficacy.

In addition, according to the discussion on clinical pharmacology (see 2.4.4), drug interaction study with lorazepam and QT/QTc study after repeated dosing will be performed to address potential interaction with concomitant benzodiazepines and QT prolongation after 2 doses. These are also part of the risk management plan (see 2.7.2).

2.6.10. Conclusions on the clinical safety

From the safety database all the adverse reactions reported in clinical trials have been included in the SmPC. Appropriate measures including additional pharmacovigilance activities and risk minimization

activities (see 2.7) have been put in place to ensure safe and effective use of the product in the recommended indication.

The CHMP considers the following measures, included as part of the risk management plan, necessary to address issues related to safety:

- A post-authorization observational study to evaluate the safety of Adasuve in agitated Persons in routine clinical care

- A multinational retrospective medical chart review to evaluate utilization patterns of ADASUVE in agitated persons in routine clinical care

- Phase 1 study to assess the safety and PD profile of concomitant administration of single doses of Staccato loxapine and lorazepam (i.m.) compared to the administration of each agent alone.

- 2 dose, double-blind, double-dummy, active and placebo controlled, randomized, 3-period cross-over study investigating a 2 doses of 10 mg of ADASUVE given 2 hours apart, a positive control with known QT/QTc prolongation (oral moxifloxacin, 400 mg), and an oral placebo/Staccato placebo.

2.7. Pharmacovigilance

2.7.1. Detailed description of the pharmacovigilance system

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

2.7.2. Risk Management Plan

The applicant submitted a risk management plan.

The applicant submitted a risk management plan, which included a risk minimisation plan.

Table 37. Summary of the risk management plan

Safety Concern	Agreed pharmacovigilance activities	Agreed risk minimisation activities
Important identified risks		
Bronchospasm	Routine pharmacovigilance Additional pharmacovigilance: Data collected from post- authorisation safety study 204-401 and post-authorisation drug utilisation study 204-403	**SPC** • Posology (SPC Section 4.2) states: *ADASUVE should **only** be administered in a hospital-setting under the supervision of a healthcare professional.* Posology (SPC Section 4.2) states: *Short-acting beta-agonist bronchodilator treatment should be available for treatment of possible severe respiratory side-effects (bronchospasm).* Posology (SPC Section 4.2) states: *Patients should be observed during the first hour after each dose for signs and symtoms of bronchospasm.* Contraindication (SPC Section 4.3) states: *Patients with acute respiratory signs/symptoms (eg, wheezing) or with active airways disease (such as*

Safety Concern	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		patients with asthma or chronic obstructive pulmonary disease [COPD]. Warnings and precautions for use in SPC Section 4.4 states: *In placebo-controlled clinical trials in subjects with asthma or COPD, bronchospasm was very commonly observed. When it occurred, it was typically reported within 25 minutes after dosing. Consequently, patients receiving ADASUVE should be observed as appropriate following dosing. ADASUVE has not been investigated in patients with other forms of lung disease. Should bronchospasm occur after treatment with ADASUVE, it can be treated with a short-acting beta-agonist bronchodilator e.g., salbutamol (see sections 4.2 and 4.8). ADASUVE should not be re-administered in patients who develop any respiratory signs/symptoms (see section 4.3).* Described and listed as ADR in Section 4.8 of the SPC: ***Respiratory, thoracic and mediastinal disorders*** *Common: throat irritation* *Uncommon: bronchospasm (including shortness of breath)* *Bronchospasm* *In short-term (24-hour), placebo-controlled trials in patients with agitation associated with schizophrenia or bipolar disorder without active airways disease, bronchospasm (which includes reports of wheezing, shortness of breath or cough) was uncommon in patients treated with ADASUVE. However, in placebo-controlled clinical trials in subjects with mild-to-moderate persistent asthma or moderate to severe chronic obstructive pulmonary disease (COPD), adverse reactions of bronchospasm were reported very commonly. Most of these events occurred within 25 minutes of dosing, were mild to moderate in severity, and could be relieved with an inhaled bronchodilator.* **Package Leaflet, Section 2:** ***Do not take ADASUVE*** *if you have symptoms of wheezing or shortness of breath;* *if you have lung problems like asthma or chronic obstructive pulmonary disease (which your doctor may have called "COPD").* ***Warnings and precautions*** *Your doctor or nurse will talk to you before you take ADASUVE and determine whether it is appropriate for you.* *ADASUVE may cause narrowing of the airways (bronchospasm) and may cause you to wheeze, cough, feel chest tightness or have shortness of breath. Typically, this occur within 25 minutes of*

Safety Concern	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		use. *Tell your doctor if you develop any of these symptoms after taking ADASUVE.* *Before treatment with ADASUVE, tell your doctor or nurse if you:* *have or had breathing problems like asthma or other chronic lung diseases such as bronchitis or emphysema* **Labelling (warnings on pouch label)** *The sealed foil pouch which contains the device (inhaler with mouthpiece) and which should be opened just before administration, will contain the following reminder text* *Do not use in patients with asthma or COPD or acute respiratory symptoms* *A short-acting beta-agonist bronchodilator should be available for treatment of possible bronchospasm.* *Patients should be observed during the first hour after each dose for signs and symptoms of bronchospasm* ***Additional Risk Minimisation Measures*** **Educational material** *Provision of educational material to HCP's providing education regarding the risk of bronchospasm by* *Mentioning the contra-indication and related warnings.* *Providing a clear recommendation to not start treatment in patients with acute respiratory signs/symptoms (e.g., wheezing) or with active airways disease (such as patients with asthma or chronic obstructive pulmonary disease [COPD].* *Stating that treatment should take place in a hospital setting* *Need for the availability of rescue medication* *Need to observe patients for 1 hour after treatment*
Extrapyramidal symptoms	Routine pharmacovigilance	Described as ADR in Section 4.8 of the SPC: *Adverse reactions seen with chronic oral loxapine use* *With chronic oral administration of loxapine, the reported adverse reactions include sedation and drowsiness; extrapyramidal symptoms (e.g., tremor, akathisia, rigidity, and dystonia); cardiovascular effects (e.g., tachycardia, hypotension, hypertension, orthostatic hypotension, light-headedness, and syncope); and anticholinergic effects (e.g., dry eyes, blurred vision, and urinary retention).*
Hypotension	Routine pharmacovigilance	Warning included in Section 4.4 of the SPC: *Hypotension* *Mild hypotension was reported in short-term (24-hour), placebo-controlled trials in agitated patients*

Safety Concern	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		administered ADASUVE. If vasopressor therapy is required, noradrenaline or phenylephrine is preferred. Adrenaline should not be used, since beta-adrenoceptor stimulation may worsen hypotension in the setting of loxapine-induced partial alpha-adrenoceptor blockade (see section 4.5). Listed and described as ADR in Section 4.8 of the SPC: *Adverse reactions seen with chronic oral loxapine use* *With chronic oral administration of loxapine, the reported adverse reactions include sedation and drowsiness; extrapyramidal symptoms (e.g., tremor, akathisia, rigidity, and dystonia); cardiovascular effects (e.g., tachycardia, hypotension, hypertension, orthostatic hypotension, light-headedness, and syncope); and anticholinergic effects (e.g., dry eyes, blurred vision, and urinary retention).*
Important potential risks		
Interaction between loxapine and adrenaline or blood pressure lowering medicinal products	Routine pharmacovigilance	Interaction mentioned in Section 4.5 of the SPC: *Adrenaline* *Co-administration of loxapine and adrenaline may cause worsening of hypotension (see section 4.4).*
Suicidality	Routine pharmacovigilance	No additional risk minimization necessary
QTc prolongation upon repeated use	Routine pharmacovigilance Additional pharmacovigilance: Data collected from post-authorisation thorough QTc study with 2 doses 204-407	Posology Section 4.2 of the SPC states: *The recommended initial dose of ADASUVE is 9.1 mg. A second dose can be given after 2 hours, if necessary. No more than two doses should be administered.* Described in Section 4.4 of the SPC: *QT interval* *Clinically relevant QT prolongation does not appear to be associated with a single dose of ADASUVE. Caution should be exercised when ADASUVE is administered in patients with known cardiovascular disease or family history of QT prolongation, and in concomitant use with other medicinal products known to prolong the QT interval. The potential risk of QTc prolongation following repeat dosing or interaction with medicinal products known to prolong QTc interval is unknown.* ***Additional Risk Minimisation Measures*** **Educational material** Provision of educational material to HCP's indicating that a maximum of 2 doses should be given and that caution should be exercised when ADASUVE is administered in patients with known cardiovascular disease or family history of QT prolongation, and in concomitant use with other medicinal products known to prolong the QT

Safety Concern	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		interval.
Interaction between loxapine (repeated use) and medicinal products known to prolong QTc interval, including other antipsychotic agents	Routine pharmacovigilance	Posology Section 4.2 of the SPC states: *The recommended initial dose of ADASUVE is 9.1 mg. A second dose can be given after 2 hours, if necessary. No more than two doses should be administered.* Described in Section 4.4 of the SPC: *QT interval* *Clinically relevant QT prolongation does not appear to be associated with a single dose of ADASUVE. Caution should be exercised when ADASUVE is administered in patients with known cardiovascular disease or family history of QT prolongation, and in concomitant use with other medicinal products known to prolong the QT interval. The potential risk of QTc prolongation following repeat dosing or interaction with medicinal products known to prolong QTc interval is unknown.* ***Additional Risk Minimisation Measures*** **Educational material** Provision of educational material to HCP's indicating that a maximum of 2 doses should be given and that caution should be exercised when ADASUVE is administered in patients with known cardiovascular disease or family history of QT prolongation, and in concomitant use with other medicinal products known to prolong the QT interval.
Interaction between loxapine and benzodiazepines including lorazepam	Routine pharmacovigilance Additional pharmacovigilance: Data collected from post-authorisation benzodiazepine interaction study 204-402	Description included in Section 4.5 of the SPC: *Concomitant administration of benzodiazepines or other hypnosedatives or respiratory depressants may be associated with excessive sedation and respiratory depression or respiratory failure. If benzodiazepine therapy is deemed necessary in addition to loxapine, patients should be monitored for excessive sedation and for orthostatic hypotension.*

Safety Concern	Agreed pharmacovigilance activities	Agreed risk minimisation activities
Interaction between loxapine and centrally depressing (ventilation) (medicinal) products	Routine pharmacovigilance Additional pharmacovigilance: Data collected from post-authorisation benzodiazepine interaction study 204-402	Warning in Section 4.4 of the SPC: *Hypoventilation* *Given the primary Central Nervous System (CNS) effects of loxapine, ADASUVE should be used with caution in patients with compromised respiration, such as hypovigilant patients or patients with CNS-depression due to alcohol or other centrally acting medicinal products, e.g., anxiolytics, most antipsychotics, hypnotics, opiates, etc. (see section 4.5).* Description included in Section 4.5 of the SmPC: *Given the primary CNS effects of loxapine, ADASUVE should be used with caution in combination with alcohol or other centrally acting medicinal products, e.g., anxiolytics, most antipsychotics, hypnotics, opiates, etc. The use of loxapine in patients with alcohol or medicinal product intoxication (either with prescribed or illicit medicinal products) has not been evaluated. Loxapine may cause severe respiratory depression if combined with other CNS depressants (see section 4.4).*
Tardive dyskinesia	Routine pharmacovigilance	Warning in Section 4.4 of the SPC: *Tardive dyskinesia* *If signs and symptoms of tardive dyskinesia appear in a patient being treated with loxapine, discontinuation should be considered. These symptoms can temporally worsen or can even arise after discontinuation of treatment.*
Neuroleptic Malignant Syndrome/ Rhabdomyolysis	Routine pharmacovigilance	Warning in Section 4.4 of the SPC: *Neuroleptic malignant syndrome (NMS)* *Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, ADASUVE must be discontinued.*
Lack of efficacy	Routine pharmacovigilance Additional pharmacovigilance: Data collected from post-authorisation safety study 204-401	Warning in Section 4.4 of the SPC: *ADASUVE may have limited effectiveness when patients are on concomitant medicinal products, predominantly other antipsychotics*
Seizures	Routine pharmacovigilance	Warning in Section 4.4 of the SPC: *Seizures / convulsions* *Loxapine should be used with caution in patients with a*

Safety Concern	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		history of convulsive disorders since it lowers the convulsive threshold. Seizures have been reported in patients receiving oral loxapine at antipsychotic dose levels, and may occur in epileptic patients even with maintenance of routine anticonvulsant drug therapy (see section 4.5).
Interaction between loxapine and products known to lower seizure threshold	Routine pharmacovigilance	Caution advised in Section 4.5 of the SPC: *Caution is advised if loxapine is combined with other medicinal products known to lower the seizure threshold e.g. phenothiazines or butyrophenones, clozapine, tricyclics or SSRIs, tramadol, mefloquine (see section 4.4).*
Missing information		
Off-label use during extended periods of time	Routine pharmacovigilance Additional pharmacovigilance: Data collected from post-authorisation safety study 204-401 and post-authorisation drug utilisation study 204-403	Information on the therapeutic indication is included in Section 4.1 of the SPC: *ADASUVE is indicated for the rapid control of mild-to-moderate agitation in adult patients with schizophrenia or bipolar disorder. Patients should receive regular treatment immediately after control of acute agitation symptoms* Information on the posology and recommended duration of use is provided in Section 4.2 of the SPC: <u>*Posology*</u> *The recommended initial dose of ADASUVE is 9.1 mg. A second dose can be given after 2 hours, if necessary. No more than two doses should be administered.*
Off-label use in elderly patients (>65 years of age)	Routine pharmacovigilance Additional pharmacovigilance: Data collected from post-authorisation safety study 204-401 and post-authorisation drug utilisation study 204-403	A sentence on the lack of information in patients older than 65 years is provided in Section 4.2 of the SPC: *Elderly* *The safety and efficacy of ADASUVE in patients older than 65 years of age have not been established. No data are available.*

Safety Concern	Agreed pharmacovigilance activities	Agreed risk minimisation activities
Off-label use in paediatric patients	Routine pharmacovigilance Additional pharmacovigilance: Data collected from post-authorisation safety study 204-401 and post-authorisation drug utilisation study 204-403	Information on the target population is included in Section 4.1 of the SPC: *ADASUVE is indicated for the rapid control of mild-to-moderate agitation in adult patients with schizophrenia or bipolar disorder. Patients should receive regular treatment immediately after control of acute agitation symptoms.* A sentence on the lack of information in paediatric patients is provided in Section 4.2 of the SPC: *Paediatric population* *The safety and efficacy of ADASUVE in children (less than 18 years of age) have not been established. No data are available.*
Safety in repeated dose (multiple doses and/or multiple cycles)	Routine pharmacovigilance Additional pharmacovigilance: Data collected from post-authorisation safety study 204-401	Information on the posology and recommended duration of use is provided in Section 4.2 of the SPC: *Posology* *The recommended initial dose of ADASUVE is 9.1 mg. A second dose can be given after 2 hours, if necessary. No more than two doses should be administered.*
Safety in patients with hepatic impairment	Routine pharmacovigilance Additional pharmacovigilance: Data collected from post-authorisation safety study 204-401	A sentence on the lack of information in patients with hepatic impairment is provided in Section 4.2 of the SPC: *Renal and/or hepatic impairment* *ADASUVE has not been studied in patients with renal or hepatic impairment. No data are available.*
Safety in patients with renal impairment	Routine pharmacovigilance Additional pharmacovigilance: Data collected from post-authorisation safety study 204-401	A sentence on the lack of information in patients with renal impairment is provided in Section 4.2 of the SPC: *Renal and/or hepatic impairment* *ADASUVE has not been studied in patients with renal or hepatic impairment. No data are available.*
Safety in patients with underlying cardiovascular disease	Routine pharmacovigilance Additional pharmacovigilance: Data collected from post- authorization	A sentence on the lack of information in patients with cardiovascular disease is provided in Section 4.4 of the SPC. Warning in Section 4.4 of the SPC: *Cardiovascular* *No data are available on the use of ADASUVE in patients with underlying cardiovascular diseases. ADASUVE is not recommended in patient populations with known*

Safety Concern	Agreed pharmacovigilance activities	Agreed risk minimisation activities
	safety study 204-401	*cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease, or conditions which would predispose patients to hypotension (dehydration, hypovolaemia, and treatment with antihypertensive medicinal products).*
Safety in patients with suicidal risk	Routine pharmacovigilance Additional pharmacovigilance: Data collected from post- authorization safety study 204-401	No additional risk minimization necessary
Safety in patients agitated due to intoxication with alcohol, medicinal products or illicit drug	Routine pharmacovigilance Additional pharmacovigilance: Data collected from post-authorisation safety study 204-401	A sentence on the lack of information in patients with alcohol or medicinal product intoxication (either with prescribed or illicit medicinal products) is provided in Section 4.4 of the SPC: *Intoxication or physical disease (delirium)* *The safety and efficacy of ADASUVE has not been evaluated in patients with agitation due to intoxication or physical disease (delirium). ADASUVE should be used with caution in patients who are intoxicated or delirious (see section 4.5).* Caution advised in Section 4.5 of the SPC: *Given the primary CNS effects of loxapine, ADASUVE should be used with caution in combination with alcohol or other centrally acting medicinal products, e.g., anxiolytics, most antipsychotics, hypnotics, opiates, etc. The use of loxapine in patients with alcohol or medicinal product intoxication (either with prescribed or illicit medicinal products) has not been evaluated. Loxapine may cause severe respiratory depression if combined with other CNS-depressants (see section 4.4).*

The below pharmacovigilance activity(ies) in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
Phase 1 study to assess the safety and PD profile of concomitant administration of single doses of Staccato loxapine and lorazepam (i.m.) compared to the administration of each agent alone (study 204-402)	Within six months after approval

Description	Due date
2 dose, double-blind, double-dummy, active and placebo controlled, randomized, 3-period cross-over study investigating a 2 doses of 10 mg of ADASUVE given 2 hours apart, a positive control with known QT/QTc prolongation (oral moxifloxacin, 400 mg), and an oral placebo/Staccato placebo (study 204-407)	Within four months after approval
Post-Authorization Observational Study to Evaluate the Safety of ADASUVE in Agitated Persons in Routine Clinical Care (study 204-401)	- Full protocol within one month after approval - Progress report with update on recruitment half a year after start of data collection - Interim results: September 2014 - Final results: September 2015 - Final report of study results: March 2016 Update within each PSUR after approval in line with EU requirements.
A Multinational Retrospective Medical Chart Review to Evaluate Utilization Patterns of ADASUVE in Agitated Persons in Routine Clinical Care (study 204-403)	- Full protocol within one month after approval - Progress report with update on recruitment half a year after start of data collection - Final results: May 2015 - Final report of study results: September 2015. Update within each PSUR after approval in line with EU requirements.

The following additional risk minimisation activities were required:

Prior to launch in each Member State the Marketing Authorisation Holder (MAH) shall agree an educational programme with the National Competent Authority.

The MAH shall ensure that, following discussions and agreement with the National Competent Authorities in each Member State where ADASUVE is marketed, at launch and after launch, all healthcare professionals who are expected to use ADASUVE are provided with an information pack containing the following items:

- Summary of Product Characteristics (SmPC) and Package Leaflet and Labelling
- Educational material for the healthcare professionals

Key elements to be included in the educational material:

General:

- Introductory statement on the purpose of the educational material
- Statement on acute setting of indication

Risk of bronchospasm:

- Mention of contra-indications and related warnings
- A clear recommendation not to start ADASUVE treatment in patients with a respiratory medical history
- Treatment with ADASUVE to be limited to a hospital setting
- Availability of rescue medications (short acting beta agonist bronchodilator) during treatment
- Observation of patients for 1 hour after each dose of ADASUVE

Risk of QT prolongation:

- Administration of a maximum of 2 doses
- Caution to be exercised when ADASUVE is administered in patients with known cardiovascular disease or a family history of QT prolongation, and in cases of concomitant use with other medicinal products known to prolong the QT interval

2.8. 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.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Adasuve (loxapine) is a pre-dispensed inhalation powder. The product is a hand-held device for single use by inhalation of a 5 mg or a 10 mg dose of the antipsychotic loxapine. This new method of administration (oral inhalation) is intended to ensure peak plasma levels in the systemic circulation within minutes after administration thus according to the applicant addressing the unmet need for rapid onset of sedation by non-invasive administration. The SAG Psychiatry group considered that there was a need for alternative options in the rapid control of agitation in adult patients with schizophrenia or bipolar disorder. In this respect, Adasuve may represent a non-invasive alternative to the more coercive intramuscular injections.

In both schizophrenia patients and bipolar I patients with mild to moderate agitation (baseline PEC score below 18) of an average of one week duration, Adasuve demonstrated improvement in agitation levels at 2 hours post dosing as compared to placebo to a statistically significant degree.

In study 004-301, efficacy of Adasuve was demonstrated over placebo, on the primary endpoint and secondary endpoints defined as PEC score at 2 hours and at 10 minutes timepoint for the tested doses.

For 5 mg dose, PEC scores were: -8.0 at 2hrs (p=0.0004) and -3.1 at 10 minutes (p=n/a). For 10 mg dose, PEC scores were: -8.7 at 2hrs (p=<0.0001) and -3.4 at 10 minutes (p<0.0001). Adasuve 5 mg dose appeared as efficacious as the 10 mg dose in decreasing PEC score. Results in the PEC score are confirmed by the effects observed on the key secondary endpoints, CGI-I score at 2 hours (for 5 mg: 2.3, p=0.0015 and for 10 mg: 2.1, p<0.0001), and in the additional secondary endpoints, with no major difference observed between 5mg and 10 mg doses.

Similar efficacy results were observed in study 004-302, conducted in acutely agitated bipolar type I patients. Efficacy of Adasuve was demonstrated over placebo at 2 hours and after 10 minutes for the tested doses. For 5 mg dose, PEC scores were: -8.2 at 2hrs (p=<0.0001) and -3.6 at 10 minutes (p=n/a). For 10 mg dose, PEC scores were: -9.2 at 2hrs (p=<0.0001) and -4 at 10 minutes (p<0.0001). No major difference was observed between 5mg and 10 mg doses in decreasing PEC score, as well as on the other main efficacy endpoints.

In both pivotal studies, from 30 minutes post dose onwards the 10 mg dose resulted in a 40% or higher decrease of agitation rating levels in about 60% of patients, as compared to 26% of patients who were given placebo and a significant proportion of the patients (approximately 25 to 45%) were administered a second dose after the 2 hours to reach an adequate control the agitation. The indirect comparison between Adasuve and i.m. aripiprazole and i.m. olanzapine showed similar order of magnitude of efficacy in the intended population.

Uncertainty in the knowledge about the beneficial effects.

In study 004-201, the design was limited to only two doses tested (5 mg and 10mg) questioning if the minimum effective dose was achieved. No pair-wise comparison was performed between loxapine 5 mg and 10 mg.

In both pivotal studies (004-301,004-302), the 24 hour duration was considered in principle adequate to assess efficacy given the intended short term treatment in acute agitation. However, no data were available on repeated use over several days in case the agitation showed a fluctuating pattern. In addition, a significant proportion of the patients (approximately 25 to 45%) were administered a second dose after the 2 hours to reach an adequate control of the agitation.

Only cooperative patients with predominantly long-standing, mild to moderately severe agitation symptoms were included. This may more accurately reflect symptoms of exacerbation of disease.

Although the study criteria for 004-301 and 004-302 were similar to the clinical studies performed for other approved drugs in this indication and used as intramuscular injection, no conclusion on added clinical benefit versus existing available therapy could be made due to the lack of active comparator in the pivotal studies.

The extrapolation of the results from clinical trials to actual clinical setting is questionable for Adasuve since the product is used as an oral inhaler and a certain level of cooperativeness from the patient is required under such administration.

There was a 1.6-2.0 point decrease in the PEC score change over time (from 4h to 24h) across all groups. According to the applicant, this may have reflected some early re-emergence of symptoms across all groups. In addition, additional analyses indicated that the efficacy of Adasuve 10 mg on acute agitation in bipolar I disorder was not significant among patients that were using stable antipsychotic medication on the primary and key secondary endpoints for 10 mg dose (PEC score at 2 hours: 1.9, p=0.3559; CGI-I at 2 hours: -0.4, p=0.3637). A possible saturation of dopamine-receptors could not be excluded in those patients. About 35% of the patients with schizophrenia were taking concomitant antipsychotics at the time of dosing while approximately 13% of the patients with bipolar

disorder were taking these drugs. Appropriate warning related to limited efficacy has been reflected in the SmPC regarding patients using concomitant medication predominantly antipsychotics.

Risks

Unfavourable effects

Loxapine is a conventional antipsychotic with a well-known safety and adverse events profile similar to other conventional antipsychotics, including the occurrence of hypokinetic rigidity syndrome.

Adasuve was reasonably well tolerated in the studied population. However, high risk of bronchospasm in lung disease patients has been identified. This risk is most likely due to specific tolerability problem in susceptible individuals, given the novel route of administration of this product, used as an inhaler. The CHMP noted that this patient population were excluded in the pivotal studies and were only investigated in phase I studies.

In subjects with asthma or COPD, bronchospasm (which included reports of wheezing, shortness of breath or cough) was reported in patients following administration of 2 inhaled doses of loxapine with a 8-10 hour interval. Bronchospasm was reported in 14 of 26 subjects (53.8%) with mild-to-moderate persistent asthma, and in 5 of 26 subjects (19.2%) with COPD. These events occurred within 25 minutes of dosing in 12 of the 14 asthma subjects and in 4 of the 5 COPD subjects. The events were rated mild to moderate in severity. Spontaneous recovery did not occur in 13 asthma and 2 COPD subjects so that treatment with an inhaled bronchodilatator was required. After the SAG Psychiatry and PRAC consultations, the following risk minimisation measures were considered sufficient to address this risk: 1) restriction to hospital use only, 2) availability of short acting beta agonist in the clinical setting, 3) the need to observe patients during the first hour after each dose for signs and symptoms of bronchospasm , 4) contraindication in patients with asthma, COPD and acute respiratory symptoms, 5) SmPC warnings related to the bronchospasm reflected on the pouch Label. In addition, educational materials to the attention of healthcare professionals were considered necessary to ensure safe and effective use of the product.

Pharmacodynamic data confirmed the fast onset of sedative effect achieved with loxapine inhalation. However this effect appeared much weaker in patients on stable, chronic antipsychotic regimens as compared to healthy subjects. A combined sedative and respiratory effect was also observed and this may predispose to over-sedation in case of co-administration with other ventilation depressants such as hypnosedatives including benzodiazepines.

Uncertainty in the knowledge about the unfavourable effects

A QT/QTc study did not reveal significant effect of a single dose of loxapine 10 mg on cardiac repolarization as compared to placebo. However, the effect on QT was not evaluated after repeated administration. Whilst similar systemic exposures to oral loxapine 50 mg and inhaled loxapine 10 mg were observed, the recommended daily dose for oral loxapine was found to be much higher than 50 mg with 200 mg/day (up to 600 mg/day in certain cases) which can be given once a day in the evening or in any fractionated doses during the day. The posology of oral loxapine hence suggested a much higher exposure to loxapine and its active metabolites (due to the high first pass effect) as compared to the proposed posology for inhaled loxapine (“no more than 2 doses”), hence the CHMP considered that on this basis and the safety profile of oral loxapine, the risk for QTc prologation appeared to be limited and manageable in clinical practice. The applicant agreed to conduct an additional investigating QT/QTc study with 2 doses of 10 mg given 2 hours apart. This study is part of the risk management plan.

There is a lack of data regarding patients using concomitantly lorazepam or other ventilation depressants and elderly patients due to the design of the submitted clinical studies. Appropriate warnings have been reflected in the SmPC regarding these patient populations. Further data are intended to be collected via a combined postauthorisation safety and drug utilisation study to characterise: 1) the safety profile of Adasuve in the broader agitated population than the one included in the clinical studies; 2) usage of Adasuve in the approved indication in the EU. This study is part of the risk management plan.

A post authorisation study (PASS) to further investigate respiratory safety concern in real world settings, together with a retrospective drug utilisation study to determine the usage of Adasuve have also been included as additional pharmacovigilance activities in the RMP. Safety data from the PASS will also be further collected regarding patients on concomitant medicinal products and potential lack of efficacy.

Benefit-risk balance

Importance of favourable and unfavourable effects

Adasuve is claimed to ensure peak plasma levels in the systemic circulation within minutes after administration thus according to the applicant addressing the unmet need for rapid onset of sedation by non-invasive administration. Whilst, the advantageous new route of administration as compared to intramuscular injection has been recognised by the SAG Psychiatry, the added benefit related to the rapid onset of sedation as compared to the available existing therapies (including oral route) has not been established due to the lack of active comparator in the pivotal studies. In addition, the studied population presented only mild to moderate agitation and was not fully representative of the patients with schizophrenia or bipolar I disorder requiring rapid control of the agitation, given a certain level of cooperativeness was required to use the oral inhaler. Limited efficacy was also observed among patients using concomitant medications, predominantly antipsychotics.

Nevertheless, Adasuve demonstrated improvement in agitation levels at 2 hours post dosing as compared to placebo to a statistically significant degree and indirect comparison with i.m. aripiprazole and i.m. olanzapine showed a similar order of magnitude in terms of efficacy.

The risk of bronchospasm is the most important unfavourable effect of Adasuve. It was however considered manageable in the intended clinical setting by the SAG-Psychiatry. The following risk minimisation measures were considered sufficient to address this risk: 1) restriction to hospital use only, 2) availability of short acting beta agonist in the clinical setting, 3) the need to observe patients during the first hour after each dose for signs and symptoms of bronchospasm , 4) contraindication in patients with asthma, COPD and acute respiratory symptoms, 5) SmPC warnings related to the bronchospasm reflected on the pouch Label. In addition, educational materials to the attention of healthcare professionals were considered necessary to ensure safe and effective use of the product.

Benefit-risk balance

In line with the SAG-Psychiatry, the CHMP concluded that there would be a patient population in which Adasuve can be used in clinical practice, provided that its use is limited to patients with mild to moderate acute agitation, without evidence of active airways disease and that only a maximum of 2 doses is administered to the patients. The CHMP therefore considered that the presented data could support the indication “rapid control of mild to moderate agitation in adult patients with schizophrenia and Bipolar I disorder”, provided the recommended measures to minimise the risk of bronchospasm are put in place.

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Adasuve in the treatment of "the rapid control of mild-to-moderate agitation in adult patients with schizophrenia or bipolar disorder" is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP shall be submitted annually until renewal.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch in each Member State the Marketing Authorisation Holder (MAH) shall agree an educational programme with the National Competent Authority.

The MAH shall ensure that, following discussions and agreement with the National Competent Authorities in each Member State where ADASUVE is marketed, at launch and after launch, all healthcare professionals who are expected to use ADASUVE are provided with an information pack containing the following items:

- Summary of Product Characteristics (SmPC) and Package Leaflet and Labelling

- Educational material for the healthcare professionals

Key elements to be included in the educational material:

General:

- Introductory statement on the purpose of the educational material
- Statement on acute setting of indication

Risk of bronchospasm:

- Mention of contra-indications and related warnings
- A clear recommendation not to start ADASUVE treatment in patients with a respiratory medical history
- Treatment with ADASUVE to be limited to a hospital setting
- Availability of rescue medications (short acting beta agonist bronchodilator) during treatment
- Observation of patients for 1 hour after each dose of ADASUVE

Risk of QT prolongation:

- Administration of a maximum of 2 doses
- Caution to be exercised when ADASUVE is administered in patients with known cardiovascular disease or a family history of QT prolongation, and in cases of concomitant use with other medicinal products known to prolong the QT interval