EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 January 2014
EMA/113836/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Latuda

International non-proprietary name: LURASIDONE

Procedure No. EMEA/H/C/002713/0000

Note

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

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List of abbreviations

1. **Term**	**Definition**
α1-AGP	alpha-1-acid glycoprotein
ADR	adverse drug reaction
α1-AGP	alpha-1-acid glycoprotein
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC0-24	AUC from time 0 to 24 hours
AUC0-tau	AUC from time 0 to 24 hours
AUC0-inf	AUC from time 0 extrapolated to infinity
BAS	Barnes Akathisia Scale
BE	bioequivalence
BID	twice daily
BMI	body mass index
BP	blood pressure
BPD	bipolar disorder
BPRSd	Brief Psychiatric Rating Scale derived
BT	bone turnover
CGI-S	Clinical Global Impression – Severity of Illness
CHMP	Committee for Medicinal Products for Human Use
CL/F	renal clearance
Cmax	maximum observed plasma concentration
Cmin	minimum observed serum concentration
CrCl	creatinine clearance
CSR	clinical study report
CYP	cytochrome P-450
DALYs	disability-adjusted life years
DDI	drug-drug interaction
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
DSP	Dainippon Sumitomo Pharma Co., Ltd.
DXA	dual-energy X-ray absorptiometry
EEG	electroencephalography
EMA	European Medicines Agency
EPS	extrapyramidal symptoms
GCP	Good Clinical Practice
GFP	global field power
H1	histamine1 receptor type
5-HT	5-hydroxytryptamine
HbA1c	glycosylated haemoglobin
HCl	hydrochloride
HDL	high-density lipoprotein
HOMA-IR	homeostasis model assessment of insulin resistance
HR	hazard ratio
ICH	International Conference on Harmonisation

Term	Definition *(continued)*
IDB	integrated Clinical Database
ITT	intent-to-treat
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LOCF	last observation carried forward
LS	least squares
M1	acetylcholine receptor
MAA	Marketing Authorisation Application
MADRS	Montgomery-Asberg Depression Rating Scale
MAV	markedly abnormal value
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
MSD	Merck, Sharp & Dohme
MTD	maximum tolerated dose
PANSS	Positive and Negative Syndrome Scale
PD	pharmacodynamics
PET	positron emission tomography
P-gp	P-glycoprotein
PIL	Patient Information Leaflet
PIP	Paediatric Investigation Plan
PK	pharmacokinetic
PSUR	Periodic Safety Update Report
PT	preferred term
PY	Person Years
QD	once daily
QTc	corrected QT
QTcI	individual QT interval correction
RBC	red blood cells
RMP	Risk Management Plan
SA	scientific advice
SAE	serious adverse event
SAS	Simpson-Angus Rating Scale
SmPC	Summary of Product Characteristics
SOC	system organ class
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
Tmax	time at maximum concentration
TQT	thorough QTc
TRAE	treatment-related adverse event
UBC	United Biosource Corporation
ULN	upper limit of normal
USAN	United States Adopted Name
V2/F	volume of distribution for the second peripheral compartment
WHO	World Health Organisation
XR	extended release
YLD	years lived with disability

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Takeda Pharma A/S submitted on 27 September 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Latuda through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 March 2012.

The applicant applied for the following indication: the treatment of schizophrenia.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application. The applicant indicated that lurasidone was considered to be a new active substance.

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 tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0145/2012 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP (EMEA-001230-PIP01-11) 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.

Applicant's request for consideration

New active Substance status

The applicant requested the active substance lurasidone contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 26 January 2006, 21 September 2009 and 19 May 2011. The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status

Latuda has been given a Marketing Authorisation in USA and Canada on 28 October 2010 and 18 June 2012, respectively.

A new application was filed in the following countries: Switzerland.

1.2. Manufacturers

Manufacturer responsible for batch release

Takeda Ireland Ltd.
Bray Business Park
Kilruddery
Co Wicklow
Ireland

1.3. Steps taken for the assessment of the product

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

Rapporteur: Bengt Ljungberg

Co-Rapporteur: Robert James Hemmings

- The application was received by the EMA on 27 September 2012.
- The procedure started on 24 October 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 January 2013. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 11 January 2013.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 7 February 2013.
- During the meeting on 21 February 2013, 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 25 February 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 May 2013.
- The summary report of the GCP inspection carried out at the following sites Ukraine, Russia and India (Mahara and Gujarat) respectively on 12-14 February 2013, 19-20 February 2013, 6-7 March 2013 and 11-12 March 2013 was issued on 8 April 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 25 June 2013.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 11 February 2013.
- During the CHMP meeting on 25 July 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 18 November 2013.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 28 November 2013
- PRAC RMP Advice and assessment overview, adopted by PRAC on 5 December 2013.
- During the CHMP meeting on 19 December 2013, 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 CHMP List of Outstanding Issues on 20 December 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 17 January 2014.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 9 January 2013.
- During the meeting on 20 - 23 January 2014, 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 Latuda.

2. Scientific discussion

2.1. Introduction

Lurasidone is a new chemical entity belonging to the chemical class of piperidinyl-benzisoxazole derivatives. It has high affinity for dopamine D2- and serotonergic 5HT2A- and 5-HT7-receptors, 0.994, 0.47 and 0.495 nM, respectively. It also inhibits α2c-adrenergic receptor and α2a-adrenergic receptors with a binding affinity of 10.8 and 40.7 nM respectively. Lurasidone also exhibits some partial agonistic effect at the 5HT1A receptor with a binding affinity of 6.38 nM. Lurasidone is not bound to cholinergic or muscarinic receptors in humans.

The pharmaceutical form is a film-coated tablet containing lurasidone and available in three strengths 18.5 mg, 37 mg and 74 mg, respectively.

Of note, the doses presented throughout the non-clinical and clinical parts of this assessment report are expressed as lurasidone hydrochloride, e.g. 20 mg, 40 mg, 80 mg, 120 mg, 160 mg.

The indication initially applied for was the treatment of schizophrenia. The recommended starting dose of Latuda is 37 mg once daily. No initial dose titration is required. It is effective in a dose range of 37 to 148 mg once daily. Dose increase should be based on physician judgement and observed clinical response. The maximum daily dose should not exceed 148 mg.

Schizophrenia is a severe, enduring and debilitating mental illness that affects approximately 1.0% of the population throughout the world. It is the 4th leading cause of disability in the developed world for ages 15 to 44 years, inclusive. Schizophrenia reduces life expectancy by approximately 10 years, mostly as a consequence of suicide.

Schizophrenia appears as a heterogeneous disorder, with substantial variability in clinical presentation, course of illness, and treatment response. Patients with schizophrenia experience positive symptoms, negative symptoms, and cognitive deficits and typically have long-term, profound psychosocial impairments and are often unresponsive in social situations and withdrawn.

Although no curative treatments currently exist, patients with schizophrenia can integrate into society with appropriate antipsychotic medication, psychological therapy, and community support.

Antipsychotics are the mainstay of pharmacological intervention in the treatment of schizophrenia. As there is large inter-individual variability in response to these drugs, several different antipsychotic medications are often tried before the most appropriate one is found. Newer atypical antipsychotic are both effective and less likely to cause extrapyramidal symptoms (EPS) (associated with typical antipsychotics) or agranulocytosis (associated with clozapine). While these medications may be less likely to cause EPS, they are associated with weight gain, which increases the risk of diabetes and metabolic abnormalities including increased cholesterol, triglyceride and glucose levels.

The chronic nature of schizophrenia requires long-term treatment with antipsychotic medications. 70% to 80% of outpatients with schizophrenia discontinue their treatment either due to lack of efficacy, side effects, or non-compliance, hence the need for additional treatments that are effective and well tolerated.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets available in three strengths designated as, 18.5 mg, 37 mg and 74 mg, corresponding to 18.6 mg, 37.2 mg and 74 g mg of lurasidone base.

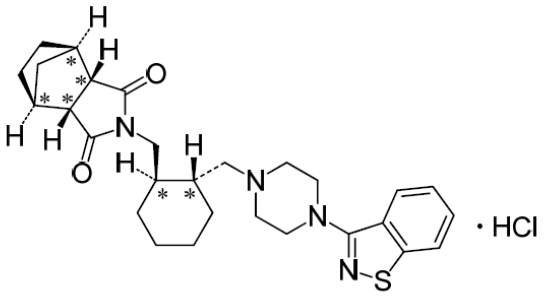
Other ingredients are mannitol, pregelatinised starch, croscarmellose sodium, hypromellose, magnesium stearate, titanium dioxide, macrogol, carnauba wax and for the 74 mg strength also the colorants indigotine and yellow iron oxide.

The product is available in aluminium/aluminium perforated unit dose blister packs.

2.2.2. Active Substance

The chemical name of the active substance lurasidone (INN) is (3aR,4S,7R,7aS)-2-{(1R,2R)-2-[4-(1,2-benzisothiazol-3-yl)piperazin-1-ylmethyl]cyclohexylmethyl}hexahydro-4,7-methano-2H-isoindole-1,3-dione hydrochloride and is a white to off-white powder.

Physico-chemical properties such as optical rotation, thermal analysis, pKa, partition coefficient, solubility in water and various solvents including ethanol, methanol, acetone and particle size have been presented. The active substance is milled to attain the desired particle size. No definite melting point has been defined but it decomposes at about 253°C. It is non-hygroscopic. Only one crystal form has been produced under the manufacturing conditions. No polymorphism has been observed by powder X-ray diffraction measurements, infrared absorption spectrometry or thermal analysis under various crystallisation conditions. The crystal X-Ray diffraction confirms the absolute configuration of the 6 chiral centres as depicted in the structure below



Asterisks (*) indicate chiral carbons

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

The active substance contained in this medicinal product was claimed by the Applicant to be qualified as a new active substance in itself. It is not considered to constitute an isomer/mixture of isomers, complex, derivative, salt of any active substance already approved in the European Union. The INN of the substance is lurasidone, the entity which should be considered the new active substance and which is used in the finished product as its hydrochloride salt.

The Applicant's justification was accepted and lurasidone is considered a new active substance in itself. It was noted, that there are some structural similarities between lurasidone and ziprasidone, another active substance approved in the EU for the treatment of schizophrenia. However, it was considered that lurasidone is not a derivative of ziprasidone.

Manufacture

Lurasidone hydrochloride is synthesised according to a nine-step process using three well-defined starting materials with acceptable specifications and three intermediates are isolated. Brief descriptions of the manufacture of the starting materials have been provided and the active substance synthesis has been described in detail including process controls.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Detailed information of the synthesis process and process controls, control of materials, critical steps and intermediates, process validation and manufacturing process development has been included in the restricted part of the ASMF and it was considered satisfactory.

The synthesis process has been redefined as compared to the original submission. As a consequence, some additional manufacturers have been involved in the regulatory synthesis. The Applicant has provided satisfactory QP declarations regarding the GMP status of all manufacturers involved in the GMP synthesis of the active substance.

Specification

The active substance lurasidone specification includes tests for: identification (IR, HPLC and chloride anion method), assay (HPLC), description (visual), heavy metals (colour identification), related substances (HPLC), residual solvents (GC), water content (Karl-Fischer), residue on ignition (Ph.Eur.) and particle size (laser light scattering). The specification (limits and methods) is in line to the one in the ASMF dossier and has been adequately justified.

The analytical methods used have been adequately described and non-compendial methods have been appropriately validated in accordance with ICH guidelines.

Batch analysis data was provided for 22 batches obtained by the latest synthetic process (16 production-scale batches) from the ASMF holder and for 26 batches from the finished product manufacturer. The results are in compliance with the proposed specification and confirm the consistency of the synthetic process.

Stability

Stability studies were presented for three commercial batches and six pilot scale batches of lurasidone stored in the commercial packaging. The batches were stored under long term (36 months at 25°C/60% RH) and accelerated (6 months at 40°C/75% RH) conditions in accordance with ICH guidelines. Stability studies were also conducted under stressed conditions (heat, humidity, light, acid, alkaline, oxidising). The stability batches were monitored for the following tests: description, assay, organic impurities, water content, XRD, particle size, identity, microbial limits, chloride content. The methods used were the same as those used for the release testing.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The objective of the pharmaceutical development was to obtain an immediate release solid dosage form of lurasidone as active substance for the treatment of schizophrenia. The finished product comprises immediate release film-coated tablets containing 20 mg, 40 mg and 80 mg lurasidone hydrochloride packaged in aluminium/aluminium blisters. With respect to the free base the content of the tablets for the respective strengths is 18.6 mg (18.5 mg), 37.2 mg (37 mg) and 74.5 mg (74 mg).

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

In addition to the strengths applied for, a 120 mg tablet (wrt lurasidone hydrochloride) has also been developed. This higher strength is not applied for in this Marketing Authorisation Application (MAA) but it is the formulation that has been used in the bioequivalence study between the pivotal clinical formulation and the proposed commercial formulation.

The pharmaceutical development has generally been satisfactorily described and discussed. During formulation development, four different formulations have been used for clinical development. Lurasidone hydrochloride has low solubility and low permeability. The tablet compositions have been developed to provide optimal dissolution from the formulation. A discriminative dissolution method has been developed for routine testing and to enable comparison between different formulations. These have been compared with respect to dissolution characteristics when changes to the formulations were introduced. The pivotal clinical studies have been performed with one “Group formulation B”. When change to the “Group C” commercial formulation was made, a bridging bioequivalence study was conducted between the formulations. Comparative dissolution profiles in different media have been provided for the two formulations and for the different strengths of the commercial formulation. The dissolution data provided show dissolution profile similarity between Group B and Group C formulations and within Group C formulations.

The development of the manufacturing process for the finished product has been sufficiently well described.

The primary packaging is aluminium/aluminium perforated unit dose blister packs. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Adventitious agents

The magnesium stearate is of vegetable origin. None of the other excipients originates from human or animal sources.

Manufacture of the product

The finished product is manufactured by a standard process consisting of the following main steps: wet granulation, drying, sizing, blending, compression and film-coating. Standard equipment is utilised. The three strengths are manufactured from a common granulate. The manufacturing process has been satisfactorily described and the in-process controls are considered adequate for this standard film-coated tablet. The manufacturing process has been validated at commercial scale.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release and shelf-life specifications for the tablets include appropriate tests for this kind of dosage form: description (visual), identification (HPLC and UV), assay (HPLC), related substances (HPLC), uniformity of dosage units (Ph.Eur.), dissolution (Ph.Eur.) and microbial limits (ICH harmonised method). Analytical methods have been described and non-compendial methods have been validated in accordance with ICH guidelines.

Batch analysis data of production-scale batches (four batches for the 18.5 mg strength, seven for the 37 mg strength and six for the 74 mg strength) have been provided confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Three production scale batches of each of the three strengths of the lurasidone film-coated tablets kept in the commercial packaging have been conducted under long term (up to 36 months, 25°C/60% RH) and accelerated (6 months, 40°C/75% RH) stability conditions according to ICH guidelines. Samples were tested for description, assay, organic impurities, dissolution, water content and microbial limits. No significant change has been observed in any of the parameters studied after accelerated and long term conditions and all batches complied with the specifications in all instances. The analytical procedures used were stability indicating.

One batch of each strength has been subjected to photostability testing according to ICH Q1B guideline. The tablets proved to be stable towards light exposure with the exception of the 80 mg tablet which demonstrated some discolouration to light.

Additionally, one batch of each strength was also subjected to stress conditions and to bulk storage stability studies. No significant change in any of the parameters tested was observed for samples subjected to heat and humidity and under bulk storage.

Based on the available stability data, the proposed shelf-life and no special storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and controls applied to lurasidone hydrochloride and the finished product has been presented in a satisfactory manner. The finished product is a standard dosage form manufactured by a standard manufacturing process. The results of the tests carried out indicate consistency and uniformity of important product quality characteristics, and these lead in turn to the conclusion that the product should have a satisfactory and uniform performance in the clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this medicinal product is considered to be acceptable when used in 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.

2.3. Non-clinical aspects

2.3.1. Introduction

The standard battery of the pharmacology and toxicology studies were completed and submitted.

All pivotal toxicity studies, including the safety pharmacology studies were performed in accordance with GLP principles, as declared by the applicant.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Dopaminergic effects

The ability of lurasidone to bind to dopamine receptor subtypes has been demonstrated in vitro in radio-ligand binding studies using receptors derived from rat striatum and human cultured cells.

Lurasidone demonstrated high affinity in vitro for the human D2L receptors with Ki values of 0.329 and 0.994 nmol/L in different cell preparations. The affinities for human D3 and human D4.4 receptors were lower, with Ki values of 15.7 and 29.7 nmol/L, respectively, and even lower for the rat D1-like receptor, with a Ki of 262 nmol/L. The two major human metabolites (ID-20129 and ID-20220) were without pharmacodynamic activity, while two other metabolites ID-14283 and ID-14326, showed affinities to dopaminergic receptors of similar magnitude as lurasidone.

Lurasidone was effective with ED50 values ranging between 2.3 and 6.3 mg/kg p.o. in rodent animal models for dopamine receptor-mediated behavioural changes. A similar effect was demonstrated by other atypical antipsychotic compounds tested (e.g. risperidone, olanzapine, ziprasidone). Metabolites ID-14283 and ID-14326 demonstrated similar dopamine mediating effects as lurasidone.

The effects of repeated oral dose administration of lurasidone on dopamine mediated behaviour and on dopamine receptor sensitivity have been examined in rats in comparison with haloperidol. The results indicate that some D2 receptor supersensitivity is produced by repeated treatment with lurasidone, but substantially less than that produced by haloperidol. No supersensitivity of D1 receptors was noted after treatment with lurasidone which was seen after repeated dosing with haloperidol.

Serotonergic effects

Lurasidone showed high affinity in vitro for the human 5-HT7 (Ki values of 0.495 and 2.10 nmol/L), human 5-HT2A (Ki values of 0.470 and 0.357 nmol/L) and human 5-HT1A receptors (Ki=6.38 nmol/L). Regarding 5-HT2C receptors, only results from pig tissues are available, and in this species the affinity was relatively low (Ki=415 nmol/L). The two major human metabolites had no affinity for 5-HT receptors whereas a number of minor metabolites demonstrated affinity in a similar range as lurasidone. Functional assays demonstrated that lurasidone, ID-14283 and ID-14326, are partial agonists at human 5-HT1A receptors (35S-GTPγS binding) and potent antagonists at the human 5-HT7 receptor (cyclic adenosine monophosphate [cAMP] assay). Metabolites ID-20239 & ID-20240 are the diastereomers of the active metabolite ID-14283 and have similar binding affinities to rat 5-HT2 and D2-like receptors. There is no data related to relevant human receptors; however the safety profile for metabolite ID-14283 has been reviewed in the 39- and 52-week toxicity studies in dogs and monkeys, respectively. Exposure to ID-14283 in the dog at the NOAEL (30 mg/kg/day) were in excess of 8 times that achieved in humans, in the monkey (NOAEL <2 mg/kg/day) this was 0.06 times in excess to that achieved in patients given 160 mg lurasidone.

In vivo, lurasidone dose-dependently inhibited behavioural changes mediated by serotonin 5-HT2 receptors in relevant rodent animal models, with ED50 values ranging from 2 to 6 mg/kg. Similar results were obtained for various reference drugs including compounds with other receptor profile than lurasidone. The three metabolites, ID-14283, ID-14326, and ID-11614, inhibited serotonin 5-HT2 receptor-mediated behaviours in rodents in vivo with a slightly higher potency than lurasidone. However, these metabolites are only present to a small extent and are not considered to markedly contribute to the overall effect of lurasidone.

Mood and cognition effects

Lurasidone was evaluated for its antidepressant- and anxiolytic-like effects through a series of behavioural experiments including the conditioned fear stress-induced freezing behaviour test, Vogel water lick conflict test, the conditioned defensive burying test, and the social interaction test. Lurasidone prolonged the social interaction time spent by pairs of naive rats under brightly illuminated conditions in the social interaction test. The effect was statistically significant for 1 and 3 mg/kg and was similar to that observed for diazepam. Lurasidone was also able to selectively suppress the burying behaviour against the shock probe, in a dose dependent manner, at doses at which the locomotor activity was not affected (up to 6 mg/kg).

The ability of lurasidone to affect learning and memory function was examined in the rat passive avoidance test. At oral doses up to 30 mg/kg it did not impair the learning or memory of male rats in a passive avoidance test. Lurasidone's ability to alleviate the memory impairment induced by the NMDA antagonist, MK-801, in the rat passive avoidance test was examined and the results compared with those of 3 reference drugs: risperidone, olanzapine, and quetiapine. Oral administration of lurasidone (3 mg/kg) at 1 hour before the training session markedly reversed the effect of MK-801 (0.05 mg/kg) on both parameters tested (step-through latency and the percent of animals showing the maximal step-through latency). In comparison, risperidone and quetiapine only partially reversed the effect of MK-801 on the percent of animals displaying the maximal step-through latency but not on step-through latencies and olanzapine failed to reverse the effect of MK-801 on either parameter. The effects of lurasidone on a muscarinic receptor antagonist, scopolamine hydrobromide (scopolamine) induced memory impairment of passive avoidance task in rats were similar. Lurasidone treatment was also able to reverse the memory deficits produced by subacute treatment of rats with the NMDA antagonist phencyclidine (PCP) and then tested on a novel object recognition task.

Secondary pharmacodynamic studies

Binding activity of lurasidone for noradrenergic receptor subtypes was evaluated in an in vitro binding assay. Lurasidone and its two active human metabolites showed a high affinity to the human α2C receptor and in contrast the two main human metabolites of lurasidone, ID-20219 and ID-20220, had negligible activity at this receptor.

Secondary pharmacology of lurasidone covered studies to measure its ability to bind to off-target receptors or channels including: 5-HT3, 5-HT4, noradrenaline β, β1, β2, adenosine A1, A2, benzodiazepine, cholecystokinin CCKA, CCKB, γ-aminobutyric acid (GABA)A, glutamate, α-amino-3-hydroxy-5-methyl-4-isoxazol-propionic acid (AMPA), kainate, NMDA, glycine, histamine H1, muscarine M1, M2, nicotine, opiate, sigma, L-type Ca2+ channel, N type Ca2+ channel, the A-type K+ channel, voltage gated K+ channel, the adenosine 5' triphosphate (ATP)-sensitive K+ channel, 5-HT uptake sites, and dopamine uptake sites. Lurasidone showed little or no affinity to these channels or receptors.

The potential of lurasidone to induce drug dependence was studied in rats and monkeys. Lurasidone appeared to be free of cross-physical dependence with barbital, and free of potential for physical

dependence formation. No reinforcing effect was noted with lurasidone, suggesting that this compound does not have the potential to induce psychic dependence.

Safety pharmacology programme

Safety pharmacological effects of lurasidone were investigated on cardiovascular, respiratory and CNS function, as well as on autonomic nervous, endocrine, renal, gastrointestinal and smooth muscle systems. In addition safety pharmacology of a number of metabolites of lurasidone was provided, including ID-14283, ID-14326, ID-11614, ID-15001, and ID-15002.

Cardiovascular System

A complete battery of cardiovascular safety studies was performed to assess the effects of lurasidone and its 2 active metabolites, ID-14283 and ID-14326. The assessment included in vitro hERG assays, ex vivo studies in guinea pig and rat tissues, as well as in vivo studies in rats, guinea pigs, cats, and dogs. Furthermore, as part of the routine toxicologic evaluation ECG was performed in the toxicity studies in dogs and Cynomolgus monkeys.

Lurasidone and the 2 active metabolites, ID-14326 and ID-14283 inhibited hERG currents at estimated IC50 values of 0.108, 0.676, and 0.821 µmol/L, respectively. A review of relative safety margins, comparing potential clinical exposure (Cmax) of free/unbound lurasidone, ID-14326 and ID-14283 to IC50 values revealed that safety margins were >100-fold for unbound molecule relative to the Cmax at a clinical dose of 160 mg administered for 6 days.

In the safety pharmacology study in female dogs QTc prolongation was seen at 300 mg/kg 4, 6, and 24 hours post-dose, with the NOEL at 100 mg/kg. At this dose, Cmax (1903 ng/mL) and AUC exposure (17000 ng*hr/mL) margins were 8.2- and 19-fold greater than human exposures at 160 mg lurasidone, respectively.

ECG changes were also observed in the toxicology studies in dogs and Cynomolgus monkeys. In a non-GLP 4-week repeat-dose toxicity study QT/QTc prolongation occurred at the end of dosing in 1 male dog dosed with 300 mg/kg/day and was associated with the highest Cmax (2.615 µg/mL) and AUC (26.15 µg*hr/mL) values in this group. Examination of data from individual animals from the GLP 39-week study revealed that the QT prolongation occurred (Weeks 13-39) in male dogs in which Cmax values exceeded 3.357 µg/mL, and AUC values exceeded 32.6 µg.hr/mL. There were no effects on the QT interval in female dogs in this study despite Cmax and AUC values up to 3.908 µg/mL and 42.3 µg*hr/mL. Using the conservative threshold exposure values [Cmax (2.383 µg/mL); AUC (26.15 µg*hr/mL)], margins relative to patients receiving 160 mg lurasidone were at least 10.2- and 29.1-fold greater than average human Cmax and AUC values, respectively.

Furthermore transient increase in heart rate was observed in a monkey cardiotoxicity study (single dose 250 mg/kg), and a lack of night-time reduction in heart rate was observed in a dog cardiotoxicity study (2-week study, 50 mg/kg/day).

Respiratory System

There were no effects on the respiratory system (respiration rate, tidal volume, and minute volume) in conscious rats (up to 1000 mg/kg, oral) for lurasidone or its metabolites. Similarly, no effects on blood gas parameters (PO2, PCO2, and pH) in anaesthetised rats (0.1, 0.3, and 1 mg/kg, IV) were seen and there were no changes in the respiration rate of anaesthetised cats, or in anaesthetised and vagotomised cats (up to 100 µg/kg, IV).

Central Nervous System

Lurasidone, when administered IV at high doses (up to 1 mg/kg), slowed spontaneous electroencephalogram (EEG) activity in rabbits, and inhibited the emetic response in APO-treated dogs following oral administration. No other potent effects on the CNS were seen (i.e., anti-acetylcholine action, anti-hypoxic action, effects on cerebral blood flow, convulsion facilitating action, and anti-adrenergic action).

Autonomic Nervous System

Lurasidone and some of its metabolites had no or only marginal effect on the autonomic nervous system.

Endocrine System

Lurasidone increased serum prolactin levels at doses 1 mg/kg or more in rats, increased adrenocorticotropic hormone (ACTH) at a dose of 10 mg/kg, and corticosterone levels at doses of ≥3 mg/kg. These effects were equal to or less than those observed for an oral dose of haloperidol at 3 mg/kg.

Urinary and Gastrointestinal System

In the rat, lurasidone increased urinary volume but had no effect on the urinary electrolyte excretion at a single oral dose of 100 mg/kg. No effects on the urinary volume or the amount of electrolyte excretion were observed in the rat at a single oral dose of 30 mg/kg.

Lurasidone had no effect on the digestive system in mice and rats at single oral doses of up to 100 mg/kg.

Smooth Muscle

Lurasidone had a weak inhibitory effect on histamine-induced contractile response at 3 µg/mL, and inhibited noradrenaline-induced contraction at 0.03 µg/mL.

Pharmacodynamic drug interactions

The potential interactions between lurasidone and haloperidol, diazepam, biperiden, imipramine, and carbamazepine were evaluated in rats and mice. Lurasidone and haloperidol potentiated the antidopaminergic activity of each other; however, lurasidone did not affect the cataleptogenic action of haloperidol. Lurasidone potentiated anxiolytic actions of diazepam but did not affect its muscle-relaxing actions. Lurasidone produced no obvious effects on the actions of other drugs.

The antidopaminergic action of lurasidone was not affected by diazepam, biperiden, imipramine, or carbamazepine; these drugs also failed to affect the antiserotonergic actions of lurasidone.

2.3.3. Pharmacokinetics

ADME studies to characterise the pharmacokinetic properties of lurasidone were performed in mice, rats, rabbits, dogs, and monkeys.

Lurasidone is relatively rapidly absorbed with peak systemic exposure occurring within 5.3 hours of administration. The absolute bioavailability is low, <12%, in all species examined. Lurasidone absorption was higher in male Cynomolgus monkeys fed prior to drug administration, with time to peak exposure of 4 hours (vs. 5.3 hours), and the peak and total systemic exposure approximately 3-fold higher. In rats and dogs, lurasidone doses above 10 mg/kg resulted in peak and total systemic exposure changes that were less than dose-proportional. Clearance ranged from 17 to 61 mL/min/kg and volume of distribution (Vdss) ranged from 2.4 to 20 L/kg. T1/2 was also variable with mean values ranging from 1.6 (monkey) to 27 hours (dog).

Tissue distribution of lurasidone was studied after single- and repeated-dose oral administration in rats. In addition, distribution studies were performed in pigmented and aged rats. Lurasidone distributed into most tissues including the brain; it also crossed the placenta and distributed into foetal tissues. Lurasidone bound to and was retained by pigmented tissues including the eye. Serum protein binding of lurasidone reached >99 %.

Lurasidone is extensively metabolised with oxidative N-dealkylation, hydroxylation of the norbornane ring or cyclohexane ring, S-oxidation, reductive cleavage of the isothiazole ring followed by S-methylation, and a combination of 2 or more of these pathways. Lurasidone is broken down into two non-major active metabolites (ID-14283 and ID-14326) and two major non-active metabolites, ID-20219 and ID-20220, present systemically at levels >10%. ID-20219 and ID-20220 are also present systemically in humans at concentrations of >10% of the total radioactivity dosed; therefore can be defined to be the 2 'major' human metabolites of lurasidone. Protein binding studies showed that these metabolites are highly bound to serum proteins (ID-14283 and ID-14326 bind ≥98.8% in human serum and ≥99.1% in dog serum).

The route, extent, and metabolic profile of total radioactivity excreted in the form of the 14C-labeled lurasidone or its metabolites in urine, faeces, and bile has been examined in several animal studies.

Radioactivity derived from labelled lurasidone was excreted after oral dosing, mostly within the first 24 hours in mouse and rat and within the first 48 hours in rabbit, dog, and monkey. Following administration of [14C]lurasidone, the majority of the radioactivity (approximately 80% of dose) was excreted in faeces as the parent compound. As demonstrated in bile-duct cannulated animals, biliary excretion was a major excretion route of absorbed lurasidone. Based on the radioactivity excreted in urine and bile after oral administration, approximately 14%-48% of the orally administered dose was absorbed. Parent compound was detected only at trace levels in bile and urine, indicating that lurasidone, once absorbed, is subject to extensive metabolism. Many products of the major metabolic pathways were excreted into bile and/or urine. Major metabolites observed in the urine of mice and rats were ID-15002 and ID-20220 and those of dogs and monkeys were ID-15001 and ID-20220. In bile, the metabolite profiles in rats, dogs, and monkeys differed. In rat, dioxy-M21 isomers, ID-14283, and M22 were the main metabolites; in dogs, dioxy-ID-14324/dioxy-ID-14323, ID-20219, and the glucuronide of ID 20219; in monkey, dioxy-ID-14324 isomers and di-, tri- and tetra-oxidised derivatives.

Lurasidone was excreted into milk. Following oral administration of [isothiazolyl-3-14C]lurasidone to lactating rats, 14C was found in milk during the 24 hours after dosing at concentrations significantly greater than those in serum (23.1% at 0.5 h, declining to 9.2% at 24h). The greatest mean radioactivity concentration in serum was 0.448 µg equivalents/mL measured at 1 hour after dosing. During the first eight hours after administration, a large proportion of the total radioactivity collected in the milk was the parent compound, lurasidone (71-78%).

Pharmacokinetic drug-drug interactions were explored for lurasidone. Due to the high level of protein binding observed with lurasidone, the potential for it to displace other co-administered drugs such as biperiden, flunitrazepam, haloperidol, or diazepam or vice versa was determined in vitro, although no changes to protein binding was seen. Metabolism of lurasidone was markedly reduced by ketoconazole, a known CYP3A4 inhibitor.

2.3.4. Toxicology

Single dose toxicity

The single dose toxicity studies conducted with lurasidone are summarised in the table below.

Table 1. Summary of the single dose toxicity studies with lurasidone.

Study ID	Species/ Sex/Number/ Group	Dose (mg/kg)/Route (vehicle)	Observed Maximun Non-Lethal Dose/ Approximate Letal Dose (mg/kg)	Major findings*
Study 2737	Rat (Sprague-Dawley) 5 animals/ sex/group	0, 1000 and 2000/ Oral gavage (0.5% methylcellulose)	2000/ >2000	No mortality Ptosis and decreased spontaneous activity observed at both dose levels. Ataxic gait observed in females at 2000 mg/kg.
	20/female/ group	0 and 2000 Oral gavage (0.5% methylcellulose)		Decreased body weight gain and/or weight loss due to the treatment were observed. A nodule was observed in the uterine horn of 1 female at 2000 mg/kg.
Study 2756	Monkey (Cynomolgus) 1 animals/ sex/group	0, 10, 50, 250, 1000 and 2000/ Oral gavage (0.5% methylcellulose)	2000/ >2000	No mortality. Decreased spontaneous activity in all treated groups. Tremors and decrease of spontaneous activity accompanied by extrapyramidal symptoms such as persistent abnormal posture and slow movement noted at 50 mg/kg or higher. Miosis in a male at 2000 mg/kg. Vomiting was observed in female at 2000 mg/kg. Food consumption was reduced at 250 mg/kg or higher. At the terminal necropsy, the liver of one male animal from 2000 mg/kg was found to contain brown foci by macroscopy and slight focal hepatocyte atrophy upon histopathologic evaluation.

* Major adverse findings are included in the table. All the effects are statistically significant, unless otherwise stated.

In rats orally administered up to 2000 mg/kg lurasidone, ptosis and reduced spontaneous activity, body weight gain and/or body weight loss were observed at ≥1000 mg/kg. The uterine horn nodule detected in a single female dosed at 2000 mg/kg was not considered to be treatment-related.

In monkeys orally administered up to 2000 mg/kg lurasidone, treatment-related findings included reduced spontaneous activity in all treated groups. Other effects observed included tremors, persistent abnormal posture and slow movement at ≥50 mg/kg, decreased food consumption at ≥250 mg/kg, closed eyelids at 250 mg/kg; miosis, closed eyelids, vomiting, increased ALT level (female), brown foci in the liver and slight focal hepatocyte atrophy (male) at 2000 mg/kg.

Repeat dose toxicity

Repeat-dose oral toxicity studies were performed in mice (for up to 13 weeks), rats (for up to 26 weeks), dogs (for up to 39 weeks) and monkeys (for up to 52 weeks). They included toxicokinetic analysis and were conducted in full compliance with GLP regulations.

Table below shows major findings observed in pivotal repeat-dose toxicology studies.

Table 2. Summary of repeat-dose toxicity studies with lurasidone.

Study ID/ Duration/ Route	Species/ Sex/ Number/ Group	Dose (mg/kg/day)	Major findings*
6645-136 (GLP) 13-week adminis-tration Oral gavage	Mouse (Crl:CD-1(ICR)) 10 animals/ sex/group+ 28/sex/ group in 4 TK groups+ 10/sex/ group in 5 groups for prolactin analysis	0, 25, 125, 250, 500	Mortality**:** No article-related mortalities. One male in the 25 mg/kg/day group and 1 female in the 500 mg/kg/day group were sacrificed on Days 14 and 89, respectively. Clinical signs: Hypoactivity at all doses. Increased body weights and body weight gains in females at all doses. Decreased body weight gains in males at 500 mg/kg/day. Haematology & clinical chemistry: Increase prolactin concentrations at all doses (markedly higher and not dose-dependent). Necropsy and organ weight: Decrease in absolute and relative uterus weights in females at all doses. Histopathology: Increase in uterus atrophy. Several histopathological not dose-dependent changes in the mammary glands. Lung tissue alveolar macrophage infiltrates in males and females ⩾ 125mg/kg/day. **NOAEL**: <25 mg/kg/day.
2813 and (GLP) **2927** 3-months+ 6 week recovery Oral gavage	Rat (Crl:CD (SD) 12 animals/ sex/group Recovery: 0, 30, 150 mg/kg/day in males 0, 300, 1000 mg/kg/day in females (6/sex/group) TK 5 animals/sex/ group	M:0, 3, 30, 150 F: 0, 3, 30, 300, 1000 F/M: 0, 0.03, 0.1, 0.3, 3	Mortality**:** No mortality. Clinical signs**:** Ptosis, decrease of spontaneous activity. lacrimation ≥30 mg/kg/day. Decreased body weight and food consumption in males (HD), females ≥ 300 mg/kg/day. Haematology & clinical chemistry: Change in prolactin serum concentration in both sexes ≥3mg/kg/day. Necropsy and organ weight: Increase in relative weights of adrenal and testis in males (150 mg/kg/day), and of pituitary in males (≥30 mg/kg/day), liver (≥300 mg/kg/day), heart, kidney and lung (1000 mg/kg/day) in females. Histopathology: Increased secretion of mammary gland (≥3 mg/kg/day). Mucification of vaginal epithelium (≥3 mg/kg/day). Increase in number of females showing dioestrus stage ≥3mg/kg/day. Miosis in females ≥30 mg/kg/day. With the exception of bone marrow changes, all other changes in females were partially or completely recovered. **NOAEL**:0.1 mg/kg/day females; 0.3 mg/kg/day males.
3259 (GLP) 6-month adminis-tration+ 3 months recovery Oral gavage	Rat (Crl:CD (SD) 12 animals/ sex/group Recovery: 6/sex/group M:0, 100 mg/kg/day F:0, 1,10,100 mg/kg/day	0, 0.03, 1, 10, 100	Mortality**:** No mortality. Clinical signs: Ptosis, decrease of spontaneous activity ≥10 mg/kg/day. Decreased body weight and food consumption at ≥ 100 mg/kg/day. Increased incidence of oestrus cycle disorder ≥ 1.0 mg/kg/day. Haematology & clinical chemistry: Increase in prolactin serum levels (F:≥0.03 mg/kg/day; M:≥1 mg/kg/day). Necropsy and organ weight: Increase in relative and absolute ovary weights ≥ 1.0 mg/kga/day. Histopathology: Increased secretion of mammary gland at ≥1 mg/kg/day. Reduced total bone mineral density (only studied in females) ≥1 mg/kg/day. Thickened zona glomerulosa adrenal gland females ≥ 1 mg. Increased fatty infiltration bone marrow females ≥ 1 mg. Miosis in females ≥10 mg/kg/day. With the exception of the effects on bone and changes in ovary weights all other effects were partially or completely recovered. **NOAEL**: 0.03 mg/kg/day.
3879 (GLP) 39-week adminis-tration Oral gavage	Dog (Beagle) 4 animals/ sex/group+ 3 animals/ sex/group for TK	0, 30, 100, 200	Mortality**:** No mortality. Clinical signs: Decrease of spontaneous activity, tremors, somnolence and dry muzzle ≥30 mg/kg/day. Decreased body weight and food consumption in males at ≥ 100 mg/kg/day Increased body weight in females (HD). Prolonged QT interval ≥100 mg/kg/day (1 male in MD and 2 males in HD). Haematology & clinical chemistry: Changes on total cholesterol and phospholipids ≥30 mg/kg/day. Increased serum prolactin levels ≥30 mg/kg/day. Necropsy and organ weight: Increase in thickened mammary gland from week 2 ≥ 30 mg/kg/day. Decrease in relative prostate weights ≥30 mg/kg/day. Small prostate, ovary, uterus ≥30 mg/kg/day. Lung: yellow to white foci in males ≥100 mg/kg/day. Histopathology: Females of ≥30 mg/kg/day exhibited uterine atrophy and

Study ID/ Duration/ Route	Species/ Sex/ Number/ Group	Dose (mg/kg/day)	Major findings*
			decreased secondary ovarian follicles. Testes exhibited exfoliated cells or giant cells ≥100 mg/kg/day. Prostate gland atrophy ≥ 30 mg/kg. Hypospermia in the epididymis ≥100 mg/kg/day. Thymus atrophy or involution in all male treated groups, in females at ⩾100 mg/kg/day. Decrease in trabecular bone males ≥100 mg/kg/day. Miosis ≥30 mg/kg/day. **NOAEL**:<30 mg/kg/day.
SUP22 (GLP) 13-week adminis-tration+ 6-week recovery Oral intubation	Monkey (Cynomol-gus) 3 animals/ sex/group+ 2 animals/ sex control+HD for recovery	0, 2, 10, 50	Mortality**:** One LD monkey was sacrificed for reason unrelated to lurasidone treatment. Clinical signs: Subdued behaviour (≥MD). Increased tremors and late-onset salivation (HD). Decreased body weight and food consumption (HD). Haematology & clinical chemistry: Serum prolactin was increased in all treated group. 24 h after dosing the serum prolactin levels in the treated groups were comparable to the controls. Necropsy and organ weight: No marked changes. Histopathology: No marked changes. **NOAEL**: 2 mg/kg/day.
SMO550 (GLP) 52-week adminis-tration Oral intubation	Monkey (Cynomol-gus) 4 animals/ sex/group	0, 2, 10, 50	Mortality**:** No mortality. Clinical signs: Subdued behaviour and fixed posture were observed at ≥ 2 mg/kg/day. Increased tremors at ⩾ 10 mg/kg/day, late-onset salivation (HD). Decreased food consumption (HD). Haematology & clinical chemistry: No marked changes. Increased serum prolactin levels ≥2 mg/kg/day. Necropsy and organ weight: No marked changes. Histopathology: Minimal enlarged pale-stained cells in pars distalis of pituitary (3 of 4 animals in both sexes of the HD). No ophthalmoscopy findings. **NOAEL**: <2 mg/kg/day.

C=control; LD= low dose; MD= middle dose; HD= high dose; RBC (red blood cells) HGB haemoglobin
* Major adverse findings are included in the table. All the effects are statistically significant, unless otherwise stated

The main toxic effects observed in the repeated dose studies involved the CNS and the endocrine systems. In all tested species, clinical signs such as decreased spontaneous activity and tremors were observed. In addition, somnolence was observed in dogs. For mice and dogs no no-effect-level could be determined for these effects. In monkey, effects such as decreased spontaneous activity, tremors and vomiting were observed at low doses (2 mg/kg/day at 0.03 fold of clinical exposure). Furthermore, decreased body weights were observed in all studies.

Levels of serum prolactin were increased in all species and at all tested doses. Changes on endocrine organ weights were observed in all tested animals. Prostatic changes were seen only in dogs, vaginal changes were observed only in rodents, whereas pituitary changes were seen in rodents and monkeys. Bone marrow and reduced bone density were seen in rats, but were not observed in mice. There was also a decrease in amount of trabecular bone in male dogs. Furthermore, in dogs effects on the thymus were observed after 4- and 39-week treatment. The majority of these effects were considered to be related to the increased prolactin levels in animals treated with lurasidone. All effects observed in the repeat-dose toxicity studies were reversible except for the histopathologic changes in the femur and changes in the bone density in rats.

QT prolongation was observed in the 4- and 39-week dog toxicology studies; for further discussion refer to the section on Safety Pharmacology.

Genotoxicity

Submitted genotoxicity studies are summarised in the table below.

Table 3. Summary of genotoxicity studies in lurasidone.

Type of test / Report No.	Test system	Test compound / Concentrations / Dosages / Metabolising system	RESULT
In vitro Gene mutations in bacteria GLP	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, (E. coli: WP2uvrA)	**Lurasidone** 15-5000 µg/plate +/- S-9 mix Adequate *positive and negative controls* included Vehicle: DMSO	**Negative**
In vitro Chromosomal aberration GLP	Chinese hamster lung cells (CHL/IU)	**Lurasidone** 50-400 µg/mL (direct method) 625-5000 µg/mL (metabolic activation method, +/- S9 mix) +/- S-9 mix Adequate *positive and negative controls* included Vehicle: 1% carboxymethylcellulose sodium	**Negative**
In vivo Bone marrow micronucleus assay GLP	Mouse/CD-1 (ICR) 5/group/harvest time Number of cell analysed/animal: 1000 polychromatic erythrocytes for toxicity	**Lurasidone** Single oral gavage dose: 0, 500, 1000, 2000 mg/kg Bone marrow samples taken 24, 48 Adequate *positive control* (cyclophosphamide) included. *Vehicle:* 0.5% methylcellulose	Mortality**:** No mortality. Clinical signs: Toxic signs of ptosis and decreased spontaneous activities. **Negative**

A complete battery of in vitro and in vivo studies has been conducted and shows that lurasidone is not genotoxic.

The mutagenic potential of one metabolite, ID-11614, and the impurity ID-15398 were evaluated in vitro in Ames test. The conclusion from the studies was that ID-11614 and ID-15398 were not mutagenic under the test conditions.

Carcinogenicity

Long-term GLP carcinogenicity studies were conducted in mice and rats administered lurasidone by oral gavage at doses of 0, 30, 100, 300, and 1200/650 mg/kg/day and 0, 3, 12, and 50/36 mg/kg/day, respectively. Generally, the survival was low especially in female mice at the middle and highest dose (22%).

In mice, the oral administration of lurasidone for 24 months caused increased serum prolactin at all dose levels administered (up to 1200/650 mg/kg/day), and increased the incidence of masses in the pituitary and the mammary glands of females. Vaginal mucification and vaginal, uterine, and cervical atrophy were also observed at these dose levels. An increase in the incidence of tumours in the pars distalis of the pituitary and in the mammary gland of females dosed at ≥30 mg/kg/day was also observed (x 1.3 of the clinical dose).

In rats, the administration of lurasidone for 24 months at doses of 3, 12, and 50/36 mg/kg/day caused an increased incidence of mammary carcinomas in females dosed at ≥12 mg/kg/day (x 2.0 of clinical

dose), and increased milk secretion in males at all dose levels. Increases in the absence of corpora lutea in the ovary and in the cornification of the vagina were noted at all doses in females. The various lurasidone-related responses observed were considered to be related to the antagonism of dopamine type 2 receptors by lurasidone and typical effects of this class of drugs.

Reproduction Toxicity

A summary on the pivotal reproductive toxicity studies submitted, including relevant findings, are summarised in the table below.

Table 4. Summary of reproductive and developmental toxicity studies with lurasidone.

Study type/ Study ID / GLP	Species; Number Female/ group	Route & dose (mg/kg/ day)	Dosing period	Major findings* NOAEL (mg/kg/day)
Fertility and early embryonic development **GLP**	**Rat** (Crl:CD (SD)) 22 males/ group	Oral gavage 0, 6, 30, 150	64 days pre-mating, through mating, until	No mortality No relevant findings on fertility **NOAEL:** >150 mg/kg/day (fertility)
Fertility and early embryonic development **GLP**	Rat (Crl:CD (SD)) 22 females/ group+ 11 females/ group	Oral gavage 0, 0.1, 1.5, 15, 150 Recovery 0, 150	15 days pre-mating, during mating, through Day 7 of gestation. Animals in recovery group were dosed for 28 days then put on 14-Day withdraw prior to mating.	No mortality Decrease body weight ≥150 mg/kg/day (up to 12.5% compared to the control). Effects on fertility Decrease number of preimplantation loss (%) in the recovery 150 mg/kg/day group. Prolonged oestrous cycle ≥1.5 mg/kg/day. Lower fertility index (%)(not significant) 60% and 78% in the 150 mg/kg/day of main and recovery groups, respectively, compared to 82 and 90 % in the controls. Decrease in number of live foetuses at 150 mg/kg/day. **Control** | **150 mg/kg/day** ***No. corpora lutea*** Without R: 18.5±3.85 | 16.0±1.73 * R: 20.2±3.01 | 18.4±3.59 ***No. live foetuses*** Without R: 14.9±2.48 | 12.7±2.06 * R: 13.8±1.87 | 15.6±1.82* R=recovery; * Significantly different from the control **NOAEL:** >15 mg/kg/day (fertility)
Teratology **GLP**	Rat (Crl:CD (SD)) 20/group	Oral gavage 0, 3, 10, 25	Day 6 through Day 17 of gestation Day of Mating: Day 0 of gestation Day of C-Section: Day 20 of gestation	Dams Decreased body weight gain at ⩾3 mg/kg/day and food consumption at ⩾10 mg/kg/day. Foetuses There were no treatment-related changes in external, skeletal and visceral observations. **NOAEL** General toxicological effects (F0 Females) 25 mg/kg/day.

Study type / Study ID / GLP	Species; Number Female / group	Route & dose (mg/kg/day)	Dosing period	Major findings* NOAEL (mg/kg/day)
				Reproductive effects 25 mg/kg/day. Developmental effects (F1 Litters) 25 mg/kg/day.
Teratology **GLP**	**Rabbit** (New Zealand White) 13-15 animals/group	Oral gavage 0, 2, 10, 50	Days 6 through 18 of gestation Day of Mating: Day of Artificial Insemination: Day 0 of gestation Day of Caesarean section: Day 28 of gestation	Dams No deaths, abortions or premature deliveries occurred. Decreased body weight gain ≥2 mg/kg/day. Foetuses There were no treatment-related changes in external, skeletal and visceral observations. **NOAEL** General toxicological effects (F0 Females) < 2 mg/kg/day. Reproductive effects at 50 mg/kg/day Developmental effects (F1 Litters) at 50 mg/kg/day.
Peri- & post-natal development **GLP**	**Rat** (Crl:CD (SD)) 22 pregnant animals/group	Oral gavage 0, 0.4, 2, 10	Day 6 of gestation to Day 21 of lactation Day of Mating: Day 0 of gestation	Dams No mortalities or adverse clinical signs. Offspring No treatment-related effects were found. **NOAEL** General toxicological effects (F0 Females), Reproductive effects and Developmental effects (F1 Litters) >10 mg/kg/day

* Major adverse findings are included in the table. All the effects are statistically significant, unless otherwise stated

In the fertility and early embryonic development rat study, lurasidone administration decreased the number of implantations at a dose of 150 mg/kg/day and lowered fertility index (60% or 78%) at the same dose. The maternal effects at 150 mg/kg/day dose level included decreased body weight (up to 12% compared to the control), prolonged oestrous cycle and slight decrease in number of corpora lutea. The effects on maternal body weight, food consumption and reproductive performance reversed in the 2-week recovery period prior to mating. No effects on fertility were observed in male rats.

Neither lethal nor teratogenic effects on embryos or foetuses were observed at tested doses in teratology studies.

In a pre and postnatal development study, pregnant rats (22/group) orally administered 4, 2, and 10 mg/kg/day from Day 6 of gestation to Day 21 of lactation, no deaths or adverse clinical signs related to lurasidone administration were observed in any group. Maternal body weight gain was reduced in groups dosed at 10 mg/kg/day during the gestation period. No treatment-related effects were observed in the offspring.

Toxicokinetic data

The results of the toxicokinetic evaluation of lurasidone and its metabolites ID 20219, ID 20220 (major human metabolites) in the oral repeated dose toxicity studies conducted in the mouse, rat, dog and monkey are presented in the table below.

Table 5. Overview of toxicokinetic data for lurasidone.

Study Title / NOAEL	Dose (mg/	Male		Human*	Female		Human
		Cmax	AUC(0-24)		Cmax	AUC(0-24)	

(mg/kg/day)		kg/day)	(ng/ml)	(ng hr/ml)	Cmax/ AUC	(ng/ml)	(ng hr/ml)	Cmax/ AUC *
Mouse 13-w p.o.	Week 13	25	88.1	337	**0.38/0.38**	148	540	**0.64/0.60**
	Day 1	500	812	5912	3.5/6.6	947	6402	4.1/7.1
<25	Week 13	500	859	7756	3.7/8.6	1112	15560	4.8/17
Rat 3-month p.o.	Week 13	0.03	0.07	NC	**0.0003/-**	0.16	NC	**0.00068/-**
		3	22.4	145	**0.09/0.16**	32.6	159	**0.14/0.18**
0.3 mg/kg/day in males	Week 13	150	465	6610	2.0/7.3	NA	NA	-
0.1 mg/kg/day in females	Week 13	300	NA	NA	-	1290	17900	5.5/20
Dog 39-week p.o.	W39	30	1150	10100	4.9/11	1150	8300	4.9/9.2
	Week 4	200	2680	32100	11/36	1990	15600	8.5/17
<30	W 39	200	5860	67000	25/75	1770	16700	7.6/19
Monkey 52-week p.o.	Week 52	2	5.83	23.8	**0.02/0.03**	2.77	13.7	**0.01/0.02**
	Day 1	50	43.1	504	**0.18/0.56**	26.5	283	**0.11/0.3**
2 mg/kg/day	Week 52	50	85.8	626	**0.37/0.70**	89.7	558	**0.38/0.62**

NA= not applicable; NC= not calculated;
* The steady state Cmax and AUC(0-t) used in the margin calculations were 233 ng/ml and 899 ng h/ml, respectively. The values were from the Study D1050160 performed in subjects with schizophrenia following 160 mg daily dosing.

In the toxicity studies in mice, rats, dogs and monkeys, systemic exposure to lurasidone was achieved in all studies. Lurasidone exposures (Cmax and AUC) generally increased with dose. The safety margins were generally low and ranged from 0.0003 to 11.35.

In 2-week toxicokinetic studies in mice, rats and dogs orally administered up to 650 mg/kg/day lurasidone, systemic exposure to lurasidone and ID-20219 but not ID-20220, generally increased with dose. In the 39- and 52-week toxicity studies in dogs and monkeys, respectively, orally administered up to 200 mg/kg/day, toxicokinetic analysis showed that animals were also exposed to the active metabolites ID-14283 and ID-14326. In the dog, the Cmax and AUC for all analytes increased dose-dependently except for ID-14326 in females. The NOAEL in dogs was considered to be <30 mg/kg/day. At week 39, the Cmax and AUC values for ID 14283 at the 30 mg/kg/day dose were >8 and >16 times, respectively, that achieved in patients administered the MRHD of lurasidone at 160 mg. At week 39, the Cmax values for ID 14326 at the 30 mg/kg/day dose were >75 and >104 times that achieved in patients administered the MRHD of lurasidone at 160 mg. In monkeys ID-14283 increased with increasing lurasidone dose. In the 52-week study, the NOAEL was considered to be <2 mg/kg/day. At week 52, the Cmax values for ID 14283 at the 2 mg/kg/day dose were 4.15 and 2.57 ng/mL in males and females, respectively. These exposures are 0.09 and 0.06 times that achieved in patients administered the MRHD of 160 mg lurasidone.

Local Tolerance

Lurasidone caused allergic reactions after subcutaneous administration in guinea pigs. However, no antigenicity in animals was observed after oral administration.

Other toxicity studies

The potential phototoxicity of lurasidone was studied after a single oral administration of vehicle, lurasidone (100, 300, and 1000 mg/kg), or positive control (8-methoxypsoralen, 10 mg/kg) to Sprague-Dawley rats (5 males/group; 5 week of age). An additional group receiving 1000 mg/kg lurasidone served as the non-irradiated control group. All but the non-irradiated control group were irradiated with ultraviolet radiation at a dose of 10 J/cm2. No remarkable skin reaction or increase in ear thickness observed in lurasidone-treated or vehicle control groups.

2.3.5. Ecotoxicity / environmental risk assessment

On the basis of a maximum recommended daily dose of 148 mg per patient, a market penetration of 1% and the available set of data from Phase II, Tier A and Tier B testing, no relevant environmental concerns are apparent from the use of lurasidone provided the usual recommendations for disposal of unused drug are followed. Suitable wording is included in the product information.

Table 6. Summary of main study results.

Substance (INN / Invented Name):			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD117	5.6	Potential PBT N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	5.6	B
	BCF	2798-2585	B
Persistence	DT50 or ready biodegradability	191 days	P
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.8	µg/L	> 0.01 threshold Y
Other concerns (e.g. chemical class)			N
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	K_d = 2400 ml/g (two different sludge) K_d = 800-7900 ml/g (3 different soil) Not dependent on the OC content	
Ready Biodegradability Test	OECD 301 B	Lurasidone is not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ < 1 day $DT_{50, whole\ system}$: 191 days (r) and 5.7 days (p) No degradation products	

		were observed above 10% of the applied radioactivity.			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	220	µg/L	*(Pseudokirchneriella subcapitata)*
Daphnia sp. Reproduction Test	OECD 211	NOEC	26	µg/L	*(Daphnia magna)*
Fish, Early Life Stage Toxicity Test/*(Brachydaniorerio)*	OECD 210	NOEC	44	µg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	EC50	>1000	mg/L	

In conclusion, lurasidone is not a PBT substance and is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential.

A concern over the dose selection as well as the low systemic exposure in the reproductive toxicity studies and their validity for assessment of risk to humans was expressed by the CHMP. The applicant has compared the proposed NOAEL to the MRHD (maximum recommended human dose) based on body surface area without showing the detected systemic levels of the substance in the animals. This comparison was not considered to be completely relevant. Furthermore, dose range finding (DRF) studies were performed to determine the appropriate dose for the pivotal studies. However, although no teratogenic effects and very slight maternal toxicity (only changes in body weight gain or food consumption) were observed at 150 mg/kg/day and 200 mg/kg/day in rats and rabbits, respectively, the chosen doses for the pivotal studies were far lower than in the DRF studies (around x 6 and x 4 in rat and rabbit, respectively). In addition, according to the toxicokinetic data from the rat 2-week study (non-pregnant), the AUC in females was determined to be around 1000 ng hr/ml after 10 mg/kg/day of lurasidone, which is at the same level as the exposure after clinical dose. No AUC values were submitted for rabbits. The applicant was requested to present relevant information on the systemic exposure of pregnant rats and rabbits after luradosine administration and to discuss the validity of the teratogenicity and peri- and postnatal developmental studies in relation to the systemic exposure and the clinical dose. The applicant provided an extensive explanation concerning the rationale for dose selection in the pivotal embryo-foetal and peri- and post natal studies. In conclusion, although the CHMP agreed that the reproductive toxicity studies did not indicate any teratogenic effects of lurasidone at an exposure identical or below the MRHD, the committee felt that the teratogenic potential has not been fully evaluated by the studies provided, in particular the rabbit study, due to the uncertainties regarding exposure to the parent compound. Accordingly, the CHMP requested the MAH to address these concerns in the product information. Consequently, the information on margin between the animal NOAELs and the MRHD is described in the SmPC sections 4.6 and 5.3. The mentioned sections (4.6, with reference to 5.3) also state the limitations of the reproductive toxicity studies with respect to effects on pregnancy, embryonal/foetal development, parturition and postnatal development.

A number of findings of QT/QTc prolongation were observed in the non-clinical studies conducted in the dog and to some extent in the monkey. At the request of the CHMP the applicant has provided a summary and discussion of all available data from both species. The committee acknowledged that exposure data from monkeys was limited and the available data provided for low or no margins for safety to the human clinical dose. Given that the effects seen in the cardiac toxicity studies revealed limited or unknown toxicological significance the CHMP agreed that the conclusions on the potential for

lurasidone to cause QT/QTc prolongation should be based on the available clinical data (see Discussion on clinical safety, section 2.6.1)

Dedicated cardiac toxicity studies in the dog and monkey were performed and two findings relating to an increase in heart rate in the monkey and a lack of nocturnal reduction in heart rate in a dog were identified. A further discussion of the toxicological significance of these findings has been provided by the applicant. The transient increase in heart rate observed in monkeys was seen in doses exceeding 250 mg/kg/day, and no further changes in cardiac parameters were observed in these animals. On the other hand, clinical findings showed slight changes in heart rate following dosing with lurasidone at 120 mg and 600 mg, although these changes were inconsistent. The applicant's argument that the finding in monkeys may have been related to D2/D3 receptor binding by lurasidone in the monkey brain may seem plausible. The CHMP agreed that the change in nocturnal heart rate seen in the dog cardiac study may have been due to the variability in animals, as only one animal was affected and such change was not observed in the other two treated animals. The lurasidone effect on the QT interval is reflected in the risk management plan (RMP) and will be monitored as a part of the requested post authorisation safety study (PASS).

Major findings in repeat-dose toxicity studies of lurasidone were centrally-mediated endocrine changes resulting from serum prolactin elevations in rats, dogs and monkeys. High serum prolactin levels in long-term repeat-dose studies in female rats were associated with effects on bones, adrenal glands, and reproductive tissues. In a long-term dog repeat-dose study, high serum prolactin levels were associated with effects on male and female reproductive tissues. Furthermore, the previously held assumption that prolactin-associated tumours in rodents are not relevant to humans has recently been challenged in the scientific literature (e.g. Harvey PW, J Appl Toxicol, 2012, 32:1-9). Therefore the applicant was asked to provide a thorough discussion regarding the neoplastic findings of the rat and mouse carcinogenicity studies and their potential relevance to humans. In the response, the applicant pointed out that clinical and epidemiologic studies conducted to date do not support a causal link between hyperprolactinaemia and breast cancer in humans. The CHMP agreed that prolactin played a different endocrinological role in rodents as compared to humans, and therefore the increase in mammary and pituitary gland tumours observed in the lurasidone carcinogenicity studies was considered to be a rodent-specific finding. The CHMP also agreed that there is currently no scientific consensus regarding a possible link between elevated prolactin levels and human breast cancer. However, despite the inconsistent results of various epidemiological studies, it was felt that it was not possible to completely rule out such a link. Accordingly, the CHMP felt that it would be important to closely monitor adverse events potentially related to prolactin increase in the clinic.

The applicant has presented data from the clinical development program of lurasidone, showing that prolactin levels in women treated with lurasidone was generally lower than that in women treated with other antipsychotics. In clinical studies of up to 22 months with lurasidone, there were no hyperprolactinaemia-related treatment-emergent adverse events (TEAEs) of gynaecomastia, breast enlargement, breast tenderness, or infertility in any treatment group. The CHMP agreed with the applicant's conclusion that available clinical data did not suggest an increased risk of human breast cancer in women treated with lurasidone.

Potential for ophthalmic changes due to the lurasidone distribution and retention to the eye were further discussed by the applicant in response to the concern from the CHMP. The applicant argued that there were no indications of ophthalmic adverse findings in the long term toxicology studies, which could support the understanding that findings for melanin binding was not indicative of ocular toxicity. The committee accepted the applicant's argumentation.

Due to inadequacies in the characterisation of the human metabolic profile for lurasidone further discussion on its complex metabolism was provided by the applicant. Exposure of additional key known

human metabolites ID-20221, ID-20222, Hydroxy-keto-ID-15002, ID-15001 and ID-14324 has been extrapolated from the existing mouse, rat and dog ADME studies, in which animals were treated with 50 mg/kg lurasidone. Results were then converted to the extrapolated levels at which these metabolites could be present at the higher doses used in the toxicity studies. The CHMP expressed concern that this extrapolation was based on assumption of linear dose-concentration relationship for each of the three non-clinical species, which was shown not to be the case for mice and rats. Therefore the applicant was requested to provide further justification for extrapolating the levels of exposure of the known metabolites: ID-20221, ID-20222, Hydroxy-keto-ID-15002, ID-15001 and ID-14324 in the non-clinical species using AUC values obtained from the single dose pharmacokinetic studies (mice, rats and dogs). The committee also felt that further evidence to demonstrate that exposure to these metabolites was adequately covered in animals might be necessary to validate such approach. The Applicant used multiple extrapolation methods to provide further information on toxicological coverage of known and unknown metabolites. The CHMP acknowledged the limitation of the analysis however found it acceptable.

Additionally, the points for clarification comprising the pharmacological activity of metabolites ID-20239 & ID-20240 and using two non-rodent species in the toxicological package have all been resolved.

According to the environmental risk assessment (ERA) lurasidone was originally proposed to be classified as a PBT substance based on the following rationale: when using normalised lipid content of 5%, the resulting bioconcentration factor (BCF) was greater than 2000 (BCF: 2798-2585) indicating that lurasidone hydrochloride is bioaccumulative. The substance does not fulfil the T-criterion based on the data from ecotoxicity studies as specified in Reach Regulation Annex XIII section 1.1.3 (a), since NOECs from long-term studies on three trophic levels are above the cut-off value of 0.01 mg/L. However, lurasidone was considered to fulfil the category 2 criterion for a reproductive toxicant, according to Regulation (EC) No. 1272/2008 (CLP). This classification of lurasidone was based on prolactin-related effects not only in rodents but also in non-rodents, as well as some effects on male reproductive organs in dogs. After further discussion, taking into account data from clinical trials showing that prolactin levels in lurasidone-treated women were generally lower than those in women treated with other antipsychotics, the CHMP considered that lurasidone does not fulfil the T-criterion. Accordingly, when looking at the totality of the data they are not considered robust enough to classify lurasidone as a PBT substance. Hence, lurasidone is not considered to be a concern to the environment and no special warnings are necessary in the SmPC, labelling and patient leaflet.

2.3.7. Conclusion on the non-clinical aspects

In conclusion the non-clinical data provided were considered sufficient together with additional measures as specified in the discussion section to support this dossier.

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.

A GCP routine inspection was requested by CHMP and was carried out on the study protocols D1050229, D1050231 and D1050233. The outcome was positive.

Tabular overview of clinical studies

A tabular summary describing lurasidone exposure in the clinical development program supporting the MAA is presented in tables 7-10.

Table 7. Completed Studies in the Clinical Development Program for lurasidone in Schizophrenia.

Study Number	Duration of Treatment	Total Number of Subjects Dosed with lurasidone	Study Objective and Doses Evaluated
Phase 2/3, Short-term, Double-blind, Placebo-Controlled (1508 subjects dosed with study drug)			
D1001002 (Phase 3)	6 weeks	258	Efficacy and safety, lurasidone 40 mg/day and 80 mg/day
D1050006 (Phase 2) *	6 weeks	99	Efficacy and safety, lurasidone 40 mg/day and 120 mg/day
D1050049 (Phase 2b)	6 weeks	209	Efficacy and safety, lurasidone 20 mg/day, 40 mg/day, and 80 mg/day
D1050196 (Phase 2) *	6 weeks	90	Efficacy and safety, lurasidone 80 mg/day
D1050229 (Phase 3) *	6 weeks	369	Efficacy and safety, lurasidone 40 mg/day, 80 mg/day, and 120 mg/day
D1050231 (Phase 3) *	6 weeks	237	Efficacy and safety, lurasidone 40 mg/day and 120 mg/day
D1050233 (Phase 3) *	6 weeks	246	Efficacy and safety, lurasidone 80 mg/day and 160 mg/day
Phase 3, Long-term, Double-blind, Active Comparator Controlled (626 subjects dosed with study drug)			
D1050237 (Phase 3) **	12 months	419	Long term safety and efficacy lurasidone 40 mg/day to 120 mg/day
D1050234 (Phase 3) **	12 months	207 (56 new exposures)	Long term efficacy and safety lurasidone 40 mg/day to 160 mg/day
Phase 2/3, Other (1737 subjects dosed with study drug)			
D1001016	8 weeks	69	Efficacy and safety, lurasidone 20 mg to 80 mg, flexibly dosed
D1001001	8 weeks	200	Dose response, safety and efficacy, lurasidone 20 mg, 40 mg, and 80 mg
D1001036 (D1001001 extension)	44 weeks	99	Efficacy and safety extension, lurasidone 20 mg to 120 mg, flexibly dosed
D1001048	52 weeks	182	Efficacy and safety, lurasidone 40 mg to 120 mg, flexibly dosed

***** Short-term efficacy and safety studies submitted as pivotal. ****** Long-term maintenance of effect and safety studies submitted as pivotal.

Table 8. Completed Studies in the Clinical Development Program for lurasidone in Schizophrenia (*Continued*).

Study Number	Duration of Treatment	Total Number of Subjects Dosed with lurasidone	Study Objective and Doses Evaluated
D1001017	8 weeks	20	PK, safety and efficacy, lurasidone 20 mg to 80 mg, flexibly dosed
D1050174 (D1050049 extension)	25 weeks OL	98 (46 new exposures)	Safety extension, lurasidone 20 mg to 80 mg, flexibly dosed

D1050199 (D1050196 extension)	12 month OL	59 (31 new exposures)	Safety extension, lurasidone 80 mg
D1050229E (D1050229 extension)	22 month OL	250 (59 new exposures)	Safety and efficacy extension, lurasidone 40 mg to 120 mg, flexibly dosed
D1050231E (D1050231 extension)	6 month OL	246 (131 new exposures)	Safety and efficacy extension, lurasidone 40 mg to 120 mg, flexibly dosed
D1050237E (D1050237 extension)	6 month OL	223 (87 new exposures)	Safety and efficacy extension, lurasidone 40 mg to 120 mg, flexibly dosed
D1050289	6 week	240	Safety and efficacy, switch from other antipsychotics, lurasidone 40 mg to 120 mg, flexibly dosed
D1050290 (D1050289 extension)	6 month OL	148	Safety and efficacy, lurasidone 40 mg to 120 mg, flexibly dosed
D1050254	21 days	150	Safety and efficacy, lurasidone 120 mg
Phase 1, non-schizophrenia (371 subjects dosed with study drug)			
D1050001 (b)	3 x 1day and 2 x 1 day	18	Safety and pharmacokinetics of single ascending doses, lurasidone 10 mg, 20 mg, 40 mg, 80 mg, or 100 mg
D1050180	1 day	22	Dopamine D2 occupancy, lurasidone 10 mg, 20 mg, 40 mg, 60 mg, or 80 mg
D1050184	1 day	5	ADME study, lurasidone 40 mg
D1050246 (b)	10 days	21	Oral contraceptive interaction, PK and safety, lurasidone 40 mg
D1050250	2 x 1 day	12	Diltiazem interaction, PK and safety, lurasidone 20 mg

Table 9**.** Completed Studies in the Clinical Development Program for lurasidone in Schizophrenia (*Continued*).

Study Number	**Duration of Treatment**	**Total Number of Subjects Dosed with lurasidone**	**Study Objective and Doses Evaluated**
D1050251 (b)	4 x 1 day	23	Comparative BA in fed/fasted state, lurasidone 20 mg
D1050252 (b)	4 x 1 day	19	Comparative BA in fed/fasted state, lurasidone 20 mg
D1050253	1 day	9	Safety and pharmacokinetics of single doses in elderly male and female subjects, lurasidone 20 mg
D1050262	1 day	6	ADME study, lurasidone 40 mg
D1050264	1 day	21	Effect of hepatic impairment on pharmacokinetics and safety, lurasidone 20 mg
D1050265	1 day	36	Effect of renal impairment on pharmacokinetics and safety, lurasidone 40 mg
D1050002	6 days	13	Safety and pharmacokinetics of multiple doses lurasidone 40 mg BID or 80 mg QD
D1050183	2 x 1 day	10	Ketoconazole interaction, pharmacokinetics and safety of lurasidone 10 mg
D1050270	2 x 1 day	20	Rifampicin interaction, pharmacokinetics and safety of lurasidone 40 mg
D1001013 (b)	2 x 1 day	15	Pharmacodynamic effect on EEG and flicker test, lurasidone 20 mg or 40 mg

D1001053	2 x 1 day	36	BE of 2 formulations lurasidone 40 mg
D1001054	2 x 1 day	12	Food effect on pharmacokinetics lurasidone 40 mg
D1001049	1 day	20	Effect of age on pharmacokinetics and safety, lurasidone 20 mg
SM-071019	1 day	29	Safety and pharmacokinetics of a single dose lurasidone 0.1 mg, 0.25 mg, 0.5 mg, 1 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, or 30 mg
S01P12 (b)	1 day	16	Food interaction on pharmacokinetics and safety, lurasidone 20 mg

Table 10. Completed Studies in the Clinical Development Program for lurasidone in Schizophrenia (*Continued*).

Study Number	**Duration of Treatment**	**Total Number of Subjects Dosed with lurasidone**	**Study Objective and Doses Evaluated**
S01P13	7 days	8	Safety and pharmacokinetics of multiple doses lurasidone 10 mg BID
Phase 1, schizophrenia (300 subjects dosed with study drug)			
D1050160	6 days	23	Safety and pharmacokinetics of multiple, ascending, doses, lurasidone 120 mg, 140 mg, and 160 mg
D1050217	6 days	52	Safety and pharmacokinetics of multiple, ascending, doses, lurasidone 160 mg, 200 mg, 240 mg, 280 mg, 320 mg, 400 mg, or 520 mg, titration (200 to 600) mg
D1050247	16 days	24	Lithium interaction, pharmacokinetics and safety of lurasidone 120 mg
D1050249	11 days	58	Effect on QTc interval, lurasidone 120 mg, titration (120 to 600 mg)
D1050263 (b)	3 x 7 days	54	BE and safety of 2 formulations lurasidone 120 mg
D1050267	30 days	26	Fed/fasted state on pharmacokinetics and safety of lurasidone 120 mg
D1050269	8 days	24	Midazolam interaction, pharmacokinetics and safety of lurasidone 120 mg
D1050279	8 days	23	Digoxin interaction, pharmacokinetics and safety of lurasidone 120 mg
D1050294	20 days	16	Low calorie effect on pharmacokinetics and safety of lurasidone 120 mg

Ongoing studies

In addition to the completed studies in subjects with schizophrenia there were ongoing studies at the time of submission. D1050238 is a randomised withdrawal, double-blind, placebo-controlled study, which has the objective of studying the long-term maintenance of effect and safety of lurasidone. There is also a short-term Japanese study, D1001056 and its open-label safety extension, D1001057.

2.4.2. Pharmacokinetics

The information on clinical pharmacology of lurasidone was collected from 31 clinical studies and 14 in vitro studies with human materials. Thirty phase I trials, in a total of 671 subjects, have been completed to investigate the clinical pharmacology of lurasidone. Of these subjects, 371 subjects were healthy and 300 subjects were diagnosed with schizophrenia or schizoaffective disorder. Furthermore, a population pharmacokinetic (popPK) analysis has been performed using data pooled from several

Phase I, II and III studies including in total 1623 subjects of which 1492 (92%) were patients with schizophrenia.

Absorption

At least 9-19% of lurasidone is absorbed after dosing in suspension form after food, based on the amount of radioactivity in urine in the two ADME studies (D1050184 and D1050262). The absolute bioavailability of lurasidone is unknown.

The steady state Cmax and AUCtau in subjects with schizophrenia following 160 mg daily dosing in study D1050160 is 233.4 ng/mL and 899.3 ng*h/mL respectively. Based on the population modelling the steady state Cmax and AUCtau in the reference subject (80 kg white male) following 160 mg daily dosing is 122 ng/mL and 817 ng*h/mL respectively. In a female Asian subject the predicted Cmax and AUCtau is 138 ng/mL and 1420 ng*h/mL respectively.

Absorption of lurasidone during fasting conditions is fairly rapid with tmax occurring at 1-3 hours after dose. The effect of a high fat/high calorie meal versus fasting conditions is an approximate 1.5- to 2-fold increase in exposure, a 2- to 3-fold increase in Cmax and a delay of peak plasma concentration to about 4 hours as assessed in five food effect studies performed, both in healthy volunteers (S01P12, D1050251, D1001054) and in subjects with schizophrenia, schizoaffective or schizophreniform disorder (D1050267 and D1050294).

Based on these results it has been recommended in the SmPC section 4.2 that lurasidone should be administered with food.

Distribution

Lurasidone has a large apparent volume of distribution (Vz/F around 6000 L) and has a high protein binding (>99%). The active metabolite ID-14283 has a protein binding of >98%. The protein binding was considered of limited clinical relevance by the CHMP.

Elimination

Clearance of lurasidone (CL/F) derived from the population PK analysis is 196 L/h. The range of the terminal half-life is 20 hours to 40 hours.

Lurasidone is converted to a large number of metabolites including active ID-14283, ID-14326, and inactive ones, i.e. ID-11614, ID-20219 and ID-20220 via multiple pathways. In vitro data and the drug-drug interaction studies with ketoconazole (a strong CYP3A4 inhibitor) and rifampin (a CYP inducer) indicate that CYP3A4 is the main enzyme.

Two studies, D1050184 and D1050262, examined the absorption, metabolism, and excretion of [14C]-lurasidone after a single 40 mg oral suspension dose (150 µCi or 5.55 megabecquerel) was given to 5 (D1050184) or 6 male subjects (D1050262) within 30 min of the start of a high fat meal. The results showed that between 67 and 80% of the substance was eliminated in faeces and 19 and 9% in urine resulting in a dose recovery of >85% in both studies, respectively. Faeces samples were only analysed in one of the studies and consisted almost entirely of unchanged lurasidone. The part of the dose excreted in urine was identified as metabolites and no unchanged lurasidone was identified in urine. Most of the radioactivity in faeces was recovered within 72 hours to 96 hours after administration of an oral dose. Based on results from study D1050184 the inactive metabolites ID-20219 and ID-20220 were the main radioactive components in serum (24%, and 11%) except for parent lurasidone (10.7%). The active metabolite ID-14283 contributed to 2.8% of total radioactivity (up to about 30%

of parent exposure). The other identified and unknown metabolites contributed to less than 10% of the total radioactivity in serum. The radioactivity data presented was based on 8 hour sampling time.

Inter-individual variability (IIV) in Cmax and AUC was moderate in healthy volunteers (46% and 35% respectively) and slightly higher in patients with schizophrenia (54% and 63% respectively). Intra-individual/inter-occasion variability (IOV) has not been determined.

Dose proportionality and time dependencies

Lurasidone demonstrated a linear PK profile at doses of 10 mg to 100 mg in healthy subjects (Study D1050001) and at doses of 120 mg to 160 mg in subjects with schizophrenia (Study D1050160). Based on the PopPK data there were no clear time-dependencies in lurasidone PK. The parent/metabolite (ID-14283) ratio seemed to be unaffected by repeat dosing and was found to be similar between patients and healthy volunteers.

Special populations

The pharmacokinetics of lurasidone has been investigated in healthy volunteers and in the patients. Generally no differences were identified except in higher inter-subject variability as mentioned above.

The effect of varying degrees of renal impairment on the single dose pharmacokinetics of postprandial, orally-administered lurasidone 40 mg was investigated in D1050265. This was an open-label, single dose, oral administration study of lurasidone 40 mg in subjects with mild, moderate and severe renal impairment including matched healthy controls. An approximate 1.5-fold increase in exposure and maximal concentrations of lurasidone was observed in mild renal impairment; in moderate and severe the increase in exposure and maximal concentrations was approximately two-fold.

The effect of hepatic impairment on lurasidone and the metabolite ID-14283 and ID-14326 was investigated in 15 subjects with varying degrees of hepatic impairment administered a single dose of 20 mg (D1050264). Compared to healthy matched control subjects, the mean AUC0-inf increased 1.5-, 1.7- and 3-fold for mild, moderate, and severe impairment groups, respectively.

The effect of race on the PK of lurasidone was evaluated in a population PK study. It was found that Asian race was associated with a 47% increase in exposure compared to the reference covariate value (Caucasian race).

Two studies evaluated the effects of age on lurasidone pharmacokinetics. D1001049 investigated the effect of age in Japanese subjects (aged, 20 to 32 years, inclusive and 65 to 79 years, inclusive); and D1050253 in Caucasian subjects (aged 65 to 85 years, inclusive). The results were compared with historical data from healthy young subjects (D1050250) given the same dose of lurasidone under similar fed conditions. The results from both studies showed a mean increase in exposure of up to 22% with a potential decrease in the rate of absorption.

Pharmacokinetic interaction studies

The *in vivo* interaction potential of lurasidone was investigated in seven drug-drug interaction studies.

Co-administration of lurasidone at 10 mg with multiple doses of ketoconazole (strong CYP3A4 inhibitor) resulted in a large increase in maximum concentration (7-fold) and exposure (9-fold) of lurasidone (D1050183). The administration of the multiple doses of moderate CYP3A4 inhibitor diltiazem at 240 mg resulted in a two-fold increase in lurasidone Cmax and AUC (lurasidone administered at 20 mg) in study D1050250.

When administered at the dose of40 mg with the single dose of the CYP enzyme inducer rifampin at 600 mg more than 5-fold reduction of Cmax and AUC of lurasidone was observed in study D1050270.

The pharmacokinetics of the CYP3A4 substrate midazolam was only marginally affected by co-administration of single- and multiple-dose of lurasidone (120 mg) (D1050269).

Lurasidone showed no effect on the pharmacokinetics of the oral contraceptive Ortho Tri Cyclen (D1050246), lithium (D1050247) and the P-gp substrate digoxin (D1050279).

Pharmacokinetics using human biomaterials

The plasma protein binding of lurasidone was determined using equilibrium dialysis at 100, 300 and 1000 ng/mL (SMT/01). The binding to human serum albumin (HSA) and alpha-1-acid glycoprotein (AAG) was specifically studied. The protein binding of lurasidone in humans was 99.8 %, independent of concentration. A high degree of protein binding of lurasidone was also noted for HSA and AAG, ≥99.1 and ≥99.6 % respectively. The plasma protein binding of the two active metabolites ID-14283 and ID-14326 was determined in vitro in study NA04101 by using equilibrium dialysis at 10, 30 and 100 ng/mL. The protein binding in humans was between 98.8 %-99.0 % for the two metabolites, independent of concentration.

Protein binding displacement was investigated between lurasidone and concomitant drugs administered intravenously (biperiden, flunitrazepam, haloperidol and diazepam) in human serum Study X1K01. It was concluded that the protein binding of lurasidone was not affected by concomitant drugs and that protein binding of concomitant drugs was not affected by lurasidone.

The inhibition of lurasidone metabolism was studied in human liver microsomes using 4 concomitant drugs (biperiden, flunitrazepam, haloperidol, and diazepam), which are substrates of CYP3A4, as well as the inhibition of metabolism of these drugs by lurasidone (Study X1K02). No inhibition of lurasidone metabolism by the 4 studied concomitant drugs (≤1 µg/mL) was observed. Similarly, no inhibition was observed by lurasidone across a range of concentrations (0.1 µg/mL-10 µg/mL) on the metabolism of the 4 studied concomitant drugs. The inhibition of lurasidone metabolism was further examined in human liver microsomes using 3 concomitant drugs (ketoconazole, quinidine and cimetidine, Study X1K02). The inhibitions associated with quinidine and cimetidine on the metabolism of lurasidone were negligible (Study X1K02). In the presence of ketoconazole, a strong CYP3A4 inhibitor, the metabolism of lurasidone was inhibited (X1K02). This finding was also demonstrated in Study A02001 which revealed an inhibition constant (Ki) of 37 nmol/L for ketoconazole. As a consequence a clinical DDI study was performed.

Two studies (6645-128 and PK007) investigated the reversible and irreversible inhibitory potential of lurasidone on CYP-mediated reactions was assessed in human liver microsomes. Lurasidone had low inhibitory effects on CYP2C9, CYP2D6 with half maximal inhibitory concentration (IC50) values of >50 µM. The Ki values for CYP2C19 and CYP3A4 were 10 µM and 17 µM, respectively. No evidence of irreversible inhibition of CYP activity was observed in this study. Lurasidone was also shown to have weak inhibitory effects on CYP2C8, CYP2C9, CYP2C19, CYP3A4, and CYP2B6, and activities with IC50 values of 6.3, 7.4, 5.9, 22 and 21 µM, respectively. Its IC50 values for the other CYPs tested were much higher; 90 µmol/L for 2D6 and >100 µmol/L for 1A2 and 2E1. Compared with lurasidone, its non-major active metabolite (ID-14283) demonstrated a similar or weaker inhibitory effect on CYP-mediated reactions, as did the major, non-active metabolite ID-20219.

Study XT093011 assessed the induction potential of lurasidone on CYP enzymes. Treatment with lurasidone (0.03, 0.3, 3, and 10 µM) once daily for 3 consecutive days in cultured fresh human hepatocytes had neither an inductive effect on CYP1A2, CYP2B6 and CYP3A4/5 enzyme activity nor an effect on messenger ribonucleic acid (mRNA) levels. The CYP inducers (omeprazole 100 µM,

phenobarbital 750 µM and rifampin 10 µM) caused increases of 37.2-, 14.9-, and 6.74-fold in CYP1A2, 2B6, and 3A4/5 activity, respectively.

Studies PK003 and GE-0535-G examined the P-glycoprotein (P-gp) multi-drug resistance 1 (MDR1) transport relationships of lurasidone and its metabolites (ID-14283 or ID-20219). In LLC-PK1 cells expressing the mouse and human P-gp, lurasidone and 1 of its active metabolites, ID-14283, did not exhibit vectorial transport, indicating that they are not substrates of P-gp. In LLC-PK1 cells expressing the human P-gp, lurasidone demonstrated an inhibitory effect on the digoxin transport activity at a concentration of 1 to 10 µM (IC50=1µM), while its major metabolite ID-20219 has no inhibitory effect on the digoxin transport activity up to 20 µmol/L. As a consequence a clinical DDI study was performed.

2.4.3. Pharmacodynamics

Mechanism of action

Lurasidone is a selective blocking agent of dopamine and monoamine effects. Lurasidone binds strongly to dopaminergic D2- and to serotonergic 5-HT2A and5-HT7- receptors with a binding affinity of 0.994, 0.47 and 0.495 nM, respectively. It also blocks α2c-adrenergic receptors and α2a-adrenergic receptors with a binding affinity of 10.8 and 40.7 nM respectively. Lurasidone also exhibits some partial agonism at the 5HT-1A receptor with a binding affinity of 6.38 nM. Lurasidone is not bound to cholinergic or muscarinic receptors.

Lurasidone doses ranging from 10 to 80 mg administered to healthy subjects produced a dose dependent reduction in the binding of 11C-raclopride, a D2/D3 receptor ligand, to the caudate, putamen and ventral striatum detected by positron emission tomography (see below).

Primary and Secondary pharmacology

The primary pharmacology of lurasidone was investigated in two clinical studies.

Study D1050180 was an open-label, single-centre, PET scan study that assessed 20 healthy Caucasian male subjects who were administered a single oral dose of lurasidone 10 mg, 20 mg, 40 mg, 60 mg and 80 mg. The study was designed to determine the dopamine D2 receptor occupancy of lurasidone using PET scans with the radioactive tracer [11C] raclopride.

The results for each dose group were similar among all 3 striatal regions (caudate, putamen, globus pallidus) of the brain that were examined. Mean D2 receptor occupancies for the 3 brain regions ranged from 41.3%-43.3% (10 mg), 51.0%-54.8% (20 mg), 63.1%-67.5% (40 mg), 77.4%-84.3% (60 mg), and 72.9%-78.9% (80 mg). A relationship between serum concentration and D2 receptor occupancy was demonstrated for lurasidone, which showed that maximal D2 receptor occupancy (80%) was observed at lurasidone doses of 60 mg and 80 mg doses of lurasidone.

Another PET study (D1050268) evaluating lurasidone occupancy at steady-state at doses up to 160 mg was being conducted at the time of assessment. In this investigator-initiated exploratory study, the results showed that dopamine D2 receptor occupancy in all examined brain regions was significantly correlated with serum concentration of lurasidone.

Study D1001013 was a randomised, double-blind, single-centre, single dose per period, crossover study designed to evaluate the pharmacological effects of lurasidone 20 mg and 40 mg, or matching placebo, on the CNS penetration in 44 healthy, Japanese, adult males, using quantitative EEG and the flicker test. In quantitative EEG evaluation, in comparison with placebo, lurasidone did not affect global field power (GFP, %) in frequency bands: delta, theta, beta 2, or beta 3 at a dose of 20 or 40 mg. A

mildly increased GFP (%) in the alpha 1 (lower alpha-wave region) band and mildly decreased GFP (%) in the alpha 2 (higher alpha-wave region) and beta 1 bands were observed at a dose of lurasidone 40 mg, although not significantly. In the flicker test, lurasidone significantly decreased the threshold of flicker discrimination at doses of 20 and 40 mg. A similar inhibitory effect has been reported with many antipsychotic agents.

A thorough QTc (TQT) study (D1050249) was conducted in subjects with schizophrenia or schizoaffective disorders. A concentration-response model was developed in order to provide a direct estimate of drug-induced QTc prolongation. According to the ICH E14 guideline, the thorough QT study (TQT) was considered inconclusive (drugs that prolong the mean QT/QTc interval by more than 5 and less than 20 ms; see clinical safety discussion on section 2.6).

2.4.4. Discussion on clinical pharmacology

The exposure to lurasidone and its active metabolite ID-14283 is sufficiently characterised in healthy volunteers and patients with schizophrenia.

Dose-proportional increase in exposure to lurasidone and ID-14283 is seen over a large dose range encompassing the therapeutic doses. High fat/high calorie food increases the exposure to lurasidone 2-fold. Therefore lurasidone was administered with food in phase 2 and 3 studies.

The CHMP agreed that the lack of an absolute bioavailability study can be accepted given the poor solubility, and thus the inability to administer lurasidone intravenously. However, the committee felt that the unknown bioavailability of lurasidone may hamper the assessment of its pharmacokinetics. Therefore the applicant was requested to use existing pharmacokinetic data to estimate product's bioavailability. In their response the applicant submitted an estimate based on mass-balance data and PBPK modelling. The estimated value ranged from 6% to 18% and was consistent with the non-clinical data. The CHMP requested further comparisons and simulations pertinent to the potential CYP mediated DDIs and multiple dosing. Based on the provided results the committee considered that although the PBPK modelling could be improved in vivo data provided enough information for dosing recommendations.

The protein binding of lurasidone and the active metabolite ID-14283 is high; hence the CHMP felt that this may affect their active moieties. Consequently, the applicant was requested to calculate the respective active moieties of lurasidone and ID-14283 in scenarios where changes in lurasidone/ID-14283 exposure ratio and protein-binding could be expected, e.g. the ketoconazole study and the hepatic impairment study. The calculations revealed that the changes were consistent with the PK results presented in the ketoconazole, rifampicin, diltiazem drug-drug interaction studies and the renal and hepatic impairment studies. According to the calculations provided the metabolite ID-14283 seems to have a major contribution to the lurasidone activity. This information is reflected in the relevant sections of the SmPC.

Two mass-balance studies have been performed for lurasidone and have provided information on the pharmacokinetics of lurasidone and its metabolites. Due to inadequacies in the design of mass-balance studies and uncertainties in the interpretation of the results, the applicant was asked to submit more detail regarding the metabolism and elimination of lurasidone. Furthermore, additional data, analyses and discussions to address the concern regarding the risk of unanticipated DDIs as a result of unidentified major metabolites of lurasidone were requested. The applicant has provided requested analyses and discussions based on the available data together with additional estimation of the likely exposure to the unknown metabolites providing therefore enough reassurance on the safety implications of the PK of the product.

It was also concluded that the elimination of ID-14283, via metabolism/active transport, should be further investigated in vitro due to its substantial contribution to efficacy. The applicant provided in vitro data to investigate the metabolism of ID-14283 and also committed to the post-authorisation measure to study ID-14283 as a substrate of OATP1B1 and OATP1B3 and to update SmPC wording accordingly.

CYP3A5 is known to exhibit polymorphism. Additionally, the CHMP noted that Asian population appeared to have higher exposure to lurasidone on average than Caucasians. Therefore, the applicant was requested to determine the contribution of CYP3A5 to the metabolism of lurasidone and discuss the potential consequences of genetic polymorphism. In response, the applicant provided the re-assessment of the clearance data from the clinical development program. The analysis indicated that CYP3A5 did not contribute significantly to the clearance of lurasidone and that genetic polymorphism of the enzyme would not be expected to impact its metabolism.

The CHMP noted that patients with creatinine clearance below 15 ml/min have not been investigated during the clinical development programme. Therefore the applicant was asked to discuss how the lurasidone PK was affected in patients with end stage renal disease (ESRD). The applicant used the available data from the renal impairment study (D1050265) to estimate lurasidone PK in subjects with ESRD. The linear regression model was used to estimate lurasidone Cmax and AUC by extrapolation of CrCl values to 0-15 mL/min. Due to the large variability of the data the model did not however provide a reliable estimate. In addition, since no unchanged lurasidone was found in urine it was not possible to estimate the impact of ESRD on lurasidone PK based on elimination pathways. Therefore, the Committee concluded that lurasidone should not be used in patients with ESRD unless the potential benefits outweigh the potential risks. This information is reflected in sections 4.2 and 4.4 of the SmPC.

Other factors found to influence lurasidone exposure were hepatic impairment, gender and race. The exposure increase 3-fold in subjects with severe hepatic impairment, while the combination of Asian race and female gender were predicted to result in 75% higher exposure compared to a white male. The applicant discussed thoroughly potential differences in the efficacy and safety profile of lurasidone related to race and gender. The results of a population pharmacokinetic (PK) meta-analysis revealed no clinically relevant race-related differences in the PK of lurasidone. A small sex and race effect observed with an increase exposure of 1.2-fold for female subjects and 1.5-fold for Asian race, was considered not to be clinically relevant and therefore not necessitating a dose adjustment in Asian women. The applicant was requested to justify the proposed doses in patients with hepatic impairment and clarify whether there was a true gender/race effect on elimination capacity. The justification provided by the applicant to allow a lurasidone starting dose of 20 mg in patients with severe hepatic impairment (SHI) was deemed acceptable by the CHMP. However, since the starting dose in SHI patients resulted in a higher exposure in SHI patients as compared to patients with normal hepatic function (NHF) caution was advised in these patients. Therefore the CHMP requested that this information should be reflected in section 4.4 in the SmPC.

In consideration of the CHMP's concern, the applicant re-examined the PopPK analyses and the results of this reanalysis emphasised Asian race as a parameter of more relevance to clearance than weight. The CHMP acknowledged the explanation provided.

The CHMP noted that there were limited data for lurasidone pharmacokinetics in the elderly and that they were based on total drug concentrations. The two proteins that bind lurasidone in plasma change with age (albumin decreasing and α1-acid glycoprotein increasing). Given the very high degree of plasma protein binding of lurasidone and ID-14283 and the fact that pharmacokinetic studies measured only total drug, a potential change in free drug concentration may not have been detected. Consequently, the applicant was requested to discuss how age related changes in protein concentrations could affect the interpretation of total concentration when used as a surrogate for free

concentration. The applicant presented additional analyses and simulations including popPK and the estimation of protein binding isotherms. The CHMP agreed with the applicant that the effect of age and protein binding on free lurasidone were not expected to impact the overall safety and efficacy in the elderly population.

The in vitro data submitted on lurasidone and ID-14283 as P-gp substrates were inconclusive. As P-gp may be involved in the absorption and/or potential biliary excretion of lurasidone the applicant was asked to submit additional in vitro data. Based on the submitted results it was concluded that lurasidone interaction at P-gp/BCRP in the intestine was possible. The section 4.5 of the SmPC has been updated to reflect this finding and to include a list of clinically relevant P-gp substrates.

Moreover, the results of the in vivo digoxin interaction study did not preclude inhibition of P-gp at the intestinal level. Consequently, the applicant was requested to discuss the potential impact of lurasidone on drugs that are substrates of intestinal P-gp transport and provide a justification for the lack of in vivo study with a sensitive substrate of intestinal P-gp (e.g. with dabigatran etexilate). In response the applicant emphasised that lurasidone had very low solubility at the pH of the small intestine which resulted in concentrations much lower than the IC50 reported for P-gp inhibition. The CHMP accepted the applicant's justification for not performing the in vivo study.

The Applicant was also requested to provide in vitro data on the inhibition of the transporters from studies ongoing in parallel to the assessment. Based on the submitted in vitro data lurasidone did not inhibit OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MATE1, MATE2-K and BSEP at clinically relevant concentrations. However, the inhibition of the P-gp, BCRP and OCT1 was observed in vitro. These findings have been reflected in the SmPC. The applicant will submit an in vitro study investigating the solubility of lurasidone in the fed state simulated intestinal fluid (FESSIF) post approval.

The absence of the data on the binding of lurasidone to plastic in the in vitro studies has been deemed acceptable by the CHMP given the indirect evidence of minimal binding based on the linearity in the bioanalytical calibration curves.

Inhibition of CYP3A4 by ketoconazole leads to a major increase (9-fold) in exposure to lurasidone while induction of the same enzyme leads to a 6-fold decrease in exposure. Thus, the CHMP agreed to the recommendation that co-administration of strong inhibitors or inducers of CYP3A4 should be contraindicated for patients taking lurasidone (reflected in SmPC section 4.3). The moderate CYP3A4 inhibitor diltiazem lead to a 2-fold increase in lurasidone Cmax and AUC and therefore the applicant recommended a starting dose of 20 mg and that the maximum dose of lurasidone should not exceed 80 mg once daily in combination with moderate CYP3A4 inhibitors (reflected in SmPC section 4.2).

Rifampin is a potent inducer of CYP3A4. Since the potency and specificity of other inducers may differ from rifampin, the applicant was requested to discuss dosing recommendations that would apply when other inducers including mild/moderate ones are administered together with lurasidone. In their response the applicant concluded that mild and moderate CYP3A4 inducers may cause less than 2-fold reduction in lurasidone exposure. The CHMP felt that this may lead to lower treatment efficacy and therefore the recommendation needed to be included in the SmPC together with examples of mild and moderate CYP3A4 inducers.

Data on lurasidone time dependent inhibition of CYP2C8 and 2B6 will be provided as a post-approval measure.

The applicant provided an analysis of the efficacy in the White North American subgroup of patients in response to the CHMP request for an overview of the available information regarding the genetic differences in the PD response, in particular between the non-EU populations from the clinical development programme and the target EU patient population. In the CHMP's view this analysis demonstrated no reduction in efficacy in one, potentially genetically distinct subgroup compared to the

overall development programme population thus supporting the claim that genetic differences between the studied and the target population are not expected to have significant influence.

Due to the heterogeneous patient population and methodological shortcomings in the Investigator-initiated PET study D1050268, the CHMP felt that results were not directly applicable to the proposed product. Therefore the applicant was requested to present the results for the subgroup of patients with schizophrenia only and present the information on delay between the scan and the efficacy assessment. The applicant explained that the overall number of subjects in the study was small (n=17), and that only 10 subjects had diagnosis of schizophrenia making the subgroup analysis unfeasible. The delay between the scan and the PANSS assessment was within 2 days. The CHMP acknowledged the response and considered the issue as closed.

2.4.5. Conclusions on clinical pharmacology

Lurasidone is extensively metabolised by CYP3A4 leading to contraindication of both strong inhibitors as well as strong inducers of this enzyme. There is an active metabolite, ID-14283, that is likely to have a substantial contribution to the pharmacological effect. Increase in exposure to lurasidone has been observed in subjects with decreased hepatic and renal function which implicates the need of dose modifications in these patients. A number of uncertainties are expressed in relation to the clinical pharmacology (see discussion on clinical pharmacology). These issues are to be investigated post approval.

The CHMP considers the following measures necessary to address the issues related to pharmacology:

1. MEA: An in vitro study to assess if the active lurasidone metabolite ID-14283 is a substrate of the liver uptake transporters (OATP1B1 and OATP1B3). The clinical relevance of the results should be assessed and further action may be required (included in RMP as Category 3).

2. MEA: An in vitro study to investigate if lurasidone causes time-dependent inhibition of CYP2C8 and CYP2B6. The clinical relevance of the results should be assessed and further action may be required (included in RMP as Category 3).

2.5. Clinical efficacy

There were 12 short-term clinical studies altogether; five 6-week studies (Study D1050006, D1050196, D 1050229, D1050231 and D1050233), and 7 other studies including 2 active controlled studies (D1001002 and D1050049) and 3 uncontrolled studies (D1001001, D001016 and D1001017) included in the lurasidone development program.

In all, there were 9 long-term studies reported in the application; 2 pivotal 12-month studies (Study D1050234 and D1050237) and another 7 long-term open-label clinical studies including three 6-month studies (D1050231E, D1050237E, D1050290), two 12-month studies (D1050199, D1001048) and one study of 22 months (D1050229E) to demonstrate maintenance of effect, tolerability and safety of lurasidone treatment of adult patients with schizophrenia. Additionally, the MAH submitted results from a long-term study D1050238 during the procedure.

2.5.1. Dose response study

Study D1050160 aimed at establishing the maximum tolerated dose of lurasidone in patients with schizophrenia.

This was a single-centre, inpatient, single-blind, fixed-dose, and sequential dose escalation study of the safety and tolerability of several doses of SM-13496 in subjects with schizophrenia. The doses

administered were 120 mg, 140 mg and 160 mg. Each panel consisted of 8 different patients. If one dose level was found to be well tolerated the study progressed to the higher dose level. Minimum intolerable dose was defined as the dose at which 50% or more of the subjects experienced multiple moderate or severe adverse events, or the dose at which at least one subject experienced a serious adverse event at least possibly related to the study medication. The dose below would then be designated as the maximum tolerated dose.

No clinically significant profile of toxicity was seen with lurasidone at 120 mg, 140 mg, or 160 mg taken once daily. The most frequently reported AEs were fatigue, restlessness, anxiety, and insomnia. The most frequently reported AEs considered drug-related were fatigue and restlessness.

The safety, tolerability, and efficacy of lurasidone at doses of up to 120 mg in the treatment of adult subjects with schizophrenia was investigated in the study D1050006. This study will be described in more detail in section Supportive studies.

2.5.2. Main studies

There were 5 short-term 6-week, fixed dose, double-blind, parallel-group and placebo controlled studies (Study D1050006, D1050196, D 1050229, D1050231 and D1050233) designed to show superiority of lurasidone as compared to placebo at a dose range of 40 mg to 160 mg, and similar short-term clinical efficacy to that of two active comparators, olanzapine 15 mg and quetiapine XR 600 mg, in the treatment of psychotic symptoms in adult patients with schizophrenia. They were submitted as pivotal trials for this application.

Due to the high discontinuation rate or small size of two of the studies (D1050006, D1050196) CHMP considered them as supportive for this application.

Short-term efficacy studies

Short Term Efficacy Study D1050229 - Randomised, Placebo-Controlled, Clinical Trial to Study the Safety and Efficacy of Three Doses of Lurasidone HCl in Acutely Psychotic Patients with Schizophrenia (Double-Blind Phase)

Methods

Study Participants

Adult male and female subjects in good physical health between 18 and 75 years of age, inclusive, who met DSM-IV™ criteria for a primary diagnosis of schizophrenia (including disorganised [295.10], paranoid [295.30], and undifferentiated [295.90] subtypes as established by clinical interview using the Mini-International Neuropsychiatric Interview [MINI] Plus) were eligible for inclusion in this study. The duration of the subject's illness, whether treated or untreated, must have been greater than one year. Subjects must have been experiencing an acute exacerbation of psychotic symptoms (no longer than 2 months) and marked deterioration of function from baseline (by history), or have been hospitalised for the purpose of treating an acute psychotic exacerbation for two consecutive weeks or less immediately before screening. Subjects must have had a PANSS total score ≥80 at screening and baseline, with a score ≥4 (moderate) on two or more on the following PANSS items: delusions, conceptual disorganisation, hallucinations, unusual thought content, and suspiciousness. Subjects must also have had a score ≥4 on the CGI-S at screening and baseline. Subjects had to agree and be able to remain off prior antipsychotic medication for the duration of the study. Subjects could not be pregnant, nursing, or planning pregnancy within the projected duration of the study. Subjects of reproductive potential had to agree to remain abstinent or use two acceptable methods of birth control during the

study. Subjects had to test negative for selected drugs of abuse at screening and baseline (in the event a subject tested positive for cannabinoids [tetrahydrocannabinol] or alcohol, the investigator evaluated the subject's ability to abstain from prohibited substances during the study). Subject needed to have a stable living arrangement for at least 3 months prior to randomisation and agree to return to a similar living arrangement after discharge.

Treatments

Subjects were evaluated for eligibility during a screening period of up to 14 days, during which they were tapered off all psychotropic medications. Subjects who met entry criteria entered a 3- to 7-day placebo washout period and remained hospitalised for the duration of the washout.

Subjects were to take the study medication containing lurasidone (40 mg/day, 80 mg/day or 120 mg/day) or matching placebo once daily in the morning by mouth with water, with a meal or within 30 minutes after eating (e.g., bowl of cereal).

Objectives

The primary objective of the study was to evaluate the efficacy of lurasidone (40, 80, or 120 mg/day) compared with placebo in the treatment of subjects with acute schizophrenia (diagnosed by Diagnostic and Statistical Manual of Mental Disorders, 4th Ed. [DSM-IV™] criteria) after 6 weeks of treatment.

Secondary objectives included evaluation of efficacy in improving functional outcome after 6 weeks of treatment; evaluation of efficacy in improving symptoms of schizophrenia during first week of treatment; evaluation of lurasidone efficacy in reducing depressive symptoms after 6 weeks of treatment; evaluation of safety and tolerability of lurasidone in acutely schizophrenic subjects during the 6-week treatment phase.

Tertiary objectives comprised evaluating the clinical relevance of lurasidone effects along with its effects on positive subscale, negative subscale and general psychopathology PANSS subscale.

Outcomes/endpoints

The primary outcome measure was the mean change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score at Week 6.

The secondary and tertiary outcomes are presented in the table below.

Table 11. Study D1050229 - secondary and tertiary outcomes.

Secondary outcomes	Tertiary/Other outcomes
Mean change from Baseline in the Clinical Global Impression – Severity Scale (CGI-S) at Week 6 [key secondary];	Responder rates in the PANSS total score (responders = 20% or greater improvement from Baseline);
Mean change from Baseline in PANSS total score at Day 4 [key secondary].	Mean change from Baseline in the PANSS positive subscale, negative subscale and general psychopathology subscale at Week 6;
	Mean change from Baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) at Week 6.

In addition a number of safety variables were followed and recorded, namely proportions of subjects with AEs, discontinuations due to AEs, and SAEs.

Sample size

Expected improvements in PANSS ratings (and SD) were estimated from 2 prior studies of lurasidone, D1050006 and D1050196. Assuming lurasidone differed from placebo in the change from baseline in PANSS total score by 6.8, 8.0, and 10.0 for the 40, 80, and 120 mg/day doses, respectively, and further assuming a standard deviation of 19.1, then n=120 subjects per group provided 97.5% power (at the α=0.05 level, two-sided test) to reject the null hypothesis of no difference from placebo for at least 1 lurasidone dose. This power calculation incorporated Bonferroni's procedure for controlling pairwise differences to placebo and was obtained via computer simulations. Therefore, the study planned to enrol 120 subjects per treatment group, for a total of 480 subjects.

Randomisation

Following the screening and washout periods, subjects who continued to meet entry criteria were randomly assigned to one of four treatment arms: Lurasidone 40 mg, Lurasidone 80 mg, Lurasidone 120 mg, or placebo (1:1:1:1 ratio).

Blinding

Study personnel had access to an IVRS (Interactive Voice Response System) to allocate subjects, to assign study medication to subjects, and to manage the distribution of clinical supplies. Each person accessing the IVRS was assigned an individual unique personal identification number (PIN). They were to only use their assigned PIN to access the system and were not to share their assigned PIN with anyone. The IVRS was to be used to unblind subjects and to unmask drug identity. Drug identification information was to be unmasked ONLY if necessary for the welfare of the subject. Every effort was to be made not to unblind the subject unless necessary. Any unblinding that occurred at a site was to be documented.

Statistical methods

Primary: The primary efficacy parameter was the change from baseline in PANSS total score at Week 6, as evaluated using a mixed model for repeated measurements (MMRM) under the assumption of an unstructured covariance matrix. The model included factors for pooled centre, time (including all scheduled post-Baseline visits, modelled as a categorical variable), baseline PANSS total score, treatment, and treatment-by-time interaction. The Kenward-Rogers method was used to estimate the denominator degrees of freedom. The treatment and treatment-by-time interaction terms allowed for comparisons of the treatment groups at each of the scheduled time points. P-values for the comparison of Lurasidone doses versus placebo at Week 6 were adjusted for multiple comparisons using the Hommel-based tree-gatekeeping procedure. The primary analysis was based on the Intent-to-Treat (ITT) population. The analysis was also conducted on the Per Protocol (PP) population.

In a supportive analysis, the change from baseline in PANSS total scores at scheduled visits and Week 6 last observation carried forward (LOCF) Endpoint were evaluated using an analysis of covariance (ANCOVA), with effects for Baseline total PANSS score, pooled centre and treatment.

Key Secondary: The first key secondary endpoint, the change from baseline in CGI-S at Week 6 was evaluated using the same MMRM model used for the PANSS total score, was included in the Hommel-based tree-gatekeeping procedure to adjust for multiple comparisons at Week 6. This was performed for the ITT and PP populations. The change from Baseline in CGI-S at scheduled visits and Week 6

LOCF Endpoint were also evaluated using ANCOVA, as supportive analysis, with effects for Baseline score, pooled centre and treatment.

The second key secondary endpoint, the change from Baseline in PANSS total score at Day 4 was evaluated from the same repeated measures model that produced the Week 6 estimates, and it was included in the Hommel-based tree-gatekeeping procedure.

Other Efficacy: PANSS responder rates were evaluated with logistic regression. PANSS subscores and MADRS were evaluated using MMRM and a supportive ANCOVA. For each parameter, the p-values for Week 6 treatment comparisons versus Placebo were adjusted for multiple comparisons using a Hommel procedure.

Results

Participant flow

A total of 480 subjects were to be randomised/enrolled. A total of 705 subjects consented and screened to participate, 205 subjects were screen failures, 500 subjects were randomised, and 328 subjects completed the double-blind phase.

Table 12. Participants flow.

Enrolment		Assessed for Eligibility n=705			
		Randomised n=500 /Excluded n=205			
		LUR 40 mg	**LUR 80 mg**	**LUR 120 mg**	**PBO**
Allocation	Allocated	n=125	n=123	n=124	n=128
	Received treatment	n=124	n=121	n=124	n=127
	Did not receive treatment	n=1	n=2	n=0	n=1
	Completed double blind phase	n=84 (67%)	n=86 (70%)	n=85 (69%)	n=73 (57%)
Follow-up	Discontinued due to insufficient response	n=20 (16%)	n=7 (6%)	n=18 (15%)	n=32 (25%)
	Discontinued due to adverse events	n=6 (5%)	n=8 (7%)	n=7 (6%)	n=3 (2%)
	Discontinued due to other reasons (lost to follow up, consent withdrawal, administrative)	n=15	n=22	n=14	n=20
Analysis	Analysed (ITT)	n=122 (98%)	n=119 (97%)	n=124 (100%)	n=124 (97%)
	Analysed (PP)	n=100 (80%)	n=89 (72%)	n=94 (76%)	n=102 (80%)
	Safety population	n=124 (99%)	n=121 (98%)	n=124 (100%)	n=127 (99%)

Recruitment

The first subject was enrolled on 26 October 2007; the last subject completed the double-blind phase on 15 December 2008.

Conduct of the study

The original protocol dated 21 August 2007 was amended 4 times. None of the changes in any of the amendments negatively impacted subject safety or integrity of the data collected during the course of the study.

Baseline data

Of the 496 subjects (Safety population data set), 346 (70%) were male and 150 (30%) were female. Subject age ranged from 18 to 72 years, with a mean age of 39.0 years. The plurality of subjects was White (49%), followed by Black or African American (34%), and Asian (15%). Native Americans and Native Hawaiian or Other Pacific Islanders made up less than 1% each of the Safety population.

The majority of subjects were treated in North America (55%, all in the US), while 30% of subjects were treated in Europe and 15% of subjects were treated in Asia.

Overall, the majority of subjects in the ITT population were diagnosed with paranoid-type schizophrenia (88%), followed by undifferentiated type (10%), and disorganised type (2%). Most of the subjects had 4 or more hospitalisations for schizophrenia. The average age (± SD) at initial onset of schizophrenia was 24.6 ± 8.3 years, with a range from 4 years to 57 years of age. The average age (± SD) at onset of the current episode of schizophrenia was 38.7 ± 10.5 years, with a range of 17 years to 72 years of age.

Psychiatric disorders, reported by 50% of subjects, was the most common class of pre-existing medical condition, including insomnia (43% of subjects), anxiety (32% of subjects), agitation (21% of subjects), and depression (11% of subjects). Other common pre-existing medical conditions by preferred term included: hypertension (14% of subjects), headache (11% of subjects), and drug hypersensitivity (6% of subjects). There were no meaningful differences between the treatment groups in the incidences of pre-existing medical conditions that might be expected to affect the interpretation of the safety or efficacy results.

The most commonly used concomitant medications were anxiolytics (used by 69% of subjects in the 40 mg group, 64% of subjects in the 80 mg group, 70% of subjects in the 120 mg group, and 61% of subjects in the placebo group) and hypnotics and sedatives (used by 41% of subjects in the 40 mg group, 40% of subjects in the 80 mg group, 45% of subjects in the 120 mg group, and 37% of subjects in the placebo group). The use of non-steroidal anti-inflammatory/antirheumatic products was also relatively common (used by 28% of subjects in the 40 mg group, 26% of subjects in the 80 mg group, 21% of subjects in the 120 mg group, and 24% of subjects in the placebo group). The use of anticholinergic agents increased with lurasidone dose (used by 14% of subjects in the 40 mg group, 23% of subjects in the 80 mg group, 29% of subjects in the 120 mg group, and 8% of subjects in the placebo group).

Numbers analysed

For the double-blind phase, a total of 489 (98%) subjects were analysed for efficacy (Intent-to-Treat population) and 496 (99%) subjects were analysed for safety (Safety population) (see table above for more detail).

Outcomes and estimation

Table 13: Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score – Repeated Measures (Intent-to-Treat Population).

Parameter	Estimate[a]	SE[a]	95% CI[a]	P-value[a]
Number of Subjects	486			
Lurasidone 40 mg	121			
Lurasidone 80 mg	118			
Lurasidone 120 mg	123			
Placebo	124			
Change from Baseline to Week 6				
Lurasidone 40 mg	-19.2	1.7	(-22.6, -15.7)	
Lurasidone 80 mg	-23.4	1.8	(-26.9, -19.9)	
Lurasidone 120 mg	-20.5	1.8	(-24.0, -17.1)	
Placebo	-17.0	1.8	(-20.5, -13.6)	
Contrast at Week 6[b]				
Lurasidone 40 mg versus Placebo	-2.1	2.5	(-7.0, 2.8)	0.394[a], 0.591[c]
Lurasidone 80 mg versus Placebo	-6.4	2.5	(-11.3, -1.5)	0.011[a], 0.034[c]
Lurasidone 120 mg versus Placebo	-3.5	2.5	(-8.4, 1.4)	0.163[a], 0.391[c]
Tests of Dose Response at Week 6				
Linear trend test of 0, 40, 80, 120 mg				0.063
120 mg versus 40 mg	-1.4	2.5	(-6.2, 3.5)	0.581
120 mg versus 80 mg	2.9	2.5	(-2.0, 7.8)	0.247
80 mg versus 40 mg	-4.3	2.5	(-9.1, 0.6)	0.087
Treatment x Pooled Center Interaction[d]				0.523

[a] Estimates, SEs, CIs, and p-values are based on a repeated measures linear regression model of the change from Baseline PANSS total score, with fixed effects for pooled center, visit as a categorical variable, Baseline score, treatment, and treatment by visit interaction, assuming an unstructured covariance matrix.
[b] Contrasts are from differences of change from Baseline treatment estimates for each lurasidone dose group versus placebo.
[c] Adjusted p-values were adjusted with Hommel-based tree-gatekeeping procedures.
[d] Treatment x Pooled Center Interaction p-value is based on the same model with the addition of a fixed effect for pooled center by treatment interaction included.
Abbreviations: CI = confidence interval; SE = standard error.

When comparing 80 mg lurasidone with placebo, there was a statistically significant treatment effect (p=0.034) in PANSS total score change demonstrated. To be noted however, neither the 40 mg nor the 120 mg patient group was statistically different from placebo.

One of the key secondary endpoints (CGI-S), showed a statistically significant difference favouring lurasidone 80 mg over placebo (Table 14).

Table 14: Clinical Global Impression – Severity Scale (CGI-S) Score –Change from Baseline (MMRM analysis).

Methods

Study Participants

The study recruited subjects between 18 and 75 years of age in good physical health (based on medical history, physical examination, and laboratory screening) who met DSM-IV criteria for a primary diagnosis of schizophrenia (including disorganised (295.10), paranoid (295.30), and undifferentiated (295.90) subtypes as established by clinical interview (using the Mini-International Neuropsychiatric Interview [MINI] Plus diagnostic interview). The duration of the subject's illness, whether treated or untreated, must have been greater than one year. Subjects may have had an acute exacerbation of psychotic symptoms (no longer than 2 months) and marked deterioration of function from Baseline (by history) or subject had been hospitalised for the purpose of treating an acute psychotic exacerbation for 2 consecutive weeks or less immediately before screening. Subjects had a PANSS total score ≥80 at Screening and Baseline, with a score ≥4 (moderate) on 2 or more on the following PANSS items: delusions, conceptual disorganisation, hallucinations, unusual thought content, and suspiciousness. Subject had a score ≥4 on the CGI-S at Screening and Baseline. Subject had to test negative for selected drugs of abuse at Screening and Baseline. Subject could not be pregnant (must have had a negative serum pregnancy test at screening) or nursing (must not have been lactating) and was not planning pregnancy within the projected duration of the study. A subject who was of reproductive potential must have agreed to remain abstinent or use adequate and reliable contraception throughout the study. Subject had to be able and agreed to remain off prior antipsychotic medication for the duration of the study. Subject had to have a stable living arrangement for at least 3 months prior to randomisation and agree to return to a similar living arrangement after discharge.

Treatments

Subjects who met entry criteria were to enter a 7-day placebo washout period during which they were not to receive any active antipsychotic medication. Subjects were to remain hospitalised for the duration of washout. During the washout period, subjects were to receive single-blind placebo for 7 days. Subsequently subjects were to be randomised to the acute treatment phase and were to receive blinded study medication containing lurasidone (40 mg/day or 120 mg/day) or olanzapine capsules or matching placebo. Subjects were eligible for hospital discharge after completing 21 days of double-blind treatment. All medication was to be taken once daily in the morning by mouth with a meal or within 30 minutes after eating (e.g., bowl of cereal), and with water.

Objectives

The primary objective was to evaluate the efficacy of lurasidone (40 mg/day or 120 mg/day) compared with placebo in subjects with acute schizophrenia (diagnosed by Diagnostic and Statistical Manual of Mental Disorders, 4th Ed. [DSM-IV™] criteria).

Secondary objectives included evaluation of efficacy in improving functional outcome after 6 weeks of treatment; evaluation of efficacy in improving symptoms of schizophrenia during first week of treatment; evaluation of lurasidone efficacy in reducing depressive symptoms after 6 weeks of treatment; evaluation of safety and tolerability of lurasidone in acutely schizophrenic subjects during the 6-week treatment phase.

Tertiary objectives comprised evaluating the clinical relevance of lurasidone effects along with its effects on positive subscale, negative subscale and general psychopathology subscale of PANSS. In

addition, the efficacy of olanzapine (15 mg per day) compared with placebo in subjects with acute schizophrenia (diagnosed by DSM-IV criteria) was also evaluated for assay sensitivity purposes.

Outcomes/endpoints

Primary endpoints included the mean change from Baseline in the Positive and Negative Syndrome Scale (PANSS) total score at Week 6.

The secondary and tertiary outcomes are presented in the table below.

Table 15. Study D1050231 - secondary and tertiary outcomes.

Secondary outcomes	Tertiary/Other outcomes
Mean change from Baseline in the Clinical Global Impression – Severity Scale (CGI-S) at Week 6 [key secondary];	Responder rates in the PANSS total score (responders = 20% or greater improvement from Baseline);
Mean change from Baseline in PANSS total score at Day 4.	Mean change from Baseline in the PANSS total score at Week 6 for Olanzapine 15 mg;
Mean change from Baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) at Week 6;	Mean change from Baseline in the PANSS positive subscale, negative subscale and general psychopathology subscale at Week 6.

In addition a number of safety variables were followed and recorded, namely proportions of subjects with AEs, discontinuations due to AEs, and SAEs.

Sample size

Expected improvements in PANSS ratings (and SD) were estimated from 2 prior studies of lurasidone, D1050006 and D1050196. Assuming lurasidone differed from placebo in the change from Baseline in PANSS total score by 6.8 and 10.0 for the 40 and 120 mg/day doses, respectively, and further assuming a SD of 19.1, then n=120 subjects per group provided 97% power (at the α=0.05 level, two-sided test) to reject the null hypothesis of no difference from placebo for at least one lurasidone dose. This power calculation incorporated Bonferroni's procedure for controlling pairwise differences with placebo and was obtained via computer simulations. Therefore, the study planned to enroll 120 subjects per treatment group, for a total of 480 subjects.

Randomisation

Following the screening and washout periods, subjects who continued to meet entry criteria were randomly assigned to one of four treatment arms: Lurasidone 40 mg, Lurasidone 120 mg, Olanzapine 15 mg or placebo (1:1:1:1 ratio).

Blinding

Study personnel had access to an IVRS (Interactive Voice Response System) to allocate subjects, to assign study medication to subjects, and to manage the distribution of clinical supplies. Each person accessing the IVRS was assigned an individual unique personal identification number (PIN). They were to only use their assigned PIN to access the system and were not to share their assigned PIN with anyone. The IVRS was to be used to unblind subjects and to unmask drug identity. Drug identification information was to be unmasked ONLY if necessary for the welfare of the subject. Every effort was to

be made not to unblind the subject unless necessary. Any unblinding that occurred at a site was to be documented.

Statistical methods

See above for study D1050229.

Results

Participant flow

Table 16. Participants flow.

Enrolment		Assessed for Eligibility n=781			
		Randomised n=478 /Excluded n=303			
		LUR 40 mg	**LUR 120 mg**	**Olanzapine 15 mg**	**PBO**
Allocation	Allocated	n=120	n=119	n=123	n=116
	Received treatment	n=119	n=118	n=122	n=116
	Did not receive treatment	n=1	n=1	n=1	n=0
	Completed double blind phase	n=77 (64%)	n=66 (55%)	n=84 (68%)	n=71 (61%)
Follow-up	Discontinued due to insufficient response	n=16 (13%)	n=9 (8%)	n=8 (7%)	n=18 (16%)
	Discontinued due to adverse events	n=8 (7%)	n=14 (12%)	n=8 (7%)	n=10 (9%)
	Discontinued due to other reasons (lost to follow up, consent withdrawal, administrative etc.)	n=19	n=30	n=23	n=17
Analysis	Analysed (ITT)	n=119 (99%)	n=118 (99%)	n=122 (99%)	n=114 (98%)
	Analysed (PP)	n=97 (81%)	n=84 (71%)	n=99 (80%)	n=84 (72%)
	Safety population	n=119 (99%)	n=118 (99%)	n=122 (99%)	n=116 (100%)

Recruitment

The first subject was enrolled on 31 January 2008; the last subject completed the acute phase on 16 June 2009.

Conduct of the study

The original protocol dated 18 December 2007 was amended 2 times. None of the changes in any of the amendments negatively impacted subject safety or integrity of the data collected during the course of the study.

Baseline data

Of the 475 subjects in the Safety population, 371 (78%) were male and 104 (22%) were female. Subject age ranged from 18 to 68 years, with a mean age of 37.7 years. The plurality of subjects was White (36%), followed by Black or African American (34%), and Asian (24%). Native Americans and Native Hawaiian or other Pacific Islanders made up less than 2% of the Safety population. No meaningful differences were observed between the treatment groups for any of the demographic variables. The majority of subjects were treated in North America (60%, all in the US), while 24% of subjects were treated in Asia (India and the Philippines), 10% in South America (Columbia), and 6% in Europe (Lithuania).

Overall, the majority of subjects in the ITT population were diagnosed with paranoid-type schizophrenia (86%), followed by undifferentiated type (10%), and disorganised type (4%). Almost half of the subjects (48%) had 4 or more hospitalisations for schizophrenia. The average age (± SD) at initial onset of schizophrenia was 23.8 ± 8.2 years, with a range from 6 years to 55 years of age. The average duration (± SD) of the current episode of schizophrenia (from onset to randomisation) was 34.0 ± 14.9 days, with a range of 8 days to 80 days. Concurrent other psychiatric diagnoses were rare, <1% overall in the ITT population. No treatment group had more than 1 subject with a concurrent other psychiatric diagnosis. There were no meaningful differences in the psychiatric histories comparing the individual treatment groups. The psychiatric histories of the subjects in the Safety and PP populations were similar to those reported for the ITT population. There were no meaningful differences between the treatment groups in the incidences of pre-existing medical conditions that might be expected to affect the interpretation of the safety or efficacy results.

The most commonly used concomitant medications were anxiolytics (used by 75% of subjects in the lurasidone 40 mg group, 81% of subjects in the lurasidone 120 mg group, 65% of subjects in the olanzapine group, and 73% of subjects in the placebo group) and hypnotics and sedatives (used by 58% of subjects in the lurasidone 40 mg group, 51% of subjects in the lurasidone 120 mg group, 52% of subjects in the olanzapine group, and 55% of subjects in the placebo group). A higher proportion of subjects in the lurasidone 120 mg group (41% of subjects) used anticholinergic agents compared with the lurasidone 40 mg group (20%) and the olanzapine group (18%). A smaller proportion of subjects in the placebo group (9%) used anticholinergic agents compared with subjects receiving either lurasidone or olanzapine.

Numbers analysed

For the double-blind phase, a total of 473 (99%) subjects were analysed for efficacy (Intent-to-Treat population) and 475 (99%) subjects were analysed for safety (Safety population) (see table above for more detail).

Outcomes and estimation

Table 17. Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score – Repeated Measures (Intent-to-Treat Population).

Parameter	Estimate[a]	SE[a]	95% CI[a]	P-value[a]
Number of Subjects (n=471)				
Lurasidone 40 mg (n=118)				
Lurasidone 120 mg (n=118)				
Olanzapine 15 mg (n=121)				
Placebo (n=114)				
Change from Baseline to Week 6				
Lurasidone 40 mg	-25.7	2.0	(-29.6, -21.8)	
Lurasidone 120 mg	-23.6	2.1	(-27.8, -19.4)	
Olanzapine 15 mg	-28.7	1.9	(-32.4, -24.9)	
Placebo	-16.0	2.1	(-20.1, -12.0)	
Contrast at Week 6 [b]				
Lurasidone 40 mg versus Placebo	-9.7	2.9	(-15.3, -4.1)	<0.001[a], 0.002[c]
Lurasidone 120 mg versus Placebo	-7.5	3.0	(-13.4, -1.7)	0.011[a], 0.022[c]
Olanzapine 15 mg versus Placebo	-12.6	2.8	(-18.2, -7.1)	<0.001[a]
Tests of Dose Response at Week 6				
Linear trend test of 0, 40, 120 mg				0.039
120 mg versus 40 mg	2.1	2.9	(-3.6, 7.9)	0.459
Treatment x Pooled Center Interaction[d]				0.137

[a] Estimates, SEs, CIs, df, and p-values are based on a repeated measures linear regression model of the change from Baseline PANSS total score, with fixed effects for pooled center, visit as a categorical variable, Baseline score, treatment, and treatment by visit interaction, assuming an unstructured covariance matrix.
[b] Contrasts are from differences of change from Baseline treatment estimates for each lurasidone dose group and olanzapine versus placebo.
[c] Adjusted p-values were adjusted with Hommel-based tree-gatekeeping procedures.
[d] Treatment x Pooled Center Interaction p-value is based on the same model with the addition of a fixed effect for pooled center by treatment interaction included.
Abbreviations: CI = confidence interval; df = degrees of freedom; SE = standard error.

There was a statistically significant difference between both lurasidone doses and placebo at Week 6 in the PANSS total score when the repeated measures analysis was used (primary endpoint). Olanzapine 15 mg was also statistically superior to placebo in the PANSS total score (see table 18).

Table 18. Clinical Global Impression – Severity Scale (CGI-S) Score – Change from Baseline (MMRM analysis).

Parameter	Estimate[a]	SE[a]	95% CI[a]	P-value[a]
Number of Subjects (n=473)				
Lurasidone 40 mg (n=119)				
Lurasidone 120 mg (n=118)				
Olanzapine 15 mg (n=122)				
Placebo (n=114)				
Change from Baseline to Week 6				
Lurasidone 40 mg	-1.5	0.1	(-1.7, -1.3)	
Lurasidone 120 mg	-1.4	0.1	(-1.6, -1.2)	
Olanzapine 15 mg	-1.5	0.1	(-1.7, -1.4)	
Placebo	-1.1	0.1	(-1.3, -0.9)	
Contrast at Week 6[b]				
Lurasidone 40 mg versus Placebo	-0.4	0.1	(-0.7, -0.1)	0.006[a], 0.011[c]
Lurasidone 120 mg	-0.3	0.1	(-0.6, -0.0)	0.040[a], 0.040[c]
Olanzapine 15 mg	-0.5	0.1	(-0.8, -0.2)	<0.001[a]
Tests of Dose Response at Week 6				
Linear trend test of 0, 40, 120 mg				0.098
120 mg versus 40 mg	0.1	0.1	(-0.2, 0.4)	0.521

[a] Estimates, SEs, CIs, and p-values are based on a repeated measures linear regression model of the change from Baseline score, with fixed effects for pooled center, visit as a categorical variable, Baseline score, treatment, and treatment by visit interaction, assuming an unstructured covariance matrix.
[b] Contrasts are from differences of change from Baseline treatment estimates for each lurasidone dose group versus placebo.
[c] Adjusted p-values were adjusted with Hommel-based tree-gatekeeping procedures.
Abbreviations: CI = confidence interval; SE = standard error.

Statistically significant differences favouring lurasidone 40 mg and 120 mg over placebo were demonstrated for the key secondary endpoint of CGI-S.

A statistically significant effect of lurasidone 40 and 120 mg over placebo was also observed for PANSS positive subscale scores (p=0.035; p=0.035); PANSS negative subscale scores (p=0.004; p=0.045); and PANSS general psychopathology subscale score (p=0.02; p=0.022). There was no difference comparing either lurasidone treatment group with placebo in the MADRS.

Olanzapine showed statistically significant superiority versus placebo in CGI-S (-0.5; p<0.001), PANSS positive subscale (-3.9; p<0.001), PANSS negative subscale (-2.6; p<0.001), PANSS general psychopathology subscale (-5.5, p<0.001), and MADRS (-2.3; p=0.003).

In the lurasidone 40 mg group, a significantly greater proportion of subjects (ITT population) compared with placebo showed a ≥30% improvement (p=0.018), ≥40% improvement (p=0.024), and ≥50% improvement (p=0.006) in the PANSS total score. The statistical significance held after adjustment for multiplicity, using Hommel's procedure, for all three categories (p=0.037, p=0.049, and p=0.012, respectively).

Ancillary analyses (LOCF Endpoint based on the ANCOVA model)

In the supportive analysis, there were statistically significant treatment differences of -7.9 (p=0.001) and -4.8 (p=0.049) in the change from Baseline to LOCF endpoint in PANSS total score at Week 6 when comparing the lurasidone 40 mg and 120 mg groups, respectively, with the placebo group.

Statistically significant differences in favour of lurasidone 40 mg and 120 mg over placebo were also seen for the secondary endpoints: CGI-S (p=0.012; 40 mg dose only); PANSS positive subscale (p=0.007;p=0.038); PANSS negative subscale (p=0.004; 40 mg dose only); and PANSS general psychopathology subscale (p=0.002; 40 mg dose only).

For the olanzapine group the treatment difference compared with the placebo was significant at LOCF endpoint for PANSS total score, positive, negative and general psychopathology subscales, CGI-S and MADRS.

A total of 371 subjects (78%) reported one or more TEAE. The proportion of subjects reporting one or more TEAE in the lurasidone treatment groups (79%) compared with the placebo group (72%) was similar. The proportion of subjects who discontinued treatment due to a TEAE (as reported on the termination page of the eCRF) was similar comparing subjects receiving lurasidone (9%) with placebo (9%). More subjects in the lurasidone 120 mg group (9%) discontinued from the study due to an event other than a worsening of the existing condition (as reported on the AE page of the eCRF) compared with subjects treated with placebo (4%); however, the proportion of subjects in the lurasidone 120 mg group was similar to the proportion in the olanzapine group (7%).

The proportion of subjects reported to have study medication-related TEAEs (possibly, probably, or related) was higher in the lurasidone 120 mg group (72%) and the olanzapine group (67%) compared with the lurasidone 40 mg group (59%) and the placebo group (53%).There seem to be dose dependant trend in the extrapyramidal symptoms (EPS). For more detailed safety assessment please refer to the safety sections of this report.

Short Term Efficacy Study D1050233 - A Phase 3 Randomised, Double-Blind, Placebo- And Active Comparator controlled Clinical Trial To Study The Efficacy And Safety Of Two Doses Of Lurasidone In Acutely Psychotic Subjects With Schizophrenia (Pearl 3)

Methods

Study Participants

Adult male and female subjects in good physical health between 18 and 75 years of age, inclusive, who met Diagnostic and Statistical Manual of Mental Disorders, 4th Ed. (DSM-IV-TR) criteria for a primary diagnosis of schizophrenia (including disorganised [295.10], paranoid [295.30], and undifferentiated [295.90] subtypes as established by clinical interview using the Mini-International Neuropsychiatric Interview [MINI] Plus) were eligible for inclusion in this study. The duration of the subject's illness, whether treated or untreated, must have been greater than one year. Subjects must have been experiencing an acute exacerbation of psychotic symptoms (no longer than 2 months) associated with marked deterioration in function and must have been hospitalised for the purpose of treating an acute psychotic exacerbation for two consecutive weeks or less immediately before Screening. Subjects must have had a PANSS total score ≥ 80 at Screening and Baseline, with a score ≥ 4 (moderate) on two or more on the following PANSS items: delusions, conceptual disorganisation, hallucinations, and unusual thought content. Subjects must also have had a score ≥ 4 on the CGI-S at Screening and Baseline. Subjects had to agree and be able to remain off prior antipsychotic medication for the duration of the study. Subjects could not be pregnant, nursing, or planning pregnancy within the projected duration of the study. Subjects of reproductive potential had to agree to remain abstinent or use two acceptable methods of birth control during the study. Subjects had to test negative for selected drugs of abuse at Screening and Baseline (in the event a subject tested positive for cannabinoids [tetrahydrocannabinol] or alcohol, the investigator evaluated the subject's ability to abstain from prohibited substances during

the study). Subjects must have had a stable living arrangement for at least 3 months prior to randomisation.

Treatments

During the washout period, subjects were to receive single-blind placebo for 7 days followed by either lurasidone 80 mg/day, or lurasidone 160 mg/day, or quetiapine XR 600 mg/day, or placebo. Subjects randomised to the lurasidone 80 mg dose group were started at the assigned dose of 80 mg/day and remained at that dose for the duration of the study. Subjects randomised to the lurasidone 160 mg dose group were to receive lurasidone 120 mg for Days 1 and 2, then the assigned dose of lurasidone 160 mg/day, thereafter. Subjects randomised to the quetiapine XR 600 mg dose group were to receive quetiapine XR 300 mg for Days 1 and 2, then the assigned dose of quetiapine XR 600 mg/day thereafter. All medication was to be taken once daily in the evening by mouth with a meal with water, or within 30 minutes after eating.

Objectives

Primary: To evaluate the efficacy of lurasidone (80 mg/day and 160 mg/day) compared with placebo in subjects with acute schizophrenia (diagnosed by Diagnostic and Statistical Manual of Mental Disorders, 4th Ed., Text Revision [DSM-IV-TR] criteria).

Secondary objectives included: evaluation of lurasidone efficacy in improving functional outcome after 6 weeks of treatment; evaluation of lurasidone efficacy in improving symptoms of schizophrenia during first week of treatment; evaluation of lurasidone efficacy in improving depressive symptoms after 6 weeks of treatment; evaluation of safety and tolerability of lurasidone in acutely schizophrenic subjects during the 6-week treatment phase; evaluation of lurasidone effects on specific domains. In addition, the efficacy of quetiapine XR (600 mg per day) compared with placebo in subjects with acute schizophrenia (diagnosed by DSM-IV criteria) was also evaluated for assay sensitivity purposes.

Outcomes/endpoints

Primary endpoints included the mean change from Baseline in the Positive and Negative Syndrome Scale (PANSS) total score at Week 6.

The secondary outcomes included:

- Mean change from Baseline in the Clinical Global Impression – Severity Scale (CGI-S) at Week 6 [key secondary].

Similarly to previous studies other efficacy endpoints were evaluated:

- Mean change from Baseline in PANSS total score at Day 4;
- Mean change from Baseline in the Montgomery-Asberg Depression Rating Scale (MADRS);
- Mean change from Baseline in the PANSS positive, negative, excitability and general psychopathology subscales;
- Mean change from Baseline in the PANSS total score at Week 6 for Quetiapine XR.

Moreover, responder rates in the PANSS total score (responders = 20% or greater improvement from Baseline) were also assessed.

Other efficacy variables assessed only in this study included:

- Change from Baseline in CogState computerised cognitive composite score and each of 7 cognitive domains at Week 6 and LOCF Endpoint;
- Change from Baseline in Negative Symptom Assessment (NSA-16) total score at Week 6 and LOCF Endpoint;
- Change from Baseline in UCSD Performance-based Skills Assessment Brief Version (UPSA-B) total score at Week 6 and LOCF Endpoint;
- Change from Baseline in Epworth Sleepiness Scale (ESS) total score at Week 3, Week 6, and LOCF Endpoint;
- Change from Baseline in Quality of Well-Being Scale-Self Administered Version (QWB-SA), at Week 6 and LOCF Endpoint;
- Change from Baseline in Medication Satisfaction Questionnaire (MSQ) score at Week 6 and LOCF Endpoint.

In addition a number of safety variables were followed and recorded, namely proportions of subjects with AEs, discontinuations due to AEs, and SAEs.

Sample size

The planned sample sizes of N=120 for lurasidone 80 mg/d and N=120 for lurasidone 160 mg/d versus N=120 for placebo will provide 82% power (all significant comparisons) or 98% any-contrast power (at least one significant comparison) to test the primary hypotheses (tree gatekeeper Family F1), assuming lurasidone differs from placebo by 8 (SD=19, effect size 0.42) and 10 (SD=19, effect size 0.53) points in the PANSS total improvement score at Week 6 for the 80 mg/d and 160 mg/d doses, respectively, and to reject the null hypotheses of no difference from placebo in at least 1 lurasidone dose. These power calculations are based on results from the Monte Carlo computer simulation, using the expected effect size from Phase II lurasidone studies (D1050006 and D1050196). The overall family-wise Type I error rate is maintained at 5%.

The planned sample sizes of N=120 for lurasidone 80 mg/d and N=120 for lurasidone 160 mg/d versus N=120 for quetiapine XR provide 91% power (at least one significant comparison) to detect an expected effect size of 0.4 for improvement in the cognitive composite score at Week 6, rejecting the null hypotheses of no treatment difference from quetiapine XR in at least one dose of lurasidone.

Randomisation

Following the screening and washout periods, subjects who continue to meet entry criteria were randomly assigned to 1 of 4 double-blind treatment arms: lurasidone 80 mg/day, lurasidone 160 mg/day, placebo, or quetiapine XR 600 mg/day (1:1:1:1 ratio).

Blinding

The placebo washout phase was single-blind such that the investigator was not be blinded. The treatment period was double-blind. A unique subject number was be assigned by the Interactive Voice Response System (IVRS) when a subject entered the screening phase. Each subject received 1 subject number. Following the 3- to 7-day washout period, subjects who continued to meet eligibility criteria were randomised to treatment in a double-blind fashion via the IVRS. The unique subject number allocated a subject to a particular treatment group and identified the subject for data collection purposes.

Statistical methods

Primary: The primary efficacy parameter was the mean change from Baseline in PANSS total score at Week 6. It was evaluated using a mixed model for repeated measurements (MMRM) model with an unstructured variance-covariance matrix. The model included factors for pooled centre, time (including all scheduled post-Baseline visits, modelled as a categorical variable), Baseline PANSS total score, treatment, and treatment-by-time interaction. The Kenward-Rogers method was used to estimate the denominator degrees of freedom. The treatment and treatment-by-time interaction terms allowed for comparisons of the treatment groups at each of the scheduled time points. P-values for the comparison of lurasidone doses versus placebo at Week 6 were adjusted for multiple comparisons using the Hommel-based tree-gatekeeping procedure. The primary analysis was based on the Intent-to-Treat (ITT) population. The analysis was also conducted on the Per Protocol (PP) population.

In the supportive analyses for the ITT and PP populations, the mean change from Baseline in PANSS total scores at scheduled visits and Week 6 last observation carried forward (LOCF) Endpoint were evaluated using an analysis of covariance (ANCOVA) model, with effects for Baseline total PANSS score, pooled centre, and treatment.

Key Secondary: In the key secondary endpoint for the ITT and PP populations, the mean change from Baseline in CGI-S score at Week 6 was evaluated using the same MMRM model used for the PANSS total score. This was included in the Hommel-based tree-gatekeeping procedure to adjust for multiple comparisons at Week 6.

The mean change from Baseline in CGI-S score at scheduled visits and Week 6 LOCF Endpoint were also evaluated using ANCOVA, as supportive analyses, with effects for Baseline score, pooled centre, and treatment.

Other Efficacy: The PANSS responder rates were evaluated with logistic regression. The PANSS subscores and symptom factor scores were evaluated using MMRM and a supportive ANCOVA. MADRS, CogState Computerised Cognitive Battery, UPSA-B, NSA-16, ESS, QWB-SA, MSQ were evaluated using ANCOVA.

Results

Participant flow

Table 19. Participants flow.

Enrolment		Assessed for Eligibility n=668			
		Randomised n=488 /Excluded n=180			
		LUR 80 mg	**LUR 160 mg**	**Quetiapine XR (600 mg)**	**PBO**
Allocation	Allocated	n=125	n=121	n=120	n=122
	Completed double blind phase	n=89 (71%)	n=93 (77%)	n=97 (81%)	n=74 (61%)
Follow-up	Discontinued due to insufficient response	n=16 (13%)	n=12 (10%)	n=6 (5%)	n=28 (23%)
	Discontinued due to adverse events	n=5 (4%)	n=4 (3%)	n=4 (3%)	n=5 (4%)

	Discontinued due to other reasons (lost to follow up, consent withdrawal, administrative)	n=15	n=12	n=13	n=15
Analysis	Analysed (ITT)	n=125 (100%)	n=121 (100%)	n=116 (97%)	n=120 (98%)
	Analysed (PP)	n=103 (82%)	n=105 (87%)	n=102 (85%)	n=96 (79%)
	Safety population	n=125 (100%)	n=121 (100%)	n=119 (99%)	n=121 (99%)

Recruitment

The first subject was enrolled on 21 October 2008; the last subject completed the acute phase on 02 June 2010.

Conduct of the study

The original protocol dated 27 May 2008 was amended 3 times. None of the changes in any of the amendments negatively impacted subject safety or integrity of the data collected during the course of the study.

Baseline data

Of the 486 subjects in the Safety population, 332 (68%) were male and 154 (32%) were female. Subject age ranged from 18 to 65 years, with a mean age of 37.2 years. The majority of subjects were White (57%), followed by Black or African American (20%), and Asian (20%). American Indian or Native Alaskan and Native Hawaiian or other Pacific Islanders had 1 subject (< 1%) in the Safety population. No meaningful differences were observed among treatment groups for any of the demographic variables.

The highest proportion of subjects treated was 43% in Europe (18% in Russia, 15% in the Ukraine, and 10% in Romania), while 31% of subjects were treated in North America (all in the US), 20% in Asia (India), and 5% in South America (Colombia).

Overall, the majority of subjects in the ITT population were diagnosed with paranoid-type schizophrenia (92%), followed by undifferentiated type (7%), and disorganised type (< 1%). Approximately half the subjects (50%) had 4 or more hospitalisations for schizophrenia. The average age (± SD) at initial onset of schizophrenia was 25.0 ± 8.2 years, with a range from 0 years (data in initial onset of schizophrenia only collected information on year. Subject 23318803 had an initial schizophrenia onset date in 1991and her birthday was 12 June 1991, therefore the initial onset age was recorded as 0) to 53 years of age. The average duration (± SD) of the current episode of schizophrenia (from onset to randomisation) was 31.7 ± 13.2 days, with a range of 8 days to 73 days. Concurrent other psychiatric diagnoses were rare; the most common other concurrent psychiatric diagnoses were major depression and insomnia, each reported in 2 subjects (Table 14.1.3.8). There were no meaningful differences in the psychiatric histories comparing the individual treatment groups. The psychiatric histories of the subjects in the Safety and PP populations were similar to those reported for the ITT population.

There were no meaningful differences between the treatment groups in the incidences of pre-existing medical conditions that might be expected to affect the interpretation of the safety or efficacy results.

A higher proportion of lurasidone-treated subjects were reported to have used anticholinergic agents (16% in the lurasidone 80 mg group and 17% in the lurasidone 160 mg group) compared with the quetiapine XR group (8%) and the placebo group (< 1%).

The most commonly used concomitant medications were anxiolytics (used by 54% of subjects in the lurasidone 80 mg group, 51% of subjects in the lurasidone 160 mg group, 53% of subjects in the quetiapine XR group, and 64% of subjects in the placebo group) and hypnotics and sedatives (used by 27% of subjects in the lurasidone 80 mg group, 26% of subjects in the lurasidone 160 mg group, 25% of subjects in the quetiapine XR group, and 32% of subjects in the placebo group). The higher frequency of anxiolytic usage in the placebo group relative to the 3 active medication groups may be reflective of a relative lack of efficacy of the placebo. A higher proportion of lurasidone-treated subjects were reported to have used anticholinergic agents (16% in the lurasidone 80 mg group and 17% in the lurasidone 160 mg group) compared with the quetiapine XR group (8%) and the placebo group (< 1%).

Numbers analysed

A total of 668 subjects consented and were screened to participate, 180 subjects were screen failures, 488 subjects were randomised, and 353 subjects completed the study. A total of 482 subjects were analysed for efficacy (Intent-to-Treat population) and 486 subjects were analysed for safety (Safety population).

Outcomes and estimation

Table 20. Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score – Repeated Measures (Intent-to-Treat Population).

Parameter Estimate	[a] SE	[a] 95%	CI[a] P-value	[a]
Number of subjects (n = 482)				
Lurasidone 80 mg (n = 125)				
Lurasidone 160 mg (n = 121)				
Quetiapine XR 600 mg (n = 116)				
Placebo (n = 120)				
Change from Baseline to Week 6				
Lurasidone 80 mg	-22.2	1.8	(-25.7, -18.7)	
Lurasidone 160 mg	-26.5	1.8	(-30.0, -23.0)	
Quetiapine XR 600 mg	-27.8	1.8	(-31.3, -24.2)	
Placebo -1	0.3	1.8	(-13.9, -6.7)	
Contrast at Week 6 [b]				
Lurasidone 80 mg versus Placebo	-11.9	2.6	(-16.9, -6.9)	< 0.001[a], < 0.001[c]
Lurasidone 160 mg versus Placebo	-16.2	2.5	(-21.2, -11.2)	< 0.001[a], < 0.001[c]
Quetiapine XR 600 mg versus Placebo -17.5		2.6	(-22.5, -12.4) <	0.001[a]
Tests of Dose Response at Week 6				
Linear trend test of 0, 80, 160 mg				< 0.001
160 mg versus 80 mg	-4.3	2.5	(-9.2, 0.6)	0.085
Treatment x Pooled Center Interaction[d]				0.430

[a] Estimates, SEs, CIs, and p-values were based on a mixed model for repeated measures linear regression model of the change from Baseline PANSS total score, with fixed effects for pooled center, visit as a categorical variable, Baseline score, treatment, and treatment by visit interaction, assuming an unstructured covariance matrix.
[b] Contrasts were from differences in change from Baseline at Week 6 for each lurasidone dose group and quetiapine XR versus placebo.
[c] Adjusted p-values were obtained with Hommel-based tree-gatekeeping procedures.
[d] Treatment x Pooled Center Interaction p-value was based on the same model with the addition of a fixed effect for pooled center by treatment interaction included.
Abbreviations: CI = confidence interval; SE = standard error.

The primary efficacy measure (change in total PANSS score from baseline to Visit 6) differentiated all active treatments from placebo in ITT population.

Table 21. Clinical Global Impression – Severity Scale (CGI-S) Score – Repeated measures (Intent-to-Treat Population).

Parameter Estimate	[a] SE	[a] 95% CI[a]	P-value [a]
Number of subjects (n = 482)			
Lurasidone 80 mg (n = 125)			
Lurasidone 160 mg (n = 121)			
Quetiapine XR 600 mg (n = 116)			
Placebo (n = 120)			
Change from Baseline to Week 6			
Lurasidone 80 mg	-1.5	0.1	(-1.7, -1.3)	
Lurasidone 160 mg	-1.7	0.1	(-1.9, -1.5)	
Quetiapine XR 600 mg	-1.7	0.1	(-1.9, -1.5)	
Placebo -0	.9	0.1	(-1.1, -0.7)	
Contrast at Week 6 [b]			
Lurasidone 80 mg versus Placebo	-0.6	0.1	(-0.8, -0.3)	< 0.001[a], < 0.001[c]
Lurasidone 160 mg versus Placebo	-0.8	0.1	(-1.1, -0.6)	< 0.001[a], < 0.001[c]
Quetiapine XR 600 mg versus Placebo -0.8		0.1	(-1.1, -0.5)	< 0.001[a]
Tests of Dose Response at Week 6			
Linear trend test of 0, 80, 160 mg				< 0.001
160 mg versus 80 mg	-0.3	0.1	(-0.5, 0.0)	0.057

[a] Estimates, SEs, CIs, and p-values were based on a repeated measures linear regression model of the change from Baseline score, with fixed effects for pooled center, visit as a categorical variable, Baseline score, treatment, and treatment by visit interaction, assuming an unstructured covariance matrix.
[b] Contrasts were from differences of change from Baseline treatment estimates for each lurasidone dose group versus placebo.
[c] Adjusted p-values were obtained with Hommel-based tree-gatekeeping procedures.
Abbreviations: CI = confidence interval; SE = standard error.

The CGI-S scores also confirmed the superiority of all three active treatments over the placebo ($p<0.001$).

All treatment groups differentiated from placebo at Day 4. The results for PANSS subscores were also in line with the results for the total score. Similarly, PANSS responder analysis confirmed the superiority of all three active treatments against the placebo.

All three active treatment arms also showed statistically significant superiority over placebo in respect to the improvements of MADRS.

A total of 294 subjects (60.5%) reported one or more TEAE. The proportion of subjects reporting one or more TEAE was similar in all groups: lurasidone combined group (60.2%), quetiapine XR group (59.7%), and placebo group (62.0%). The proportion of subjects who discontinued treatment due to a TEAE (as reported on the termination page of the eCRF) was also similar across all groups: lurasidone combined group (4%), quetiapine XR group (3%), and placebo group (4%). The proportion of subjects reported to have study medication-related TEAEs (possibly, probably, or related) was lowest in the placebo group (29.8%) followed by the lurasidone 80 mg group (40.8%), the quetiapine XR group (47.9%), and the lurasidone 160 mg group (49.6%). A greater proportion of subjects in the lurasidone treatment groups were reported with EPS-related TEAEs (12.2%) than in the quetiapine XR group (5.9%) or the placebo group (0.8%), although the lurasidone frequencies did not appear to vary with dose. A smaller proportion of subjects in the lurasidone treatment groups and the placebo group were reported with metabolic TEAEs (1.6% and 2.5%, respectively) than in the quetiapine XR group (7.6%).

Ancillary analyses (LOCF Endpoint based on the ANCOVA model)

There were statistically significant treatment differences in primary efficacy endpoint (total PANSS scores at Week 6) between Baseline and study endpoint when comparing the results from 80 mg and 160 mg groups to placebo using ANCOVA at LOCF endpoint ($p<0.001$). The ANCOVA analysis of the change in CGI-S score from Baseline to LOCF Endpoint demonstrated a significant treatment difference comparing the lurasidone 80 mg group (-0.6, $p < 0.001$) and the lurasidone 160 mg group (-0.8, $p < 0.001$) with placebo. The ancillary analysis confirmed the significant difference between placebo and treatment groups in total PANSS scores at Day 4.

There was a significant treatment difference in both the lurasidone 80 mg group (-2.0, $p = 0.002$ and -2.9, $p < 0.001$, respectively) and the lurasidone 160 mg group (-1.9, $p = 0.004$ and -3.3, $p < 0.001$, respectively) compared with placebo in the MADRS total score at LOCF endpoint.

ANCOVA analysis of scores from additional tools used in the study showed improvement in lurasidone groups as compared with placebo in NSA-16, QWB-SA, UPSA-B and MSQ scores, while the results from CogState Computerised Cognitive Battery and Epworth Sleepiness Scale did not show significant differences versus placebo.

A total of 294 subjects (60.5%) reported one or more TEAE. The proportion of subjects reporting one or more TEAE was similar in all groups: lurasidone combined group (60.2%), quetiapine XR group (59.7%), and placebo group (62.0%).

The proportion of subjects who discontinued treatment due to a TEAE (as reported on the termination page of the eCRF) was also similar across all groups: lurasidone combined group (4%), quetiapine XR group (3%), and placebo group (4%). The proportion of subjects reported to have study medication-related TEAEs (possibly, probably, or related) was lowest in the placebo group (29.8%) followed by the lurasidone 80 mg group (40.8%), the quetiapine XR group (47.9%), and the lurasidone 160 mg group (49.6%). A greater proportion of subjects in the lurasidone treatment groups were reported with EPS-related TEAEs (12.2%) than in the quetiapine XR group (5.9%) or the placebo group (0.8%), although the lurasidone frequencies did not appear to vary with dose. A smaller proportion of subjects in the lurasidone treatment groups and the placebo group were reported with metabolic TEAEs (1.6% and 2.5%, respectively) than in the quetiapine XR group (7.6%). For more detailed safety assessment please refer to the safety sections of this report.

Long-term efficacy studies

Study D1050234 - A Phase 3 Randomised, Double-Blind, Active Comparator-Controlled Clinical Trial to Study the Safety and Efficacy of Lurasidone in Subjects with Schizophrenia (PEARL 3 Extension Study).

Methods

Study Participants

To be eligible subject had to agree to participate by providing written informed consent, complete all required assessments on the final study visit (Day 42, Visit 10) in Study D1050233 and be judged by the investigator to be suitable for treatment in an outpatient setting.

Treatments

Subjects who met entry criteria continued treatment with either flexibly dosed lurasidone or quetiapine XR (QXR), based on their treatment assignment in Study D1050233 in a double-blinded fashion. Subjects previously treated with either 80 or 160 mg/day of lurasidone or placebo were to be treated with lurasidone 120 mg/day for Days 0 to 6. Likewise, subjects previously treated with quetiapine XR (600 mg) were to be treated with quetiapine XR 600 mg/day for Days 0 to 6. Beginning on Day 7, the dose of study medication could be adjusted (40 to 160 mg/day for lurasidone; 200 to 800 mg/day for quetiapine XR) if deemed clinically appropriate by the treating psychiatrist.

Objectives

The primary objective of the study was to evaluate the long-term maintenance of antipsychotic efficacy of lurasidone (40 to 160 mg/day, flexibly dosed) compared with quetiapine XR (200 to 800 mg/day, flexibly dosed) in subjects with schizophrenia who have demonstrated clinical response to a 6-week course of treatment with either lurasidone or quetiapine XR in Study D1050233.

Secondary objectives included:

- Evaluation of the efficacy of lurasidone compared with quetiapine XR in the treatment of impaired cognition associated with schizophrenia at Endpoint (Month 6);
- Evaluation of the safety and tolerability of lurasidone as measured by the proportion of subjects with adverse events (AEs), discontinuations due to AEs, and serious AEs (SAEs);
- Evaluation of the long-term efficacy, safety, and tolerability of lurasidone compared with quetiapine XR.

Outcomes/endpoints

The primary efficacy endpoint was time to relapse of psychotic symptoms defined as the earliest occurrence of any of the following*:*

- Worsening of ≥ 30% Positive and Negative Syndrome Scale (PANSS) total score from D1050233 Day 42 and CGI-S ≥ 3*;*
- Re-hospitalisation for worsening of psychosis;
- Emergence of suicidal ideation, homicidal ideation, and/or risk of harm to self or others.

Other endpoints included the PANSS total score, CGI-S score, PANSS subscores, MADRS total score, NSA-16 total score , Epworth Sleepiness Scale (ESS), the Quality of Well-Being Scale, Self-Administered Version (QWB-SA), CogState computerised cognitive composite score and individual domain scores, and UPSA-B total score.

The primary safety endpoints included evaluation of Adverse events (AEs); discontinuations due to AEs; and serious AEs (SAEs).

Sample size

All subjects completing Study D1050233 were eligible for the present study. No formal sample size estimation was carried out.

Blinding

Subjects who met entry criteria and provided informed consent were assigned a new subject number by the Interactive Voice Response System (IVRS). The IVRS assigned a new subject number to be used for the duration of the present study. As the primary objective of the present study was to evaluate the maintenance of antipsychotic efficacy, subjects continued double-blind treatment with either lurasidone or quetiapine XR, based on their treatment assignment in Study D1050233. Subjects who had been assigned to placebo in D1050233 were switched to lurasidone. Subjects and study personnel were not blinded to dose level. They remained blinded to treatment (lurasidone or quetiapine XR) for the duration of the study.

Statistical methods

Primary Analysis – Time to Relapse

The primary efficacy analysis was a comparison of time to relapse of psychotic symptoms between lurasidone (40 to 160 mg/day, flexibly dosed) and quetiapine XR (200 to 800 mg/day, flexibly dosed). The population for the relapse analysis (Relapse population) included those subjects who demonstrated clinical response (a CGI-S score ≤ 4 and at least a 20% decrease [improvement] in PANSS total score from Baseline) to 6 weeks of treatment with either lurasidone or quetiapine XR in the core study and then took at least one dose in the extension study (D1050234) of either lurasidone (Lur-Lur) or quetiapine XR (QXR-QXR). Differences in time to relapse between the Lur-Lur group and the QXR-QXR group were analysed using a Cox proportional hazards model with country as a covariate. Lurasidone was demonstrated as non-inferior to quetiapine XR in preventing relapse if the upper limit of the 95% confidence interval for the hazard ratio was no greater than a non-inferiority margin of 1.93.

Other Efficacy Analyses

Efficacy information for subjects who received placebo in Study D1050233 was summarised and analysed separately from subjects who were assigned to active treatment.

Analyses of the PANSS total score, PANSS subscores (Positive, Negative, General Psychopathology, Excitability, and Cognition), PANSS Symptom Factor Scores (Positive, Negative, Depression/Anxiety, Disorganised Thought, and Hostility), CGI-S scores, MADRS total score, NSA-16 total score, ESS total score, MSQ score, QWB-SA total score, CogState computerised cognitive scores, and UPSA-B total score were based on a mixed models for repeated measurement (MMRM) model with restricted maximum likelihood estimation under the assumption of an unstructured covariance matrix.

Safety Analyses

The safety data including AEs, laboratory values, electrocardiogram (ECG), and vital signs were summarised and subjected to clinical review.

Results

Participants flow

A total of 353 subjects (72%) completed the 6-week phase of the D1050233 study. Of the subjects who completed the 6-week phase of the study, 83% (292 subjects) continued into the D1050234 extension phase, with 72 (58%) subjects from the lurasidone 80 mg group, 79 (65%) subjects from the lurasidone 160 mg group, 85 (73%) subjects from the quetiapine XR group, and 56 (47%) subjects from the placebo group continuing into the extension phase. A total of 140 subjects completed the study (107 lurasidone-treated subjects and 33 quetiapine XR-treated subjects).

Recruitment

The first subject was enrolled in study D1050233 on 21 October 2008; the first subject started study D1050234 on 08 December 2008, the last subject completed study D1050234 on 01 June 2011.

Conduct of the study

Overall, 45 subjects (21%) were excluded from the Relapse population due to one or more major protocol deviation to form the PP population. The most common protocol deviation was "did not have post-extension Baseline efficacy measurement," with 17 Lurasidone-treated subjects (12%) and 13 quetiapine XR-treated subjects (16%) not having a post-extension Baseline efficacy measurement. Overall, 14 subjects (6%) did not have ≥ 14 days of continuous exposure, 8 lurasidone-treated subjects (6%) and 6 quetiapine XR-treated subjects (8%).

Baseline data

Of the 292 subjects in the Safety population, 195 subjects (67%) were male and 97 subjects (33%) were female. Subject age ranged from 18 to 65 years, with a mean age of 37.6 years. The majority of subjects were White (60%), followed by Asian (22%), and Black or African American (15%). No meaningful differences were observed among treatment groups for any of the demographic variables.

The highest proportion of subjects treated was 48% in Europe (20% in the Ukraine, 19% in Russia, and 9% in Romania), while 24% of subjects were treated in North America (all in the US), 23% in Asia (all in India), and 5% in South America (all in Colombia).

The majority of subjects in the ITT population were diagnosed with paranoid-type schizophrenia (94%), followed by undifferentiated type (5%), and disorganised type (1%). Almost half the subjects (47%) had 4 or more hospitalisations for schizophrenia. The average age (± SD) at initial onset of schizophrenia was 25.5 ± 8.2 years, with a range from 3 to 53 years of age. The average duration (± SD) of the current episode of schizophrenia (from onset to randomisation in the core D1050333 study) was 31.7 ± 12.5 days, with a range of 8 days to 71 days. Concurrent other psychiatric diagnoses were rare; major depression, acute psychosis, agoraphobia, insomnia, and enuresis were diagnosed in one subject each. There were no meaningful differences in the psychiatric histories comparing the individual treatment groups. The psychiatric histories of the subjects in the Relapse, Safety, and PP populations were similar to those reported for the ITT population.

The most commonly used concomitant medications were anxiolytics (used by 33% of lurasidone-treated subjects and 32% of quetiapine XR-treated subjects), anticholinergic agents (used by 20% of lurasidone-treated subjects and 6% of quetiapine XR-treated subjects), and hypnotics and sedatives (used by 15% of lurasidone-treated subjects and 11% of quetiapine XR-treated subjects).

Numbers analysed

The 292 received at least one dose of Study D1050234 study medication and were evaluated for safety, 256 were evaluated for efficacy (ITT population), and 218 subjects were analysed for the primary analysis of relapse (Relapse population).

Outcomes and estimation

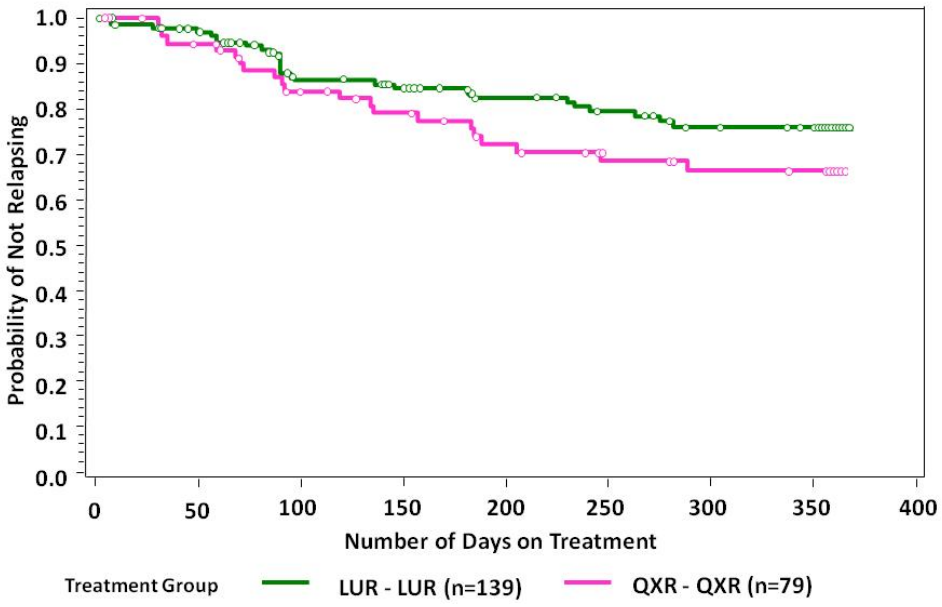
The results for the primary endpoint - Time to relapse - are presented in the table below.

Table 22. Time to Relapse of Psychotic Symptoms in Study D1050234 (Relapse Population).

Parameter	Lur-Lur (N = 139)	QXR-QXR (N = 79)	Total (N = 218)
Time to Relapse[a]			
Number of subjects relapsed (%)[b]	29 (21)	21 (27)	50 (23)
Number of subjects censored (%)[b]	110 (79)	58 (73)	168 (77)
Kaplan-Meier 25th percentile (days)	369	184	276
95% CI	(184, 376)	(91, -)	(183, 376)
Kaplan-Meier median (days)	376	-	376
95% CI	(-, -)	(-, -)	(-, -)
Kaplan-Meier 75th percentile (days)	376	-	376
95% CI	(-, -)	(-, -)	(-, -)
Kaplan-Meier Estimate of Probability of Relapse			
Month 3 (up to Day 91)	0.120	0.143	0.128
Month 6 (up to Day 182)	0.155	0.224	0.179
Month 12 (up to Day 364)	0.237	0.336	0.271
Cox Proportional Hazards Model[c]			
Country: p-value			0.015
Treatment: p-value			0.280
Hazard Ratio: Lurasidone versus Quetiapine XR			
Estimate			0.728
95% CI			(0.410, 1.295)

[a] Relapse was defined as the earliest occurrence of any of the following: Worsening of ≥ 30% PANSS total score from Study D1050233 Day 42 and CGI-S ≥ 3; re-hospitalization for worsening of psychosis; and/or emergence of suicidal ideation, homicidal ideation, and/or risk to self or others.
[b] Percentages were based on the number of subjects in the Relapse population.
[c] Estimates, p-values, hazard ratio for the 2 treatments groups, and hazard ratio 95% CI were based on a Cox proportional hazards regression model with fixed effects for treatment and country.
Abbreviations: CI = confidence interval.

Figure 1. Kaplan-Meier Plot of Time to Relapse in Study D1050234 (Relapse Population).



The probability of relapse at Month 12 was 23.7% for lurasidone and 33.6% for Quetiapine XR. The relapse HR comparing lurasidone vs. Quetiapine XR was 0.728 (95% CI [0.410, 1.295]). The upper

limit of the 95% CI was below the predefined non-inferiority threshold (1.93). The Kaplan-Meier estimate of the probability of relapse is presented in Table 22 and Figure 1.

The PANSS total score continued to decrease from the extension Baseline through Month 12 in the Lur-Lur group (-5.0, 95% CI: -7.8, -2.1), while it increased in the QXR-QXR group (1.7, 95% CI: -2.4, 5.9). In the analysis of the change from the core Baseline contrasting the Lur-Lur group with the QXR-QXR group, there were significant treatment differences from Month 3 (-4.7, p = 0.022) through Month 12 (-8.9, p = 0.006).

The CGI-S remained stable through Month 12 after the initial decrease in the Lur-Lur group, from a change of -1.9 (95% CI: -2.0, -1.8) at Day 42 to -1.9 (95% CI: -2.1, -1.7) at Month 12. In the QXR-QXR group, CGI-S increased from -1.8 (95% CI: -2.0, -1.7) at Day 42 to -1.6 (95% CI: -1.9, -1.4) at Month 12. In the analysis of the change from the core Baseline contrasting the Lur-Lur group with the QXR-QXR group, there were statistically significant treatment differences at Month 6 (-0.4, p = 0.003) and Month 9 (-0.6, p < 0.001). At Month 12, the treatment difference was -0.3 (p = 0.069).

In the Lur-Lur group, scores continued to decrease through to Month 12 for all of the PANSS subscores. For the QXR-QXR group, scores continued to decrease through Month 12 in the PANSS Negative subscore and the Cognition subscore, but increased overall from the extension Baseline to Month 12 for the PANSS Positive subscore, the General Psychopathology subscore, and the Excitability subscore. In the analysis of the change from the core Baseline, there were significant treatment differences at Month 12 contrasting the Lur-Lur group with the QXR-QXR group for the Positive subscore (-2.7, p = 0.002), the General Psychopathology subscore (-4.3, p = 0.012), the Excitability subscore (-1.3, p = 0.003), and the Cognition subscore (-1.1, p = 0.037).

MADRS total score increased slightly after Day 42 of Study D1050233 through Month 12 in both the Lur-Lur and the QXR-QXR groups, from a change of -6.2 (95% CI: -6.9, -5.5) at Day 42 to -6.0 (95% CI: -7.2, -4.8) and a change of -5.3 (95% CI: -6.3, -4.4) to -3.8 (95% CI: -5.6, -2.1), respectively at Month 12. In the analysis of the change from the core Baseline contrasting the Lur-Lur group with the QXR-QXR group, there were statistically significant treatment differences at Month 3 (-1.4, p = 0.045) and Month 12 (-2.2, p = 0.043), but not at Month 6 (-1.4, p = 0.074).

For the other secondary endpoints the analyses of the change from the extension Baseline were consistent with the changes seen at Day 42 in the analyses of changes from the core Baseline.

132 lurasidone-treated subjects (All-Lur, 63.8%) and 61 quetiapine XR-treated subjects (71.8%) reported one or more TEAE. In subjects who had received lurasidone since the beginning of the core Baseline (Lur-Lur, Study D1050233), 97 subjects (64.2%), reported one or more TEAE, which was similar to the proportion of quetiapine XR-treated subjects, with a difference in proportion of -7.5% (95% CI: -19.4%, 5.4%). In the All-Lur group, 30 subjects (14.5%) were reported with EPS-related TEAEs. A greater proportion of subjects in the Lur-Lur group were reported with EPS-related TEAEs (18 subjects, 11.9%) compared with the QXR-QXR group (3 subjects, 3.5%), with a treatment difference of 8.4% (95% CI: 1.0%, 15.4%). When comparing the Lur-Lur group with the QXR-QXR group, the proportion of subjects with metabolic TEAEs was similar, with a treatment difference of -3.3% (95% CI: -12.4%, 4.0%).

Ancillary analyses

The applicant received the scientific advice from the CHMP Scientific Advice Working Party on the development programme for lurasidone. The working party expressed concerns about the study design including:

- the randomisation. The CHMP SA concluded that a trial can only be accepted as an extension if the populations correspond to the initially randomised groups;

- the impact of dose adjustments in the early phase of the D1050234 study and the inclusion of a sub-therapeutic dose of quetiapine XR (200 mg) within a flexible dosing range;

- the duration of the initial trial that which may not have allowed for true stabilisation with potential carried over effects from the previous short-term (6 week) study D1050233 to the extension and maintenance of effect study D1050234 with an increased risk for discontinuation due to relapse during the initial phase of that study.

The Applicant performed post-hoc sensitivity analyses to address the critical issues pertinent to the study design.

The analysis considered to be crucial by the CHMP included all ITT subjects from study D1050233 except for placebo subjects with a relapse event artificially assigned at Baseline for those who did not enter Study D1050234. In this analysis, the HR (CI) of lurasidone versus quetiapine XR increased to 1.08 (95% CI: 0.79, 1.49) due to the greater number of lurasidone subjects being assigned an early "relapse". It was concluded that non-inferiority remained consistent with the primary analysis.

Another post-hoc sensitivity analyses was performed after excluding those subjects who ever received quetiapine XR 200 mg/day (n=4). It did not support a significant difference in risk for relapse between the lurasidone and quetiapine patient groups, most likely due to the low number that were treated with the expected sub-therapeutic dose of 200 mg.

Furthermore, the impact of the length of the stabilisation phase, and analyses considering alternative definitions for response in the short-term study, Study D1050233, and relapse in the long-term efficacy study, Study D1050234, were explored. It was concluded by the Applicant that the results of those post-hoc sensitivity analyses were consistent with the primary analysis.

Sensitivity analyses were additionally performed based on key Baseline characteristics between lurasidone and quetiapine XR in the subset of originally randomised subjects included in the Relapse and ITT Populations in Study D1050234. It was concluded that the results of these post-hoc sensitivity analyses support a comparable baseline for the efficacy evaluations in the subsequent extension phase.

Study D1050237 - Long-Term Safety, Tolerability, and Effectiveness of Lurasidone in Subjects with Schizophrenia or Schizoaffective Disorder: A Randomised, Active Comparator-Controlled Trial (Double-Blind Phase)

Methods

Study Participants

The study included subjects between 18 to 75 years with DSM-IV criteria for a primary diagnosis of schizophrenia, including disorganised (295.10), paranoid (295.30), undifferentiated (295.90), catatonic (295.20), or residual (295.60) or schizoaffective disorder (295.70) subtypes, as established by a structured diagnostic interview (Mini-International Neuropsychiatric Interview [MINI]-Plus) and application of DSM-IV subtypes who agreed to participate in the study. The duration of the subject's illness, whether treated or untreated, must have been at least one year. Only schizophrenic subjects were permitted to participate in the sub-study. Subject must have been "clinically stable" (non-acute phase of illness) for at least 8 weeks prior to Baseline defined as CGI-S ≤ 4 (at both Screening and

Baseline); No change in antipsychotic medications (minor dose adjustments for tolerability purposes were permitted) for at least 6 weeks prior to Screening; No hospitalisation for psychiatric illness for at least 8 weeks prior to Screening; Moderate or less (≤ 4) severity rating on PANSS Positive Scale Items (at both Screening and Baseline) for Delusions (P1); Conceptual Disorganisation (P2); Hallucinations (P3); Unusual Thought Content (G9). Subject could not be pregnant (negative serum pregnancy test at Screening) or nursing (not be lactating) and was not planning pregnancy within the projected duration of the study. Subjects of childbearing age needed to agree to remain abstinent or use adequate and reliable contraception throughout the study. Subjects needed to test negative on the urine drug test for drugs of abuse at Screening. Subjects would comply with the study procedures and outpatient visit requirements in the opinion of the investigator.

Treatments

Lurasidone was to be dosed at 80 mg/day for Days 1 to 7, after which the dose could be adjusted to between 40 and 120 mg/day. Risperidone was to be dosed at 2 mg/day for Day 1 and Day 2 and then increased to 4 mg/day on Day 3. Beginning with Day 8, risperidone dosing could be adjusted to between 2 and 6 mg/day. Flexible dosing of study medication earlier than Day 8 required approval by the Medical Monitor.

Lurasidone 40 mg oral tablets with matching placebo and risperidone over-encapsulated oral capsules (containing 2, 4, or 6 mg) with matching placebo were utilised in a double-dummy design. All study medication was blinded (double-blind) at the beginning of the double-blind phase. Subjects could participate in day hospital or outpatient programs throughout all phases of the study.

All study medication was to be taken once daily by mouth with the morning meal or within 30 minutes after eating. Subjects who experienced sedation, with investigator concurrence, could take the study medication with their evening meal; this change in dosing schedule was permitted after Week 1 and was to be recorded in the eCRF. If a subject elected to take his/her dose in the evening, then the subject was to continue to take the study medication in the evening for the remainder of the study.

Objectives

The primary objective of the long-term safety study was to assess the safety and tolerability of lurasidone in up to 12 months of double-blind treatment, followed by 6 months of open-label treatment, in clinically stable outpatients with chronic schizophrenia or schizoaffective disorder.

Furthermore treatments effects on metabolic, endocrinologic and ophthalmic function were assessed.

Other objectives consisted of the evaluation of the long-term efficacy of lurasidone and risperidone including the maintenance of clinical stability and relapse prevention.

Outcomes/endpoints

Safety was assessed by the proportion of subjects with: Adverse events (AEs); Discontinuations due to AEs; Serious AEs (SAEs).

The main secondary endpoints included: changes in weight, body mass index (BMI), waist circumference, serum prolactin, testosterone, N-telopeptide (NTx), osteocalcin, bone alkaline phosphatase, parathyroid hormone (PTH), and ECG parameters; changes in BMD for subjects treated with lurasidone and risperidone after 6, 12, and 18 (lurasidone only) months using dual-energy x-ray absorptiometry (DXA) scans (cognition sub-study centres); ophthalmologic assessments for lurasidone and risperidone groups after 6, 12, and 18 (lurasidone only) months of treatment (cognition sub-study centres);

Relapse was defined as the earliest occurrence of any of the following:

- Worsening of > 30% PANSS total score from Baseline (Day 0) and CGI-S > 3;
- Re-hospitalisation for worsening of psychosis;
- Emergence of suicidal ideation, homicidal ideation, and/or risk of harm to self or others.

The other efficacy endpoints assessed were: change in Positive and Negative Syndrome Scale (PANSS) total and subscale scores; change in Clinical Global Impression – Severity of Illness (CGI-S) scores; change in Montgomery-Asberg Depression Rating Scale (MADRS) scores.

Sample size

A non-inferiority log-rank test with the planned sample size of 600 subjects using a 2:1 allocation ratio of lurasidone (N = 400) versus risperidone (N = 200) has approximately 85% power at a 0.025 significance level to demonstrate non-inferiority of lurasidone relative to risperidone in preventing relapse over a 1-year double-blind period, based on the following assumptions:

A1. A non-inferiority hazard ratio margin of 1.6 (hazard rate 0.058 in the lurasidone group to 0.036 in the risperidone group) in log-rank test, corresponding to the non-inferiority margin 0.15 for difference in survival estimate of relapse rate between lurasidone (0.50) and risperidone (0.35) after 1 year;

A2. True (actual) hazard ratio = 1 (equivalence in actual hazard rate between lurasidone and risperidone).

Therefore, the planned sample size of 400 lurasidone and 200 risperidone subjects would provide 85% power to demonstrate if lurasidone was as effective as risperidone in preventing relapse using a non-inferiority hazard ratio margin of 1.6, or a non-inferiority margin of 0.15 for the upper of two-sided 95% confidence limit of the risk difference (lurasidone minus risperidone) in survival estimate of relapse rates after 1 year. The planned sample size could detect an effect size of 0.398 for a difference between the two treatments with 90% power in a two-sided test at a 0.05 level of significance.

Randomisation

Subjects who met entry criteria were randomised (2:1 ratio) to receive, starting on Study Day 1, either lurasidone 80 mg/day or risperidone 2 mg/day.

Blinding

Study personnel had access to the IVRS to allocate subjects, to assign study medication to subjects, and to manage the distribution of clinical supplies. Each person accessing the IVRS was assigned an individual unique personal identification number (PIN). They were to only use their assigned PIN to access the system and were not to share their assigned PIN with anyone.

The IVRS was to be used to unblind subjects and to unmask study medication identity. Study medication identification information was to be unmasked ONLY if necessary for the welfare of the subject. Every effort was to be made not to unblind the subject unless necessary. Any unblinding that occurred at a study centre was to be documented.

Statistical methods

A response maintenance analysis for relapse rate was performed using a Cox regression survival model including terms for treatment and pooled centre. Time to relapse (days) is defined as: date of relapse – date of first study medication + 1. Subjects who did not relapse, including those who withdrew early

and did not meet the criteria for relapse, were censored on the last dose of study medication in the double-blind phase. Subjects who did not complete the double-blind phase, but entered into the open-label extension phase due to lack of drug supply, were censored on the last dose of double-blind study medication. Subjects who were lost to follow-up immediately following randomisation and had no time-to-event outcomes were considered having been on treatment 1 day without an event. Non-inferiority for lurasidone relative to risperidone was assessed by comparing the upper bound of the 95% confidence interval (CI) for the hazard ratio from a Cox proportional hazards model with the non-inferiority margin of 1.6.

The observed PANSS total score, PANSS subscores, CGI-S score, and MADRS score at each planned visit were analysed using a mixed model for repeated measurement (MMRM, i.e., mixed-effects longitudinal data analysis [LDA]) model with adjustment for Baseline and pooled centre effects. The mixed-effects model included fixed effects terms for time (as a categorical variable), pooled centre, and treatment-by-time interaction. The response (dependent) variables consisted of the observed scores in individual visits, including the Baseline visit, using the Baseline adjusted mixed-effects model. Without the main effect of treatment in this model, the analysis estimated an overall mean of the efficacy variable at Baseline for both treatment groups combined. The change from Baseline value for efficacy parameters was also evaluated at each planned visit and Month 12 last observation carried forward (LOCF) Endpoint using an analysis of covariance (ANCOVA), with effects for Baseline score, pooled centre, and treatment.

Safety: The change from Baseline value for selected laboratory parameters and bone turnover markers was evaluated using a nonparametric rank ANCOVA with adjustment for Baseline at Month 12 LOCF Endpoint. The change from Baseline for DXA parameters was evaluated at each planned visit and Month12 LOCF Endpoint using an ANCOVA, with effects for Baseline parameter score, pooled centre, and treatment.

Results

Participants flow

A total of 1090 subjects provided informed consent and were screened to participate in the current study, 461 (42%) of whom were screen failures. Of the 629 subjects who were randomised to receive study medication, 427 subjects were randomised to receive lurasidone and 202 subjects were randomised to receive risperidone.

Recruitment

The first subject was enrolled on 17 March 2008; the last subject completed the double blind phase on 23 July 2010 and the extension phase on 28 January 2011.

Conduct of the study

The original protocol dated 10 December 2007 was amended 3 times.

Baseline data

Of the 621 subjects in the Safety population, 428 (69%) were male and 193 (31%) were female. Subject age ranged from 18 to 73 years, with a mean age of 41.7 years. The majority of subjects were Black or African American (51%), followed by White (38%), Other (6%), and Asian (3%). Native Americans and Native Hawaiian or other Pacific Islanders made up less than 2% of the Safety population. No meaningful differences were observed between the treatment groups for any of the

demographic variables. The majority of subjects were treated in North America (66%, all in the US), while 15% of subjects were treated in Africa (South Africa), 14% in South America (Argentina [6%], Brazil [4%], and Chile [4%]), 4% in Asia (Thailand [3%] and Israel [< 1%]), and 2% in Europe (Croatia).

Overall, the majority of subjects in the Safety population were diagnosed with paranoid-type schizophrenia (72%), followed by undifferentiated type (9%), disorganised type (6%), residual type (6%), and catatonic type (< 1%). Schizoaffective disorder was the diagnosis in 6% of subjects. Almost half of the subjects (47%) had 3 or more hospitalisations for schizophrenia. The average age (± SD) at initial onset of schizophrenia or schizoaffective disorder was 24.5 ± 9.3 years, with a range from 3 years to 57 years of age. Concurrent other psychiatric diagnoses were rare. Neither treatment group had more than one subject with a concurrent other psychiatric diagnosis. There were no meaningful differences in the psychiatric histories comparing the individual treatment groups. The psychiatric histories of the subjects in the Safety and PP populations were similar to those reported for the ITT population. One difference between the treatment groups in the incidences of pre-existing medical conditions that might be expected to affect the interpretation of the safety results was in suicide attempts; 6% of subjects in the lurasidone group had a history of suicide attempt compared with 1% in the risperidone group.

The most commonly used concomitant medications were anxiolytics (used by 29% of subjects in the lurasidone group compared with 25% of subjects in the risperidone group) and hypnotics and sedatives (used by 23% of subjects in the lurasidone group compared with 21% of subjects in the risperidone group). A lower proportion of subjects in the lurasidone group (11% of subjects) used anticholinergic agents compared with the risperidone group (15%).

Numbers analysed

For the double-blind phase, a total of 608 subjects were analysed for efficacy (Intent-to-Treat population) and 621 subjects were analysed for safety (Safety population).

Outcomes and estimation

Table 23. Relapse Rate – Cox Proportional Hazards Model (Intent-to-Treat Population).

Parameter	Lurasidone (N = 410)	Risperidone (N = 198)	Total (N = 608)
Time to Relapse[a]			
Number of subjects relapsed (%)[b]	82 (20)	32 (16)	114 (19)
Number of subjects censored (%)[b]	328 (80)	166 (84)	494 (81)
Kaplan-Meier 25th percentile (days)	302	-	371
95% CI	(184, -)	(262, -)	(255, -)
Kaplan-Meier median (days)	-	-	-
95% CI	(-, -)	(-, -)	(-, -)
Kaplan-Meier 75th percentile (days)	-	-	-
95% CI	(-, -)	(-, -)	(-, -)
Kaplan-Meier Estimate of Probability of Relapse			
Week 6 (up to Day 42)	0.098	0.102	0.099
Week 12 (up to Day 84)	0.139	0.115	0.131
Month 6 (up to Day 183)	0.199	0.159	0.186
Month 12 (up to Day 364)	0.265	0.210	0.247
Cox Proportional Hazards Model[c]			
Pooled site: p-value			0.051
Treatment: p-value			0.194
Hazard Ratio: Lurasidone versus Risperidone			
Estimate			1.31
p-value			0.194
95% CI			(0.87, 1.97)

[a] Relapse was defined as the earliest occurrence of any of the following: Worsening of > 30% PANSS total score from Baseline (Day 0) and CGI-S > 3; re-hospitalization for worsening of psychosis; and/or emergence of suicidal ideation, homicidal ideation, and/or risk to self or others.
[b] Percentages are based on the number of subjects in the Intent-to-Treat population.
[c] Estimates, p-values, hazard ratio for the 2 treatments groups and hazard ratio 95% CI were based on a Cox proportional hazards regression model with fixed effects for pooled site and treatment.
Abbreviations: CI = confidence interval.

The relapse hazard ratio comparing lurasidone versus risperidone was 1.31 (95% CI: 0.87, 1.97, p = 0.194). Non-inferiority of lurasidone relative to risperidone was not demonstrated since the upper bound of the 95% CI was greater than the non-inferiority margin of 1.6. The results using the PP population were qualitatively similar. In order to evaluate the influence of potentially important Baseline covariate on relapse, Baseline PANSS total score was added to the Cox proportional hazard model as a covariate. The relapse hazard ratio comparing lurasidone versus risperidone was 1.30 (95% CI: 0.87, 1.96, p = 0.205). This was similar to the main analysis; non-inferiority of lurasidone relative to risperidone was not demonstrated.

According to the MMRM, there were no significant differences in PANSS total scores at any time during the 12-month double-blind treatment period between lurasidone and risperidone on the PANSS total score and CGI-S score.

The MADRS scores decreased from Baseline to Month 12 in both the lurasidone group (-0.8, 95% CI: -1.6, -0.0) and the risperidone group (-2.4, 95% CI: -3.4, -1.4). Contrasting the lurasidone group with the risperidone group, there were no significant treatment differences in the decrease at any time point except for Month 12 (treatment difference = 1.6, p = 0.007).

The proportion of subjects reported to have study medication-related TEAEs (possibly, probably, or related) was similar in the lurasidone group (70.2%) compared with the risperidone group (74.8%). The proportion of subjects reported with an EPS-related TEAE was also similar comparing the

lurasidone group (12.9%) with the risperidone group (15.8%). A smaller proportion of subjects in the lurasidone group (11.7%) reported at least one metabolic TEAE compared with the risperidone group (20.8%) for a difference in proportion of 9.1% (95% CI: -15.8%, -3.0%).

Ancillary analyses (LOCF Endpoint based on the ANCOVA model)

No significant treatment differences comparing the lurasidone group with the risperidone group at any time point were observed on PANSS positive, negative, general psychopathology, and cognition subscores.

According to the ANCOVA analysis, the mean CGI-S decreased significantly ($p < 0.001$) in both treatment groups from Baseline to Month 12. The change from Baseline to Month 12 (LS mean ± SE) in CGI-S was similar ($p = 0.402$) comparing the lurasidone group (-0.6 ± 0.1) with the risperidone group (-0.5 ± 0.1). There was also no difference at LOCF Endpoint ($p = 0.320$).

According to the ANCOVA analysis, there was a significant decrease in MADRS total score (LS mean ± SE) from Baseline to Month 12 in both the lurasidone group (-1.6 ± 0.4, $p < 0.001$) and the risperidone group (-2.4 ± 0.5, $p < 0.001$). Comparing lurasidone with risperidone at Month 12, there was no significant treatment difference (0.8 ± 0.6, $p = 0.229$).

Study D1050238 - A Double-Blind, Placebo-Controlled, Randomised Withdrawal Study Of Lurasidone For The Maintenance Treatment Of Subjects With Schizophrenia

The study consisted of a Screening/Washout Phase followed by an open-label stabilisation phase (up to a maximum of 24 weeks), a double-blind, randomised withdrawal phase (maximum of 28 weeks) and a follow-up 12-week open-label extension or Follow-up visit.

Methods

Study Participants

Acutely psychotic patients, male and female subjects ≥18 and ≤75 years of age with a primary diagnosis of schizophrenia including disorganised, paranoid, or undifferentiated subtypes, were eligible to be enrolled. Subject must have has had at least one prior episode of psychotic exacerbation as judged by the Investigator in the two years preceding screening. Subjects must have had a PANSS Total score ≥ 80 with a score ≥ 4 on 1 or more of any PANSS Positive subscale items at screening and open-label baseline (Visit 2), and a CGI-S score of ≥ 4 at screening and open-label baseline (Visit 2). Subject could not have been pregnant (must have a negative serum pregnancy test at screening) or nursing (must not be lactating) and is not planning pregnancy within the projected duration of the study. Female subject of reproductive potential needed to agree to remain abstinent or use adequate and reliable contraception throughout the study and for at least 30 days after the last dose of lurasidone has been taken. Subject must have been able and agrees to remain off prior antipsychotic medication for the duration of the study. Subjects must have had a stable living arrangement at the time of screening and agrees to return to a similar living arrangement after discharge, if hospitalised. Subjects must have been in good physical health on the basis of medical history, physical examination, and laboratory screening. Subjects who required concomitant medication treatment with the following agents may have been included if they have been on stable doses.

Furthermore, there were criteria set for inclusion in the double-blind phase, such that subjects had to have achieved and maintained clinical stability for a total of at least 12 weeks in the open-label phase, defined as:

- A PANSS total score ≤70, a CGI-S score <4, and a PANSS item score of ≤4 (moderate or less) on all PANSS Positive subscale items over at least 12 weeks with the allowance of 2 excursions (except during the last 4 weeks of the open-label phase) assessed at weekly study visits: an excursion is defined as a PANSS total score up to a maximum of 80 and/or a CGI-S score up to a maximum of 4 and/or a PANSS Positive subscale item score up to a maximum of 5.

- A PANSS item score of ≤4 (moderate or less) on item G8 (uncooperativeness).

- Taking a stable dose of lurasidone for the last 4 weeks of the open-label phase.

This ensured that the double-blind population consisted of subjects enrolled during an acute episode of schizophrenia that responded to lurasidone treatment and remained stable for a minimum of 3 months before entering the double-blind phase.

Treatments

During the open-label stabilisation phase patients received flexibly-dosed lurasidone 40 mg/day or 80 mg/day (which was the approved dose range for lurasidone at the study start in September 2011. Subjects who responded to lurasidone treatment and remained stable for a minimum of 12 weeks were eligible to be randomised to the double-blind phase where they received either the same dose of lurasidone as at the end of the open-label stabilisation period or matching placebo during the double-blind phase.

Hypnotics and sedatives were more frequently used concomitant to placebo compared to the study drug. About 25% of the study population received antidepressants together with placebo or lurasidone, respectively with no significant difference between these subpopulations.

Objectives

The primary objective of D1050238 was to evaluate the efficacy of lurasidone for the maintenance treatment of subjects with schizophrenia.

The secondary objectives of this study are to evaluate the safety and tolerability of lurasidone for the maintenance treatment of subjects with schizophrenia.

Outcomes/endpoints

Efficacy was assessed by the time to the first relapse event defined as one or more of the following during the double-blind phase:

- An increase from double-blind phase Baseline in both PANSS total score of ≥25% and a CGI S worsening of ≥1 point, for 2 consecutive visits, occurring no more than 10 days apart.
- At any single visit a PANSS item score of ≥5 (moderately severe) on hostility or uncooperativeness, or PANSS item score ≥5 on ≥2 items of unusual thought content, delusions, conceptual disorganisation, or hallucinatory behaviour.
- Initiation of any of the following treatment interventions for any reason, including worsening of schizophrenia, deliberate self-injury /aggressive behaviour, or suicidal ideation:
  - The initiation of an antipsychotic agent (other than the study drug lurasidone);
  - The initiation or need for an increase in dose of an antidepressant or mood stabiliser;
  - An increase of lorazepam (or equivalent) dosage ≥2 mg/day for a minimum of 3 days relative to the previous dose;

- Transfer to an increased level or increased intensity of psychiatric care;
- Initiation of electroconvulsive therapy;
- Insufficient clinical response or exacerbation of underlying disease (reported as an adverse event [AE]) as determined by the principal investigator;
- Deliberate self-injury or repeated aggressive behaviour; active suicidal or homicidal ideation or attempt;
- Psychiatric hospitalisation (voluntary or involuntary) due to worsening schizophrenia.

The secondary endpoints reported included:

- Time to all-cause discontinuation;
- PANSS Total score and PANSS subscores (positive, negative, general psychopathology and excitability).

Safety was assessed by the proportion of subjects with the following clinical and laboratory adverse events (AEs), discontinuations due to AEs, serious adverse events (SAEs).

Sample size

It was assumed that the relapse event rates at the end of the double-blind phase (Week 28) would be 30% and 50% for subjects treated with lurasidone and placebo, respectively. These assumptions were based on previous placebo-controlled randomised withdrawal studies for antipsychotics, for example, quetiapine, aripiprazole, and olanzapine. A total of 98 relapse events were required to achieve 90% power to detect the 20% difference in subjects who had relapse events at the end of the double-blind phase (Week 28) between the treatment groups using a log-rank test with 2-sided alpha level of 0.05 (EAST Version 5.2). This calculation assumed that 2 group sequential tests (1 interim analysis and the final analysis) would be performed using a rho (ρ) family spending function with ρ=2 in order to determine the stopping boundaries. Based on data safety monitoring board (DSMB) recommendation, 3 group sequential tests (2 interim analyses and the final analysis) using Haybittle-Peto boundary with Z=2.516 for 2 interim analyses were performed instead. With this plan, a total of 98 relapse events would still provide 90% power with 2-sided alpha level of 0.05 (EAST Version 5.4).

It was estimated that 244 subjects would need to be randomized in the double-blind phase to achieve 98 relapse events. In order to randomize 244 subjects, it was estimated that approximately 610 subjects (2.5 times the number of randomized subjects) would be enrolled in the open-label phase.

Randomisation and Blinding

Following the open-label phase, subjects who meet eligibility criteria were randomly assigned by IXRS to receive either lurasidone or matching placebo in a double-blind manner (1:1). Randomisation was performed at double-blind baseline (Visit 27) to ensure balance across the two treatment groups. A unique subject number was assigned by the IXRS when a subject enters the screening/washout period. Each subject was given one subject number comprised of 9 digits which allocated a subject to a particular treatment group and identified the subject for data collection purposes.

Statistical methods

The primary efficacy analysis was performed on the ITT population, which included all subjects who were randomised and received at least 1 dose of study medication in the double-blind phase. The

primary efficacy analysis for the time to relapse was performed using an unstratified log-rank test to assess the difference in survival curves between the 2 treatment groups.

A secondary efficacy analysis of time to relapse based on the per-protocol (PP) population was also performed. The PP population included all ITT subjects under specified conditions in the protocol. Change from double-blind baseline to each post-baseline visit in the following scales; PANSS total score and PANSS subscale scores; CGI-S score; Montgomery-Asberg Depression Rating Scale total score and Short Form-12 version 2 scores was analysed using a mixed model for repeated measures (MMRM). Sensitivity and subgroup analyses were also performed.

Results

Participants flow

Subject disposition data for the nonrandomised group (i.e., those who did not enter the double blind phase) in the open-label and double-blind phase of D1050238 is presented in Table 24 and 25, respectively. All subjects randomised to the double-blind phase were included in, and are equal to, the ITT population for the lurasidone and placebo treatment groups.

Table 24. Nonrandomised Subject Disposition: Open-Label Phase.

Number of Subjects	Nonrandomized n (%)
Entered OL phase (a)	391
Discontinued from OL phase	389 (99.5)
Reason for discontinuation	
Did not meet criteria for clinical stability	44 (11.3)
Insufficient clinical response	46 (11.8)
Due to worsening of existing condition on AE page	0
Not due to worsening of existing condition on AE page	46 (11.8)
AE	84 (21.5)
Associated with worsening of schizophrenia	39 (10.0)
Not associated with worsening of schizophrenia	45 (11.5)
Lost to follow-up	60 (15.3)
Protocol violation	39 (10.0)
Withdrawal of consent	96 (24.6)
Administrative	14 (3.6)
Study terminated by Sponsor	6 (1.5)
Not due to study termination by Sponsor	383 (98.0)
Insufficient clinical response or worsening of schizophrenia	85 (21.7)
Continuing into extension study	6 (1.5)

Table 25. Subject Disposition: Double-Blind Phase, All Randomised Subjects.

Number of Subjects (a)	n (%)		
	Lurasidone N=144	Placebo N=141	Total N=285
Completed the DB phase (b)	28 (19.4)	20 (14.2)	48 (16.8)
Discontinued	116 (80.6)	121 (85.8)	237 (83.2)
Relapse criteria met	43 (29.9)	58 (41.1)	101 (35.4)
AEs (c)	3 (2.1)	1 (0.7)	4 (1.4)
Lost to follow-up	2 (1.4)	5 (3.5)	7 (2.5)
Protocol violation	11 (7.6)	4 (2.8)	15 (5.3)
Withdrawal of consent	5 (3.5)	12 (8.5)	17 (6.0)
Administrative	5 (3.5)	2 (1.4)	7 (2.5)
Study terminated by sponsor	47 (32.6)	39 (27.7)	86 (30.2)
Discontinued from the DB phase for all reasons other than study terminated by Sponsor	69 (47.9)	82 (58.2)	151 (53.0)
Continuing into extension study	97 (67.4)	88 (62.4)	185 (64.9)

Recruitment

The study started in September 2011 and completed in August 2013.

Conduct of the study

The study protocol was amended twice; the amendments did not affect the study results analysis.

Baseline data

A summary of the demographic data for the double-blind phase ITT population from D1050238 by region is presented in Table 26. Demographic characteristics were well balanced across the lurasidone and placebo treatment groups in each region. The majority of subjects in each group were male (62% and 64% for US and non-US, respectively), less than 55 years old (83% and 87%), and mean ages were 44 and 40 years for US and non-US, respectively. Black or African American (65%) was the most common racial category in US subjects and White (84%) was the most common racial category in non-US subjects.

Table 26. Summary of Double-Blind Phase Demographics by Region (ITT Population).

	Statistic	Lurasidone	Placebo	Total
US				
		N=103	N=97	N=200
Sex				
Male	n (%)	63 (61.2)	61 (62.9)	124 (62.0)
Female	n (%)	40 (38.8)	36 (37.1)	76 (38.0)
Age (years)				
	Mean (SD)	44.0 (10.9)	43.7 (11.5)	43.9 (11.2)
	Median	44.0	46.0	45.0
	Min, max	18, 71	18, 63	18, 71
<55 years	n (%)	85 (82.5)	80 (82.5)	165 (82.5)
≥55 years	n (%)	18 (17.5)	17 (17.5)	35 (17.5)
<65 years	n (%)	102 (99.0)	97 (100.0)	199 (99.5)
≥65 years	n (%)	1 (1.0)	0	1 (0.5)
Race				
White	n (%)	31 (30.1)	34 (35.1)	65 (32.5)
Black or African American	n (%)	70 (68.0)	59 (60.8)	129 (64.5)
Asian	n (%)	0	1 (1.0)	1 (0.5)
American Indian or Alaska Native	n (%)	2 (1.9)	1 (1.0)	3 (1.5)
Native Hawaiian or Other Pacific Islander	n (%)	0	1 (1.0)	1 (0.5)
Other	n (%)	0	1 (1.0)	1 (0.5)
Non-US				
		N=41	N=44	N=85
Sex				
Male	n (%)	27 (65.9)	27 (61.4)	54 (63.5)
Female	n (%)	14 (34.1)	17 (38.6)	31 (36.5)
Age (years)				
	Mean (SD)	40.5 (12.3)	39.7 (13.5)	40.1 (12.9)
	Median	41.0	39.5	40.0
	Min, max	22, 64	19, 64	19,64
<55 years	n (%)	35 (85.4)	39 (88.6)	74 (87.1)
≥55 years	n (%)	6 (14.6)	5 (11.4)	11 (12.9)
<65 years	n (%)	41 (100.0)	44 (100.0)	85 (100.0)
≥65 years	n (%)	0	0	0
Race				
White	n (%)	34 (82.9)	37 (84.1)	71 (83.5)
Black or African American	n (%)	2 (4.9)	3 (6.8)	5 (5.9)
Asian	n (%)	0	0	0
American Indian or Alaska Native	n (%)	0	0	0
Native Hawaiian or Other Pacific Islander	n (%)	0	0	0
Other	n (%)	5 (12.2)	4 (9.1)	9 (10.6)

The percentages of subjects for each subtype of schizophrenia were similar between the 2 treatment groups, as well as across nonrandomised and randomised groups. The majority of subjects (approximately 90%) were diagnosed with paranoid-type of schizophrenia, though this proportion was higher in US subjects than non-US (97% vs. 66% of randomized subjects, respectively).

The baseline PANSS and CGI-S scores in the open-label study were 90 in the randomised group and 93 in the nonrandomised group, and a mean CGI-S score of 5 at Baseline, which is consistent with previous studies. Subjects who were randomised achieved a greater mean change from open-label Baseline than subjects who were nonrandomised (-36 vs. -16 for PANSS total score).

Subjects entering the double-blind phase had a mean PANSS total score of 54, which indicates that symptoms were stabilised. Baseline PANSS total and CGI-S scores were similar across the 2 treatment groups, and were consistent with PANSS scores seen in stable patients on treatment, and with having been stabilised during the open-label phase of the study (PANSS scores <70 suggest stabilisation of an

acutely symptomatic state). There was a 3.6 difference in PANSS total score, and 0.29 difference in CGI-S score, between the total US and non-US subgroups.

There was a similar distribution of medication use between the lurasidone and placebo treatment groups in the double-blind phase. There was a greater use of hypnotics and sedatives in the placebo treatment group, however the study protocol specified clear restrictions on the use of hypnotics and sedatives in relation to administration, dose and timing of dosing in relation to study assessments.

Numbers analysed

Please see below.

Outcomes and estimation

Table 27. Time to Relapse (ITT Population).

Parameter	Lurasidone (N=144)	Placebo (N=141)	Total (N=285)
Time to relapse (a)			
Number of subjects relapsed (%) (b)	43 (29.9)	58 (41.1)	101 (35.4)
Number of subjects censored (%) (b)	101 (70.1)	83 (58.9)	184 (65.6)
Kaplan-Meier median (days)	NE	192	NE
95% CI	(174, NE)	(113, NE)	(158, NE)
Kaplan-Meier estimate of probability of relapse event			
DB Week 14 (up to Day 98)	0.219	0.404	0.312
DB Week 28 (up to Day 204)	0.422	0.512	0.467
Log-rank test for treatment effect (c)			
Z-statistics			2.067
p-value			0.039*
Sensitivity analysis: Cox proportional hazard model (d)			
HR: lurasidone vs placebo			
Estimate			0.66
95% CI - Wald			(0.45, 0.98)
p-value			0.041*

Source: Table 14.2.1.1.1. NE=not estimated. * p <0.042; statistically significant.

(a) The definition of relapse event can be found in the SAP Section 6.1 of D1050238 Protocol and in Section Error! Reference source not found.. For subjects who terminated or completed study but not experienced the relapse event, time to relapse is censored at time of termination or completion.

(b) Percentages were based on the number of subjects in the population.

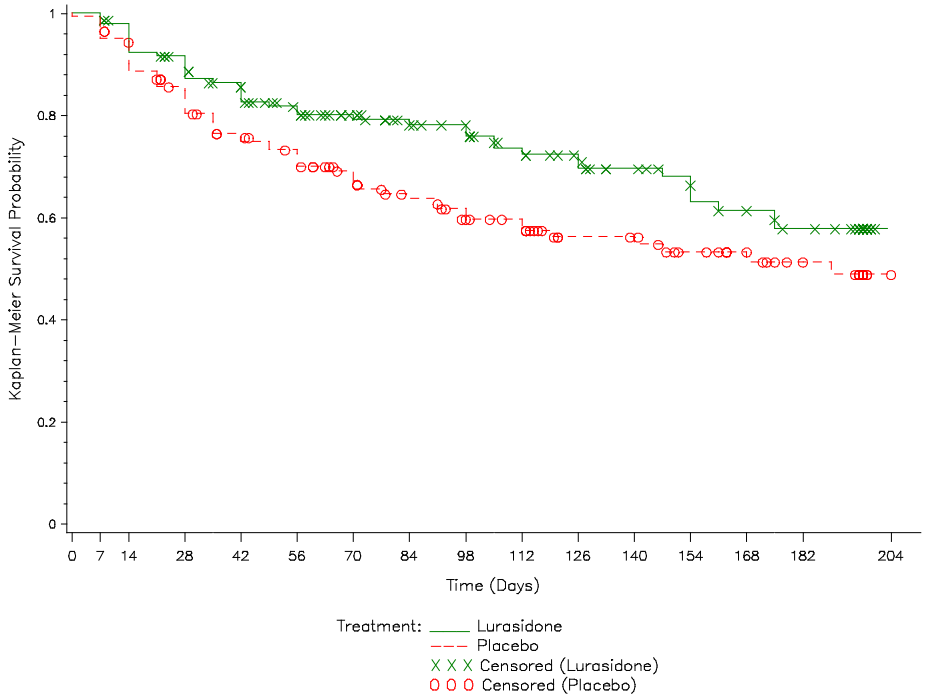
(c) The Z-statistics and p-value are based on the log-rank test with treatment as the fixed effect.

(d) Estimates, p-values, HR, and associated 95% CI were based on a Cox proportional hazard model with treatment as the fixed effects.

Overall, 35% of subjects relapsed at some point during the randomised or double-blind phase of the study, with 30% of lurasidone subjects and 41% of placebo subjects experiencing a relapse. The Kaplan-Meier estimates of relapse at Week 28 were 0.422 and 0.512 for lurasidone and placebo, respectively, and overall there was a statistically significant increase in the time to relapse for lurasidone compared with placebo (p=0.039). A sensitivity analysis performed using the Cox proportional hazard model for lurasidone vs. placebo produced a HR estimate of 0.66 (0.45, 098) and was statistically significant (p=0.041).

The time to relapse Kaplan-Meier survival plot for the ITT population is shown in Figure 2.

Figure 2. Kaplan-Meier estimates of relapse for the ITT population.



The Kaplan-Meier estimates of relapse at Week 28 and the sensitivity analysis performed using the Cox proportional hazard model for lurasidone vs placebo both supported superiority of lurasidone compared to placebo in the maintenance treatment of schizophrenia.

A summary of the relapse criteria that were fulfilled by each relapse event is presented in Table 28.

Table 28. Summary of Relapse Criteria.

	Treatment Group		
	Lurasidone (N=144)	Placebo (N=141)	Total (N=285)
Relapse Criteria, n (%)			
Met any relapse criteria	43 (29.9)	58 (41.1)	101 (35.4)
1. An increase from double-blind phase baseline in both PANSS total score of ≥25% and a CGI-S worsening.	13 (9.0)	25 (17.7)	38 (13.3)
2. At any single visit a PANSS item score of ≥5 (moderately severe) on hostility or uncooperativeness, or a PANSS item score ≥5 on ≥2 items of unusual thought content, delusions, conceptual disorganisation, or hallucinatory behavior.	16 (11.1)	29 (20.6)	45 (15.8)
3. Initiation of any of the following treatment interventions, for any reason, including worsening schizophrenia, deliberate self injury/aggressive behavior or suicidal ideation.	11 (7.6)	12 (8.5)	23 (8.1)
a) Initiation of an antipsychotic agent (other than the study drug lurasidone).	4 (2.8)	2 (1.4)	6 (2.1)
b) Initiation or need for an increase in dose of an antidepressant or mood stabilizer.	3 (2.1)	1 (0.7)	4 (1.4)
c) An increase of lorazepam (or equivalent) dosage ≥2 mg/day for a minimum of 3 days relative to the previous dose.	4 (2.8)	7 (5.0)	11 (3.9)
d) Transfer to an increased level or increased intensity of psychiatric care.	1 (0.7)	3 (2.1)	4 (1.4)
e) Initiation of electroconvulsive therapy.	0	0	0
4. Insufficient clinical response (or exacerbation of underlying disease) reported as an AE as determined by the principal investigator.	16 (11.1)	24 (17.0)	40 (14.0)
5. Deliberate self-injury or repeated aggressive behavior; active suicidal or homicidal ideation or attempt.	1 (0.7)	1 (0.7)	2 (0.7)

6. Psychiatric hospitalisation (voluntary or involuntary) due to worsening schizophrenia.	4 (2.8)	7 (5.0)	11 (3.9)

The most common reasons for relapse in the lurasidone treatment group were any single visit having a PANSS item score ≥5, and insufficient clinical response, with 11% for both categories. In the placebo treatment group the most common reason for relapse was having a PANSS item score ≥5, with 20% of subjects, Table 28.

The most common reason for relapse in the non-US subgroup the most common reason for relapse was an increase in both PANSS total score and CGI-S, with 10% and 32% of subjects, respectively. In the US subgroup the most common reason for both lurasidone and placebo treatment-groups was insufficient clinical response, with 14% and 22% respectively, but most of these also fulfilled other relapse criteria. The regional subgroup analysis indicated that the treatment effect in the non-US and European populations were statistically significant. However, in the US subgroup there was no difference in Kaplan-Meier estimates at Week 28 but the observed relapse rate for lurasidone was lower for the lurasidone group than placebo.

Time to Relapse Subgroups for lurasidone vs placebo treated patients differed between the US, non-US and EU populations. While there was a statistical significant difference in maintenance of treatment effect from lurasidone treatment exceeding that for placebo, this was only demonstrated for the non-US and EU populations. To explore potential differences in baseline subject characterisation and explain the non-significant results in the US subgroup, a post-hoc analysis was performed based on hospitalisation status at screening. This exploratory analysis showed that within the US subgroup, a further subgroup of subjects who were hospitalised at Screening, showed a numerical separation in favor of lurasidone, with an estimated HR (CI) of 0.590 (0.297, 1.174). However, there were no differences in either PANSS total scores or other demographic features at open-label baseline. This would thus imply a more favourable treatment effect within the US subgroup of patients who were hospitalised at screening compared to the out-patient subgroup.

It is of note that time to relapse was statistically significantly longer only in males treated with lurasidone compared to placebo while such an effect was not demonstrated in females. Numerically however, there were less patients relapsing following active treatment than for placebo for both genders. With regard to race, there was a statistical separation observed in the Male and Black of African American subgroups only which could be due to lower subject numbers resulting in wide CIs.

Secondary Efficacy Analyses

Time to all-cause discontinuation

There was numerical separation between lurasidone and placebo over the 28-week period in the total population, with the lurasidone treatment group having lower rates of discontinuation. The observed numerical difference in all-cause discontinuation (10%) is primarily driven by a higher proportion of placebo-treated subjects discontinuing for relapse. With regard to total discontinuation, there was a statistical significant difference between the lurasidone and placebo treated patient groups only for the non-US subpopulation. The higher discontinuation rate observed due to reasons other than relapse or study termination in the US group could be explained by this group having spent longer time in the double-blind phase than non-US subjects. The discontinuation rate in the US subpopulation did not separate between lurasidone and placebo treated subjects.

PANSS and CGI-S

During the course of the double-blind phase of the study, in the lurasidone treatment group LS mean PANSS total scores increased by 2 to 4 points in the first 6 weeks but thereafter remained broadly stable compared with Baseline. In the placebo group LS mean PANSS total score increased by approximately 6 points in the first 4 weeks and thereafter was stable compared with Baseline. Overall,

there was less increase in PANSS total score in the lurasidone group compared with the placebo group, consistent with the effect of lurasidone in maintenance of efficacy, and this was statistically significant (p=0.019). Over the course of the double-blind phase the change in CGI-S compared with Baseline was assessed at regular intervals (Weeks 1, 2, 4, and every 2 weeks thereafter). A smaller overall increase in CGI-S scores was observed from the double-blind Baseline through to Week 28 in the lurasidone group compared with placebo, consistent with the effect of lurasidone in maintenance of efficacy, and this difference was statistically significant (p=0.002).

Safety

In D1050238, there were no new safety risks identified and the overall safety and tolerability profile was consistent with previous observations from the lurasidone clinical program.

The overall safety profile of lurasidone in this study was broadly comparable to placebo during the double-blind phase. The overall rate of TEAEs in the double-blind phase was lower than previous studies. This was most likely due to the exposure of all subjects to lurasidone in the open-label phase of the study. Additionally, metabolic laboratory parameters, prolactin and weight increase were comparable to placebo. No abnormal QTc signal was observed with lurasidone treatment. No signal was noted for suicidality with lurasidone treatment.

The overall safety profile is consistent with previous observations from the lurasidone clinical program.

Summary of main studies

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).

Short term efficacy studies

Table 29**.** Summary of efficacy for trial D1050229.

Title: Short-term Efficacy Study		
Study identifier	D1050229	
Design	Randomised, fixed dose, double-blind, parallel-group, placebo-controlled study. The study comprised a screening period; a 3- to 7-day inpatient, single-blind placebo washout period; a Baseline assessment; and a 6-week double-blind treatment period (mandatory inpatient treatment during the initial 3 weeks, optional outpatient treatment thereafter).	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	6 weeks not applicable not applicable
Hypothesis	Superiority to placebo	
Treatment groups	Acutely psychotic hospitalized patients with chronic schizophrenia	3 fixed dose of lurasidone (40 mg, 80 mg and 120 mg) versus placebo. Randomized, n=500; included in the ITT population used for efficacy evaluations, n=489.
	LUR	40 mg/d, n=122, 80 mg/d, n=119 or 120 mg/d, n=124
	PBO	Placebo, n=124

Endpoints and definitions	Primary endpoint	PANSS-T	PANSS total score change from Baseline to Week 6, MMRM, ITT
	Secondary endpoint	PANSS-T	PANSS total score change from Baseline to Week 6, ANCOVA, ITT, LOCF
	Key Secondary endpoint	CGI-S	CGI-S change from Baseline to Week 6, MMRM, ITT
	Secondary endpoint	CGI-S	CGI-S change from Baseline to Week 6, ANCOVA, ITT, LOCF
	Key Secondary endpoint	PANSS-T	PANSS total score change from Baseline to Day 4, MMRM, ITT, LOCF
	Secondary endpoint	PANSS-T	PANSS total score change from Baseline to Day 4, ANCOVA, ITT, LOCF
	Secondary endpoint	PANSS	PANSS change from Baseline to Week 6 in positive syndrome, negative syndrome, and general psychopathology subscale scores, ANCOVA, ITT, LOCF
	Other	PANSS-T	PANSS total score change from Baseline to each visit, MMRM, ITT
	Other	MADRS	MADRS change from Baseline to Week 6, ANCOVA, ITT, LOCF
	Tertiary	Proportion responders (≥20%)	Proportion of responders (≥20% decrease from Baseline in PANSS Total Score), Logistic regression, ITT, LOCF
	Other	Proportion responders (≥30%, ≥40%, ≥50%)	Proportion of responders (≥30%, ≥40% or ≥50% decrease from Baseline in PANSS Total Score), Logistic regression, ITT, LOCF
Database lock	26 Oct 2007 to 15 Dec 2008		

Results and Analysis

Analysis description	**Primary Analysis**
Descriptive statistics and estimate variability	

Analysis population and time point description	The Intent-to-Treat (ITT) population was used to assess efficacy. An ANCOVA model analysis was applied to the dataset. All randomized subjects who received at least one dose of double-blind study medication and had a Baseline and at least 1 post-Baseline efficacy measure. A total of 328 subjects (66% of the randomized subjects) completed the study: 84 (67%) subjects in the lurasidone 40 mg group; 86 (70%) subjects in the lurasidone 80 mg group; 85 (69%) subjects in the lurasidone 120 mg group; and 73 (57%) subjects in the placebo group. The Hommel-based tree-gatekeeping procedure was applied to control the family-wise Type 1 error rate. The hypotheses (each lurasidone dose vs placebo) associated with the primary and key secondary variables for efficacy claim are grouped into hierarchical families. The gatekeeping procedure accounts for the logical restrictions in the problem by performing stepwise multiplicity adjustment. The hypotheses in the first and subsequent (except the last) families are performed using a truncated version of the Hommel test. Only comparisons corresponding to doses significant in the preceding step are tested. The comparisons in the last family are performed using a regular Hommel test. The truncated version of the Hommel test is defined as a convex combination of the regular Hommel test and the Bonferroni test. The resulting truncated test satisfies the separability condition. The Hommel-based tree-gatekeeping procedure controls the overall Type I error rate in the strong sense at the 5% α level.				
PANSS total score change from Baseline to Week 6, MMRM, ITT	Treatment group	PBO	LUR 40 mg	LUR 80 mg	LUR 120 mg
	Number of subject	124	121	118	123
	Estimate (SE)	-17.0 (1.8)	-19.2 (1.7)	-23.4 (1.8)	-20.5 (1.8)
	Treatment difference at week 6 (d)				
	Estimate (SE) (c)		-2.1 (2.5)	-6.4 (2.5)	-3.5 (2.5)
	95% CI (c)		(-7.0, 2.8)	(-11.3, -1.5)	(-8.4, 1.4)
	p-value		0.394 (c), 0.591 (e)	0.011 (c)*, 0.034 (e)*	0.163 (c), 0.391 (e)
Analysis description	**Secondary (S), Key secondary (KS), Tertiary analysis (T) and Other**				
PANSS total score change from Baseline to Week 6, ANCOVA, ITT, LOCF (S)	Treatment group	PBO	LUR 40 mg	LUR 80 mg	LUR 120 mg
	Number of subject	124	121	118	123
	LS mean (SE)	-14.7 (1.6)	-17.4 (1.6)	-20.8 (1.6)	-18.5 (1.6)
	Treatment difference at week 6 (d)				
	LS Mean (SE)		-2.7 (2.2)	-6.1 (2.3)	-3.8 (2.2)
	p-value		0.236	0.007**	0.086
CGI-S change from Baseline to Day 42/LOCF Endpoint in: MMRM, ITT analysis (KS)	Estimate (SE) (c)	-1.0 (0.1)	-1.1 (0.1)	-1.4 (0.1)	-1.2 (0.1)
	Treatment difference at week 6 (d)				
	Estimate (SE) (c)		-0.1 (0.1)	-0.4 (0.1)	-0.2 (0.1)

	95% CI (c)		(-0.4, 0.1)	(-0.7, -0.1)	(-0.5, 0.1)
	p-value		0.365 (c), 0.591 (e)	0.005 (c)**, 0.034 (e)*	0.169 (c), 0.543 (e)
CGI-S change from Baseline to Day 42/LOCF Endpoint in: ANCOVA analysis (S)	Treatment group	PBO	LUR 40 mg	LUR 80 mg	LUR 120 mg
	Number of subject	124	122	119	124
	LS mean (SE)	-0.8 (0.1)	-0.9 (0.1)	-1.2 (0.1)	-1.0 (0.1)
	Treatment Difference				
	LS Mean (SE)		-0.2 (0.1)	-0.4 (0.1)	-0.2 (0.1)
	p-value		0.237	0.001**	0.113
Proportion of Responders (≥20% Improvement from Baseline) at Day 42/LOCF Endpoint (T)	Treatment group	PBO	LUR 40 mg	LUR 80 mg	LUR 120 mg
	Number of subject	124	121	118	123
	n (%) of responders (e)	67 (54)	70 (58)	79 (67)	80 (65)
	p-value (f)		0.545	0.039*	0.076
Proportion of Responders (≥30% Improvement from Baseline) at Day 42/LOCF Endpoint (Other)	Treatment group	PBO	LUR 40 mg	LUR 80 mg	LUR 120 mg
	Number of subject	124	121	118	123
	n (%) of responders (e)	47 (38)	56 (46)	61 (52)	61 (50)
	p-value (f)		0.181	0.028*	0.058
Notes	The study was conducted in 48 centres including; US: 21 sites (n=278), India: 6 sites (n=66), Russia: 7 sites (n=57), Ukraine: 6 sites (n=51), Romania: 5 sites (n=37), France: 1 site (n=3), Malaysia: 2 sites (n=8). *p≤0.05; **p≤0.01 vs. placebo; (c) Estimates, SEs, CIs, and p-values are based on a MMRM model of the change from Baseline PANSS total score, with fixed effects for pooled centre, visit as a categorical variable, Baseline score, treatment, and treatment by visit interaction, assuming an unstructured covariance matrix. (e) P-values were adjusted with Hommel-based tree-gatekeeping procedures. (f) Logistic regression on response, with effects for treatment group and Baseline score.				

Table 30**.** Summary of efficacy for trial D1050231.

Title: Short-term Efficacy Study		
Study identifier	D1050231	
Design	Randomised, fixed dose, double-blind, placebo- and active controlled study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	6 weeks not applicable not applicable
Hypothesis	Superiority to placebo	

Treatment groups	Hospitalised patients with an acute exacerbation of schizophrenia		2 fixed oral doses of lurasidone (40 mg and 120 mg), olanzapine 15 mg and placebo, were respectively evaluated over 6 weeks. Randomized, n=478; included in the ITT population used for efficacy evaluations n=473.
	Lurasidone		40 mg/d, n=119 or 120 mg/d, n=118
	Olanzapine		15 mg/day, n=122
	PBO		Placebo, n=114
Endpoints and definitions	Primary endpoint	PANSS-T	PANSS total score change from Baseline to Week 6, MMRM, ITT
	Secondary endpoint	PANSS-T	PANSS total score change from Baseline to Week 6, ANCOVA, ITT, LOCF
	Key Secondary endpoint	CGI-S	CGI-S change from Baseline to Week 6, MMRM, ITT free text
	Secondary endpoint	CGI-S	CGI-S change from Baseline to Week 6, ANCOVA, ITT, LOCF
	Secondary endpoint	PANSS-T	CGI-S change from Baseline to Day 4, ANCOVA, ITT, LOCF
	Tertiary	PANSS	PANSS change from Baseline to Week 6 in positive syndrome, negative syndrome, and general psychopathology subscale scores
	Other	PANSS-T	PANSS total score change from Baseline to each visit, MMRM, ITT
	Other	MADRS	MADRS change from Baseline to Week 6, ANCOVA, ITT, LOCF
	Tertiary	Proportion responders (≥20%)	Proportion of responders (≥20% decrease from Baseline in PANSS Total Score), Logistic regression, ITT, LOCF
	Other	Proportion responders (≥30%, ≥40%, ≥50%)	Proportion of responders (≥30%, ≥40% or ≥50% decrease from Baseline in PANSS Total Score), Logistic regression, ITT, LOCF
Database lock	31 Jan 2008 to 16 June 2009		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	The Intent-to-Treat (ITT) population was used to assess efficacy. An ANCOVA model analysis was applied to the dataset. All randomized subjects who received at least one dose of double-blind study medication and had a Baseline and at least 1 post-Baseline efficacy measure. Of the subjects in the ITT population (n=473), 119 subjects received lurasidone 40 mg, 118 subjects received lurasidone 120 mg, 122 subjects received olanzapine 15 mg, and 114 subjects received placebo. A total of 51 subjects (34% of the randomized subjects) completed the study: 16 (32%) subjects in the lurasidone 40 mg group; 20 (41%) subjects in the lurasidone 120 mg group, and 15 (30%) subjects in the placebo group. The Hommel-based tree-gatekeeping procedure was used to adjust for multiple comparisons, taking into account multiple doses and multiple endpoints (PANSS Total Score at Week 6 [primary], and CGI-S at Week 6 [key secondary]). The Hommel-based tree-gatekeeping procedure was applied to control the family-wise Type 1 error rate. The hypotheses (each lurasidone dose vs. placebo) associated with the primary and key secondary variables for efficacy claim were grouped into hierarchical families. The gatekeeping procedure accounts for the logical restrictions in the problem by performing stepwise multiplicity adjustment. The hypotheses in the first and subsequent (except the last) families were performed using a truncated version of the Hommel test. Only comparisons corresponding to doses significant in the preceding step were tested. The comparisons in the last family were performed using a regular Hommel test. The truncated version of the Hommel test was defined as a convex combination of the regular Hommel test and the Bonferroni test. The resulting truncated test satisfied the separability condition. The Hommel-based tree-gatekeeping procedure controls the overall Type I error rate in the strong sense at the 5% α level.				
PANSS total score change from Baseline to Week 6, MMRM, ITT Descriptive statistics and estimate variability	*Treatment group*	*PBO*	*LUR 40 mg*	*LUR 120 mg*	*OLA 15 mg*
	Number of subject	114	118	118	121
	Estimate (SE) (c)	-16.0 (2.1)	-25.7 (2.0)	-23.6 (2.1)	-28.7 (1.9)
	Treatment Difference at Week 6 (d)				
	Estimate (SE) (c)		-9.7 (2.9)	-7.5 (3.0)	-12.6 (2.8)
	95% CI (c)		(-15.3, -4.1)	(-13.4, -1.7)	(-18.2, --7.1)
	p-value		<0.001 (c)**, 0.002 (e)**	0.011 (c)**, 0.022 (e)*	<0.001 (c)**
Analysis description	**Secondary (S), Key Secondary (KS) and Tertiary analysis (T)**				
PANSS total score change from Baseline to Week 6, ANCOVA, ITT, LOCF (S)	*Treatment group*	*PBO*	*LUR 40 mg*	*LUR 120 mg*	*OLA 15 mg*
	Number of subject	114	118	118	121
	LS mean (SE)	-15.2 (1.7)	-23.1 (1.7)	-20.0 (1.7)	-26.7 (1.7)
	Treatment Difference				
	LS Mean (SE)		-7.9 (2.4)	-4.8 (2.4)	-11.4 (2.4)

	p-value		0.001**	0.049*	<0.001**
CGI-S change from Baseline to Week 6, MMRM, ITT (KS)	*Treatment group*	*PBO*	*LUR 40 mg*	*LUR 120 mg*	*OLA 15 mg*
	Number of subject	114	119	118	122
	Estimate (SE) (c)	-1.1 (0.1)	-1.5 (0.1)	-1.4 (0.1)	-1.5 (0.1)
	Treatment Difference at Week 6 (d)				
	Estimate (SE) (c)		-0.4 (0.1)	-0.3 (0.1)	-0.5 (0.1)
	95% CI (c)		(-0.7, -0.1)	(-0.6, -0.0)	
	p-value		0.006 (c)**, 0.011 (e)*	0.040 (c)*, 0.040 (e)*	<0.001 (c)**
CGI-S change from Baseline to Week 6, ANCOVA, ITT, LOCF (S)	*Treatment group*	*PBO*	*LUR 40 mg*	*LUR 120 mg*	*OLA 15 mg*
	Number of subject	114	119	118	122
	LS mean (SE)	-0.9 (0.1)	-1.2 (0.1)	-1.1 (1.0)	-1.4 (0.1)
	Treatment Difference at Week 6 (d)				
	LS mean (SE)		-0.3 (0.1)	-0.2 (0.1)	-0.5 (0.1)
	p-value		0.012*	0.075	<0.001**
Proportion of responders (≥20% decrease from Baseline in PANSS Total Score), Logistic regression, ITT, LOCF (T)	*Treatment group*	*PBO*	*LUR 40 mg*	*LUR 120 mg*	*OLA 15 mg*
	Number of subject	114	119	118	122
	n (%) of responders (e)	56 (49)	73 (62)	71 (60)	89 (74)
	p-value (f)		0.054	0.108	<0.001**
Proportion of responders (≥30%, ≥40% or ≥50% decrease from Baseline in PANSS Total Score), Logistic regression, ITT, LOCF (T)	Treatment group	PBO	LUR 40 mg	LUR 120 mg	OLA 15 mg
	Number of subject	114	118	118	121
	n (%) of responders (b)	43 (38)	63 (53)	55 (47)	78 (64)
	p-value (f)		0.018*	0.206	<0.001**
Notes	The study was conducted in 52 centres including; US: 25 sites (n=286), India: 14 sites (n=89), Lithuania: 4 sites (n=29), Philippines: 4 sites (n=26), Colombia: 5 sites (n=48) *p≤0.05; **p≤0.01 vs. placebo; (c) Estimates, SEs, CIs, and p-values are based on a MMRM model of the change from Baseline PANSS total score, with fixed effects for pooled centre, visit as a categorical variable, Baseline score, treatment, and treatment by visit interaction, assuming an unstructured covariance matrix. (e) P-values were adjusted with Hommel-based tree-gatekeeping procedures. (f) Logistic regression on response, with effects for treatment group and Baseline score.				

Table 31**.** Summary of efficacy for trial D1050233.

Title: Short-term Efficacy Study			
Study identifier	D1050233		
Design	Randomised, fixed dose, double-blind, parallel-group, placebo- and active controlled study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		6 weeks not applicable not applicable
Hypothesis	Superiority		
Treatment groups	Acutely psychotic in-patients with chronic schizophrenia.		2 fixed oral doses of lurasidone (80 mg and 160 mg) were compared to placebo and quetiapine XR treatment over 6 weeks. Randomised, n=488; included in the ITT population used for efficacy evaluations, n=482.
	Lurasidone		80 mg/d, n=125 or 160 mg/d, n=121
	Quetiapine XR		600 mg/d, n=116
	PBO		Placebo, n=120
Endpoints and definitions	Primary endpoint	PANSS-T	PANSS total score change from Baseline to Week 6, MMRM, ITT
	Secondary endpoint	PANSS-T	PANSS total score change from Baseline to Week 6, ANCOVA, ITT, LOCF
	Key Secondary endpoint	CGI-S	CGI-S change from Baseline to Week 6, MMRM, ITT
	Secondary endpoint	CGI-S	CGI-S change from Baseline to Week 6, ANCOVA, ITT, LOCF
	Secondary endpoint	PANSS-T	PANSS total score change from Baseline to Day 4, MMRM, ITT, LOCF
	Secondary endpoint	PANSS-T	PANSS total score change from Baseline to Day 4, ANCOVA, ITT, LOCF
	Secondary endpoint	PANSS	PANSS change from Baseline to Week 6 in positive syndrome, negative syndrome, and general psychopathology subscale scores
	Secondary endpoint	PANSS-T	PANSS total score change from Baseline to each visit, MMRM, ITT
	Secondary endpoint	MADRS	MADRS change from Baseline to Week 6, ANCOVA, ITT, LOCF
	Other	Responders (≥20%)	Proportion of responders (≥20% decrease from Baseline in PANSS Total Score), Logistic regression, ITT, LOCF
	Other	Responders (≥30%)	Proportion of responders (≥30%, ≥40% or ≥50% decrease from Baseline in PANSS Total Score), Logistic regression, ITT, LOCF
Database lock	21 Oct 2008 to 2 June 2010date		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	The Intent-to-Treat (ITT) population was used to assess efficacy. An ANCOVA model analysis was applied to the dataset. All randomised subjects who received at least 1 dose of double-blind study medication, and had either a PANSS or CGI-S baseline efficacy measurement as well as at least 1 post-Baseline efficacy measurement for PANSS or CGI-S were included in the assessment of efficacy. All randomised subjects who received at least 1 dose of study medication at the target dose (40 mg or 120 mg lurasidone, or placebo) and had at least 1 efficacy evaluation during the double-blind treatment period (from Day 3 or after). A total of 353 subjects (72% of the randomised subjects) completed the study: 89 (71%) subjects in the lurasidone 80 mg group; 93 (77%) subjects in the lurasidone 160 mg group; 97 (81%) subjects in the quetiapine XR 600 mg group; and 74 (61%) subjects in the placebo group. The Hommel-based tree-gatekeeping procedure was applied to control the family-wise Type 1 error rate. The hypotheses (each lurasidone dose vs. placebo) associated with the primary and key secondary variables for efficacy claim are grouped into hierarchical families. The gatekeeping procedure accounts for the logical restrictions in the problem by performing stepwise multiplicity adjustment. The hypotheses in the first and subsequent (except the last) families are performed using a truncated version of the Hommel test. Only comparisons corresponding to doses significant in the preceding step are tested. The comparisons in the last family are performed using a regular Hommel test. The truncated version of the Hommel test is defined as a convex combination of the regular Hommel test and the Bonferroni test. The resulting truncated test satisfies the separability condition. The Hommel-based tree-gatekeeping procedure controls the overall Type I error rate in the strong sense at the 5% α level.

PANSS total score change from Baseline to Week 6, MMRM, ITT Descriptive statistics and estimate variability	*Treatment group*	*PBO*	*LUR 80 mg*	*LUR 120 mg*	*QUE XR 600 mg*
	Number of subject	120	125	121	116
	Estimate (SE) (c)	-10.3 (1.8)	-22.2 (1.8)	-26.5 (1.8)	-27.8 (1.8)
	Treatment Difference at Week 6 (d)				
	Estimate (SE) (c)		-11.9 (2.6)	-16.2 (2.5)	-17.5 (2.6)
	95% CI (c)		(-16.9, -6.9)	(-21.2, -11.2)	(-22.5, -12.4)
	p-value		<0.001 (c)**, <0.001 (e)**	<0.001 (c)**, <0.001 (e)**	<0.001 (c)**

Analysis description	**Secondary analysis (SA), Key secondary analysis KS) and Other**

PANSS total score change from Baseline to Week 6, ANCOVA, ITT, LOCF (SA)	*Treatment group*	*PBO*	*LUR 80 mg*	*LUR 120 mg*	*QUE XR 600 mg*
	Number of subject	120	125	121	116
	LS mean (SE)	-9.4 (1.6)	-19.7 (1.6)	-24.2 (1.6)	-25.6 (1.7)
	Treatment Difference at Week 6 (d)				
	LS Mean (SE)		-10.4 (2.3)	-14.8 (2.3)	-16.2 (2.3)
	p-value		<0.001**	<0.001**	<0.001**

CGI-S change from Baseline to Week 6, MMRM, ITT (KS)	*Treatment group*	*PBO*	*LUR 80 mg*	*LUR 120 mg*	*QUE XR 600 mg*
	Number of subject	120	125	121	116
	Estimate (SE) (c)	-0.9 (0.1)	-1.5 (0.1)	-1.7 (0.1)	-1.7 (0.1)
	Treatment Difference at Week 6 (d)				
	Estimate (SE) (c)		-0.6 (0.1)	-0.8 (0.1)	-0.8 (0.1)
	95% CI (c)		(-0.8, -0.3)	(-1.1, -0.6)	(-1.1, -0.5)
	p-value		<0.001 (c)**, <0.001 (e)**	<0.001 (c)**, <0.001 (e)**	<0.001 (c)**
Proportion of responders (≥20% decrease from Baseline in PANSS Total Score), Logistic regression, ITT, LOCF (Other)	*Treatment group*	*PBO*	*LUR 80 mg*	*LUR 120 mg*	*QUE XR 600 mg*
	Number of subject	120	125	121	116
	n (%) of responders (e)	49 (41)	81 (65)	95 (79)	92 (79)
	p-value (f)		<0.001**	<0.001**	<0.001**
Proportion of responders (≥30%, ≥40% or ≥50% decrease from Baseline in PANSS Total Score), Logistic regression, ITT, LOCF (Other)	*Treatment group*	*PBO*	*LUR 80 mg*	*LUR 120 mg*	*QUE XR 600 mg*
	Number of subject	*120*	*125*	*121*	*116*
	n (%) of responders (b)	36 (30)	62 (50)	76 (63)	82 (71)
	p-value (c)		0.002**	<0.001**	<0.001**
Notes	US: 24 sites (n=151), India: 10 sites (n=98), Russia: 10 sites (n=87), Ukraine: 9 sites (n=76), Romania: 6 sites (n=49), Colombia: 4 sites (n=27). *p≤0.05; **p≤0.01 vs. placebo; (c) Estimates, SEs, CIs, and p-values are based on an MMRM model of the change from Baseline CGI-S, with fixed effects for pooled centre, visit as a categorical variable, Baseline score, treatment, and treatment by visit interaction, assuming an unstructured covariance matrix. (e) Adjusted p-values were adjusted with Hommel-based tree-gatekeeping procedures. (f) Logistic regression on response, with effects for treatment group and Baseline score.				

Long-term efficacy studies

Table 32**.** Summary of efficacy for trial D1050234.

Title: Long-term Efficacy Study

Study identifier	D1050234		
Design	Randomised, double-blind, flexible dose, active-controlled, extension study. Designed as extension to Study D1050233. Non-inferiority study.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		In total 52 weeks 6 weeks 45 weeks
Hypothesis	Confirmation of long-term maintenance of efficacy of lurasidone and non-inferiority to quetiapine XR in subjects with schizophrenia who demonstrated clinical response to 6 weeks of treatment with either lurasidone or quetiapine XR in Study D1050233, as measured by the time to relapse of psychotic symptoms.		
Treatment groups	Stable outpatients with schizophrenia.		
	Lurasidone		N=207. Fixed dosing 120 mg po QD, Day 1-6, Flexible dosing 40 mg-160 mg po QD from Day 7, n=207
	Quetiapine XR		N=85. Fixed dosing 600 mg po QD, Day 1-6, Flexible dosing 200 mg-800 mg po QD from Day 7, n=85
Endpoints and definitions	Primary endpoint	Time to Relapse	The earliest occurrence of a worsening of ≥30% PANSS total score from Baseline (Day 42 of Study D1050233) and a CGI-S score ≥3, re-hospitalisation for worsening of psychosis, or the emergence of suicidal or homicidal ideation, and/or risk of harm to self or others
	Secondary endpoint	PANSS-T	Change from Baseline on the PANSS total score
	Secondary endpoint	CGI-S	Change from Baseline on the CGI-S score
	Secondary endpoint	MADRS	Change from Baseline on the MADRS score
	Secondary endpoint	NSA-16	Change from Baseline on the 16-item Negative Symptom Assessment Scale
	Secondary endpoint	ESS	Change from Baseline on the Epworth Sleepiness Scale
	Secondary endpoint	QWB-SA	Change from Baseline on the Quality of Well-Being Scale, Self-Administered Version
	Secondary endpoint	CogState	CogState computerised cognitive composite score and individual domain scores
	Secondary endpoint	UPSA-B	UPSA-B total score, and safety and tolerability
Database lock	08DEC08 to 01 JUN11		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	A total of 292 subjects were eligible for inclusion (207 received lurasidone and 85 received quetiapine XR). In total, 140 subjects completed the study: 107 lurasidone-treated subjects and 33 quetiapine XR-treated subjects. All 292 patients that were included received at least 1 dose of study medication and were evaluated for safety, 256 were evaluated for efficacy and 218 were analysed for relapse.		
Primary analysis (Relapse population)	*Treatment group*	*LUR* *40 mg-160 mg*	*QUE* *200 mg-800 mg*
	Time to Relapse (a)	139	79
	Number of patients relapsed (%)	29 (21)	21 (27)
	Number of patients censored (%)	110 (79)	58 (73)
	Kaplan-Meier Estimate of Probability of Relapse		
	Month 12	23.7%	33.6%
	HR (95% CI) (b)	0.728 (0.410, 1.295)	
Analysis description	**Secondary analysis and Post Hoc Sensitivity Analyses**		
Secondary efficacy analysis (Intent-to-Treat population) (c)	PANSS Total score	N=132	N=72
	Change from extension study Baseline to Month 12 (95% CI)	-5.0 (-7.8, -2.1)	1.7 (-2.4, 5.9)
	Treatment Difference (95% CI)	-6.7 (-11.7, -1.7), p=0.010	
	Change from core study Baseline to Month 12 (95% CI)	-34.8 (-37.7, -31.9)	-26.3 (-31.1,-21.5)
	Treatment Difference (95% CI)	-8.5 (-14.1, -2.9), p=0.003	
Secondary efficacy analysis (Intent-to-Treat population) (c)	MADRS Total score	N=132	N=72
	Change from extension study Baseline to Month 12 (95% CI)	0.1 (-1.1, 1.2)	1.3 (-0.3, 3.0)
	Treatment Difference (95% CI)	-1.3 (-3.3, 0.7), p=0.216	
	Change from core study Baseline to Month 12 (95% CI)	-6.0 (-7.2, -4.8)	-3.8 (-5.6, -2.1)
	Treatment Difference (95% CI)	-2.2 (-4.3, 0.1), p=0.043	
	Treatment group	*LUR* *40 mg-160 mg*	*QUE* *200 mg-800 mg*
Post-hoc sensitivity analysis I "excluding patients who ever received Quetiapine XR	Time to Relapse (d)	N=139	N=75
	Kaplan-Meier Estimate of Probability of Relapse		

200 mg/day"	Month 12	23.7%	32.9%
	HR (95% CI)	0.737 (0.410, 1.324)	
Post-hoc sensitivity analysis II "all subjects originally randomised to LUR and QUE in D1050233 who entered D1050234, even if they did not meet clinical response criteria"	Time to Relapse (e)	N=151	N=85
	Kaplan-Meier Estimate of Probability of Relapse		
	Month 12	23.0%	35.8%
	HR (95% CI)	0.660 (0.381, 1.143)	
Post-hoc sensitivity analysis III "all ITT subjects from D1050233 with the exception of placebo and assigning a relapse event at the D1050234 baseline for those who did not enter D1050234"	Time to Relapse (f)	N=246	N=116
	Kaplan-Meier Estimate of Probability of Relapse		
	Month 12	52.7%	53.0%
	HR (95% CI)	1.084 (0.788, 1.490)	
Post-hoc sensitivity analysis IV "one of the clinical response criteria changed to "≥30% reduction in PANSS Total Score"	Time to Relapse (g)	N=139	N=75
	Kaplan-Meier Estimate of Probability of Relapse		
	Month 12	24.3%	35.0%
	HR (95% CI)	0.745 (0.406, 1.366)	
	Treatment group	*LUR 40 mg-160 mg*	*QUE 200 mg-800 mg*
Post-hoc sensitivity analysis V "one of the relapse criteria changed to "worsening of ≥20% PANSS Total Score from D1050233 Day 42"	Time to Relapse (h)	N=139	N=75
	Kaplan-Meier Estimate of Probability of Relapse		
	Month 12	11.4%	23.1%
	HR (95% CI)	0.548 (0.251, 1.196)	
Post-hoc sensitivity analysis VI "one of the relapse criteria changed to	Time to Relapse (i)	N=139	N=75
	Kaplan-Meier Estimate of Probability of Relapse		
	Month 12	21.7%	33.9%

an increase of ≥10 in PANSS total score if extension Baseline PANSS Total Score was ≤50, or worsening of ≥30% PANSS Total Score if extension Baseline PANSS Total Baseline was >50"	HR (95% CI)	0.689 (0.384, 1.235)	
Post-hoc sensitivity analysis VII "Per Protocol Population"	Time to Relapse (j)	N=139	N=75
	Kaplan-Meier Estimate of Probability of Relapse		
	Month 12	19.4%	32.9%
	HR (95% CI)	0.572 (0.301, 1.090)	
Post-hoc sensitivity analysis VIII "relapse due to re-hospitalisation only"	Time to Relapse (k)	N=139	N=75
	Kaplan-Meier Estimate of Probability of Relapse		
	Month 12	10.0%	25.2%
	HR (95% CI)	0.414 (0.189, 0.909)	
	Treatment group	*LUR 40 mg-160 mg*	*QUE 200 mg-800 mg*
Post hoc sensitivity analysis IX "relapse population, discontinuations counted as relapse events"	Time to Relapse (l)	N=139	N=79
	Kaplan-Meier Estimate of Probability of Relapse		
	Month 12	51.8%	62.03%
	HR (95% CI)	0.780 (0.541,1.125)	
Notes	The study was conducted in 58 sites altogether; US: 20 sites (n=70), India: 10 sites (n=66), Ukraine: 9 sites (n=59), Russia: 9 sites (n=55), Romania: 6 sites (n=27) and Colombia: 4 sites (n=15).		

Table 33**.** Summary of efficacy for trial D1050237.

Title: Long-term Tolerability, Safety and Efficacy Study		
Study identifier	D1050237	
Design	Intention To Treat analysis. Randomised, double-blind, flexible-dose, parallel-group, active-controlled multicentre study in clinically stable outpatients with schizophrenia	
	Duration of main phase:	12 months
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable
Hypotheses	Lurasidone displays a beneficial tolerability and safety in the treatment of adult patients with schizophrenia. Lurasidone is not non-inferior to the active comparator risperidone at clinical dosages	

Treatment groups	Clinically stable outpatients with schizophrenia.		Lurasidone at a dose-range of 40 mg-120 mg and risperidone 2-6 mg was administered orally as daily doses for the comparison of results on tolerability, safety and efficacy. Risperidone was used as the active comparator. A total of 629 subjects were randomised to lurasidone or risperidone treatment.	
	Lurasidone		n=410 (Entered=ITT/Completed, n=427/147) 80 mg oral daily dose (initial dose), and flexible 40 mg-120 mg oral daily doses beginning at Day 8	
	Risperidone		n=198 (Entered=ITT/Completed, n=202/89) 2 mg on Day 1 and 2, then 4 mg on Day 3, and flexible 2 mg-6 mg oral daily doses beginning at Day 8	
Endpoints and definitions	Primary endpoints	Long-term safety measures	The proportion of subjects with AEs, discontinuations due to AEs or serious AEs, monitored vital signs, ECGs, laboratory values, markers on bone metabolism, bone mineral density assessments, ophthalmologic assessments, and physical examinations	
	Secondary endpoints	Long-term efficacy measures	PANSS-T	LS mean change from Baseline
			CGI-S	LS mean change from Baseline
			MADRS	LS mean change from Baseline
		Time to Relapse	Non-inferiority analysis using a Cox-proportional hazards model. Non-inferiority defined as the earliest occurrence of any of the following; worsening of ≥30% in PANSS total score from Baseline (Day 0) and CGI-S ≥3; re-hospitalisation for worsening of psychosis; and/or emergence of suicidal/homicidal ideation, and/or risk of harm to self or others. Relapse percentages were based on the number of subjects in the ITT population.	
			Non-inferiority margin	1.6
Database lock	17Mar08 to 23Jul10			

Results and Analysis

Estimates, p-value, HR for the 2 treatment groups (Lurasidone vs. Risperidone) and HR 95% CI were based on a Cox proportional hazards regression model with fixed effects for pooled site and treatment.

Analyses of the PANSS total score, CGI-S and MADRS total score were based on a mixed model for repeated measurement (MMRM), based on the mean change from Baseline (Day 0). The model included factors for treatment, pooled centre, time (as a categorical variable), Baseline score, and treatment-by-time interaction. Treatment comparisons reflected differences in change from Baseline estimates between the Lurasidone and Risperidone groups.

Analysis description	**Primary Efficacy Analyses**		
Analysis population and time point description	Number of subjects entered (ITT), Total n=629; LUR n=427; RIS n=202. Number of subjects completed, Total n=236; LUR n=147; RIS n=89. Percentage of subjects completed; LUR 34%, RIS 44%.		
Descriptive statistics and estimate	Treatment group	LUR 40-120 mg	RIS 2-6 mg
	Number of subject	410	198

variability	Number of patients relapsed (%) Number of patients censored (%)	82 (20) 328 (80)	32 (16) 166 (84)
	Kaplan-Meier Estimate of Probability of Relapse		
	Month 12	26.5%	21.0%
	Hazard Ratio (96% CI)	1.31 (0.87, 1.97), p=0.194	
Effect estimate per comparison	PANSS Total Score	N=410	N=198
	Change from Baseline (Day 0) to Month 12 (95% CI)	-4.7 (-6.4,-3.0)	-6.5 (-8.8,-4.3)
	Treatment Difference (95% CI)	1.9 (-0.9, 4.6), p=0.181	
Effect estimate per comparison	CGI-S score	N=410	N=198
	Change from Baseline (Day 0) to Month 12 (95% CI)	-0.4 (-0.5, -0.3)	-0.4 (-0.5, -0.2)
	Treatment Difference (95% CI)	-0.0 (-0.2, 0.2), p=0.929	
Effect estimate per comparison	MADRS Total score	N=410	N=176
	Change from Baseline (Day 0) to Month 12 (95% CI)	-0.4 (-0.5, -0.3)	-2.4 (-3.4, -1.4)
	Treatment Difference (95% CI)	1.6 (0.4, 2.8), p=0.007	
Analysis description	**Secondary analysis**		
Effect estimate per comparison	Relapse rate	20%	16%
	Kaplan-Meier estimation; the probability of relapse at week 6 and month 12, respectively	0.098 (week 6) 0.265 (month 12)	0.102 (week 6) 0.210 (month 12)
	HR Relapse; LUR versus RIS	1.31 (95% CI: 0.87, 1.97)	
		p=0.194	
Notes	The study was conducted at 68 centres; US: 40 sites (n=417), Chile: 5 sites (n=26), South Africa: 7 sites (n=92), Argentina: 5 sites (n=38). Brazil: 4 sites (n=25), Croatia: 3 sites (n=12), Thailand: 3 sites (n=16) and Israel: 1 site (n=3)		

Table 34. Summary of efficacy for trial D1050238.

Title: A double-blind, placebo-controlled, randomised withdrawal study of lurasidone for the maintenance treatment of subjects with schizophrenia		
Study identifier	D1050238	
Design	Multicentre, double-blind, placebo-controlled, randomised withdrawal study	
	This study includes 3 phases: 1. Screening/Washout (Run-in) phase:	Duration: ≤14 days (including hospitalisation max 7 days if needed)

	2. Open-label stabilisation phase: 3. Double-blind randomised, withdrawal phase: Follow-up visit or open-label extension phase	≤12 weeks and ≤24 weeks Maximum 28 weeks
Hypotheses	Lurasidone is effective for the maintenance treatment of subjects with schizophrenia	
Treatment groups	Hospitalised or outpatients with an acute episode schizophrenia. Open-label stabilisation phase ; Lurasidone flexible oral daily dosage. Double-blind phase (up to 28 weeks); Lurasidone or placebo oral daily dosage.	Subjects aged 18-75 years with an acute episode of schizophrenia (diagnosed by Diagnostic and Statistical Manual of Mental Disorders, 4th Ed, Text Revisions [DSM-IV-TR] criteria and confirmed by SCID-CT). Lurasidone 40 mg/d or 80 mg/d. Responders and stabilised patients for a minimum of 12 weeks were eligible to be randomised to the double-blind phase. Random assignment to placebo or to continued treatment with lurasidone until completion or discontinuation from the double-blind phase. Flexible oral lurasidone dosage (40 mg to 80 mg) taken once-daily in the evening, with a meal (at least 350 calories) or within 30 minutes after eating. Lurasidone 40 mg/day on Days 1 through 3. On Day 4, a scheduled visit and thereafter, increase of dose is necessary to optimise efficacy at weekly intervals (starting from Visit 4) based on Investigator judgment. A dose reduction for tolerability purposes is permitted to occur more frequently than at weekly intervals. Subjects will continue to be flexibly dosed, as necessary, up until the last 4 weeks of their 12 week stabilisation period where the dose must remain fixed. All psychotropic medications, except those specified in the protocol, were prohibited during both the open-label phase and the double-blind phase. Dose tapering of protocol prohibited medications were done during the screening phase.
	Lurasidone Double-Blind Phase, All Randomised Subjects	Entered=ITT/Completed/Discontinued, n=144/28/116 Continuing into extension study, n=97
	Placebo	Entered=ITT/Completed/Discontinued, n=141/20/121 Continuing into extension study, n=88

<table>
<tr><td rowspan="9">Endpoints and definitions</td><td>Primary endpoints

The primary efficacy analysis was performed on the ITT population, which included all subjects who were randomised and received at least 1 dose of study medication in the double-blind phase.</td><td>Long-term efficacy Measures

Time to relapse defined as meeting any one of the following criteria:</td><td colspan="2">1. An increase from double-blind phase baseline in both PANSS Total score of ≥ 25% and a CGI-S worsening of ≥ 1 point, for two consecutive visits, occurring no more than 10 days apart.
2. At any single visit a PANSS item score of ≥ 5 (moderately severe) on hostility or uncooperativeness, or a PANSS item score ≥ 5 on ≥ 2 items of unusual thought content, delusions, conceptual disorganisation, or hallucinatory behaviour.
3. Initiation of any of the following treatment interventions, for any reason, including worsening schizophrenia, deliberate self-injury / aggressive behaviour or suicidal ideation:
a. the initiation of an antipsychotic agent (other than the study drug lurasidone)
b. the initiation or need for an increase in dose of an antidepressant or mood stabiliser
c. an increase of lorazepam (or equivalent) dosage ≥ 2 mg/day for a minimum of 3 days relative to the previous dose
d. transfer to an increased level or increased intensity of psychiatric care
e. initiation of electroconvulsive therapy.
4. Insufficient clinical response (or exacerbation of underlying disease) reported as an adverse event as determined by the Principal Investigator.
5. Deliberate self-injury or repeated aggressive behaviour; active suicidal or homicidal ideation or attempt.
6. Psychiatric hospitalisation (voluntary or involuntary) due to worsening schizophrenia.</td></tr>
<tr><td colspan="4">*The primary efficacy analysis* for the time to relapse was performed using an unstratified log-rank test to assess the difference in survival curves between the 2 treatment groups. The time to event was censored in the following cases: 1) when a subject discontinued from or completed the double-blind phase of the study without experiencing any relapse event, 2) for the interim analyses: when a subject was on-going during the double-blind phase without experiencing any relapse event at the time of database freeze for the interim analysis, or 3) for the final analysis: when an on-going subject terminated the double-blind phase without experiencing any relapse event, due to the Sponsor's decision to stop the study.</td></tr>
<tr><td rowspan="7">Secondary endpoints</td><td rowspan="7">Time to all-cause discontinuation</td><td>PANSS-T and PANSS subscores (positive, negative, general psychopathology and excitability</td><td>Change from Double-blind Baseline</td></tr>
<tr><td>GI-S</td><td>Change from Double-blind Baseline</td></tr>
<tr><td>MADRS total score</td><td>Change from Double-blind Baseline</td></tr>
<tr><td>Short Form-12v2 Health Survey (SF-12v2)</td><td></td></tr>
<tr><td>Modified SLOF total and subscale scores (social functioning and community living skills)</td><td></td></tr>
<tr><td>Brief Adherence Rating Scale</td><td></td></tr>
<tr><td>Smoking questionnaire</td><td></td></tr>
</table>

			Intent to Attend assessment	
	A *secondary analysis of time to relapse* based on the per-protocol (PP) population was performed. The PP population included all ITT subjects satisfying the following conditions; received assigned study medication as randomised; had 75% to 125% compliance after the calculated compliance was rounded to the whole number (both limit values inclusive in the double-blind phase); hand no major protocol deviations.			
			PANSS total score and PANSS subscale scores	Change from Double-blind Baseline
			CGI-s score	Change from Double-blind Baseline
			MADRS total score	Change from Double-blind Baseline
			Short Form-12 version 2 scores	Change from Double-blind Baseline
	Health Economics Endpoints		Euroqol (EQ-5D)	
			Health Services Utilisation Questionnaire (HSUQ)	
			Health Economics Exit Questionnaire	
Sensitivity Analyses	Sensitivity analyses were performed with time to relapse redefined as the following and were analysed using log-rank test on the ITT population:			
	Relapse defined as:	PANSS change from the double-blind Baseline	≥30% at any visit during the double-blind phase	
	Relapse defined as:	PANSS change from double-blind Baseline and a CGI-S worsening occurring no more than 10 days apart during the double-blind phase	≥25% ≥1 point, for 2 consecutive visits	
	Relapse defined as:	The relapse event or a discontinuation due to all other causes during the double-blind phase		
	Relapse defined as:	The relapse event or a discontinuation due to any AE during the double-blind phase		
	Relapse defined as:	An increase from double-blind Baseline in PANSS total score of ≥25% for 2 consecutive visits during the double-blind phase		
Subgroup analyses	Analyses of time to relapse and some secondary efficacy endpoints (time to all-cause discontinuations, PANSS, and CGI-S) were performed on subgroups of interest using the ITT population, and included:			
	Region (US vs. non-US sites)			
	Sex (male, female)			
	Race (White, Black, Other)			
	Age (<55 years and ≥55 years)			
Analysis description	**Primary Efficacy Analyses**			

Analysis population and time point description	Number of subjects entered (ITT), Total n=285; LUR n=144; Placebo n=141. Number of subjects completed, Total n=48; LUR n=28; Placebo n=20. Percentage of subjects completed; LUR 19.4%, Placebo 14.2%.		
Primary analysis: Time to relapse	Treatment group	LUR 40-80 mg	Placebo
	Number of subject	144	141
	Number of patients relapsed (%)	43	58
	Number of patients censored (%)	101	83
	Kaplan-Meier Estimate of Probability of Relapse at Week 28	0.422	0.512
	Hazard Ratio (95% CI)	0.66 (0.45, 0.98)	
	p-value (Log-Rank test)	0.039*	
Analysis description	**Secondary analysis**		
Time to all-cause discontinuation			
	Kaplan-Meier Estimate of Probability of all-cause discontinuation at Week 28	0.582	0.699
	HR(95% CI); LUR versus Placebo	0.75 (0.54, 1.03)	
	p-value (Log-Rank test)	0.070	
PANSS Total Score (a)		N=143	N=141
	Change from Baseline (Day 0) to Week 28 (95% CI)	3.6 (0.5, 6.7)	6.6 (3.0, 10.1)
	Treatment Difference (95% CI)	-3.0 (-7.6, 1.7)	
	p-value (overall effect of treatment)	0.019	
CGI-S score (a)		N=143	N=141
	Change from Baseline (Day 0) to Week 28 (95% CI)	0.10 (-0.07, 0.28)	0.28 (0.08, 0.48)
	Treatment Difference (95% CI)	-0.18 (-0.45, 0.09)	
	p-value (overall effect of treatment)	0.002	
MADRS Total score (a)		N=140	N=139
	Change from Baseline (Day 0) to Week 28 (95% CI)	1.7 (0.2, 3.1)	1.2 (-0.5, 2.9)
	Treatment Difference (95% CI)	0.5 (-1.8, 2.7)	

	p-value (overall effect of treatment)	0.179
Notes	US: 49 sites (n=200), Russia: 6 sites (n=16), France: 4 sites (n=5), Italy: 3 sites (n=1), Slovakia: 7 sites (n=22), Serbia: 6 sites (n=20), South Africa: 3 sites (n=21). (a) Estimates, CIs, and p-values are based on an MMRM model of the change from Baseline, with fixed effects for treatment, visit (as a categorical variable), pooled center, DB phase baseline score, and a treatment-by-visit interaction, assuming an unstructured covariance matrix. *p<0.042	

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

Short-term efficacy studies

Two comparisons of treatment effect of lurasidone 40 mg, 80 mg, 120 mg and 160 mg and placebo in the 5 pivotal short-term studies using pooled data were performed.

Figure 3. LS Mean Treatment Difference (95% CI) for PANSS Total Score Change from Baseline to LOCF Endpoint: ANCOVA Analysis.

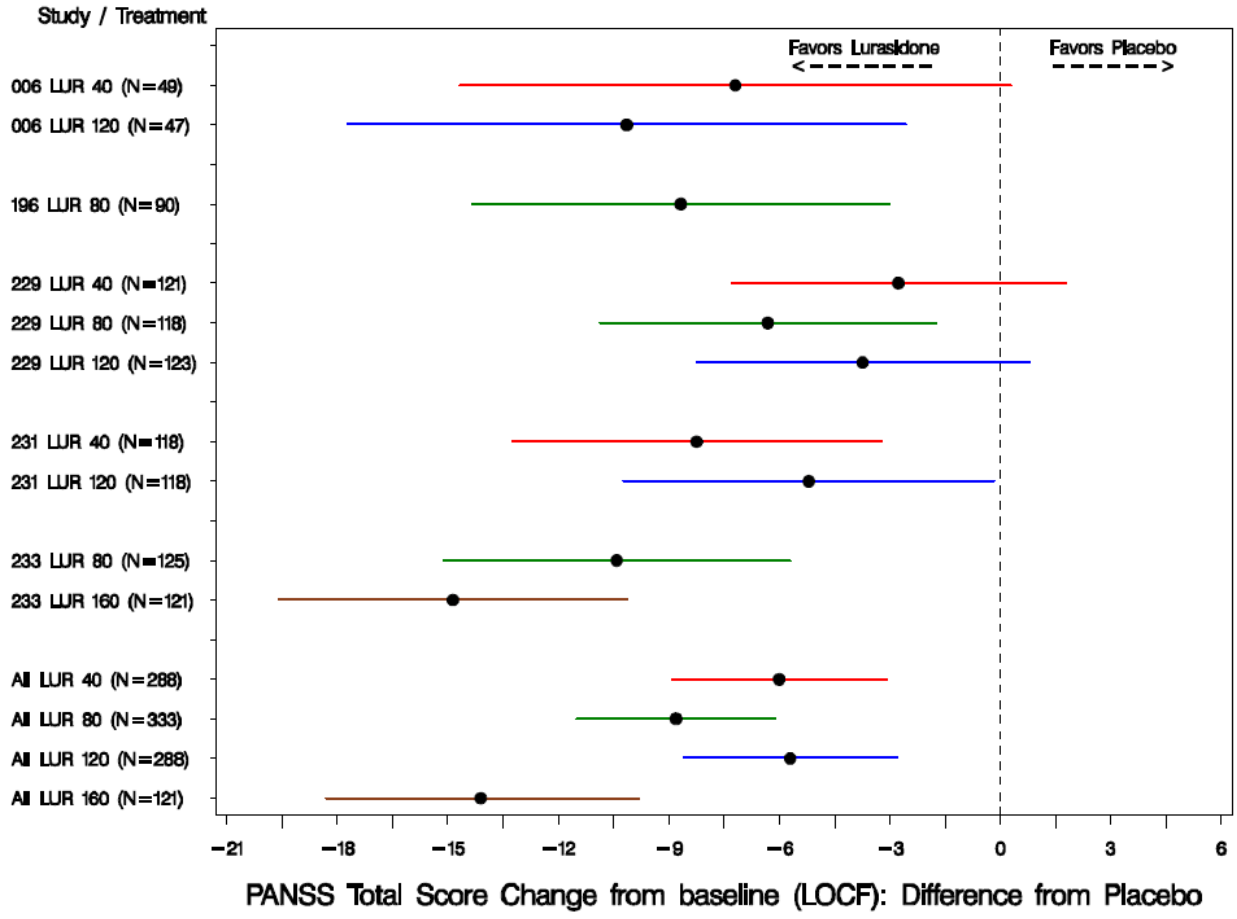
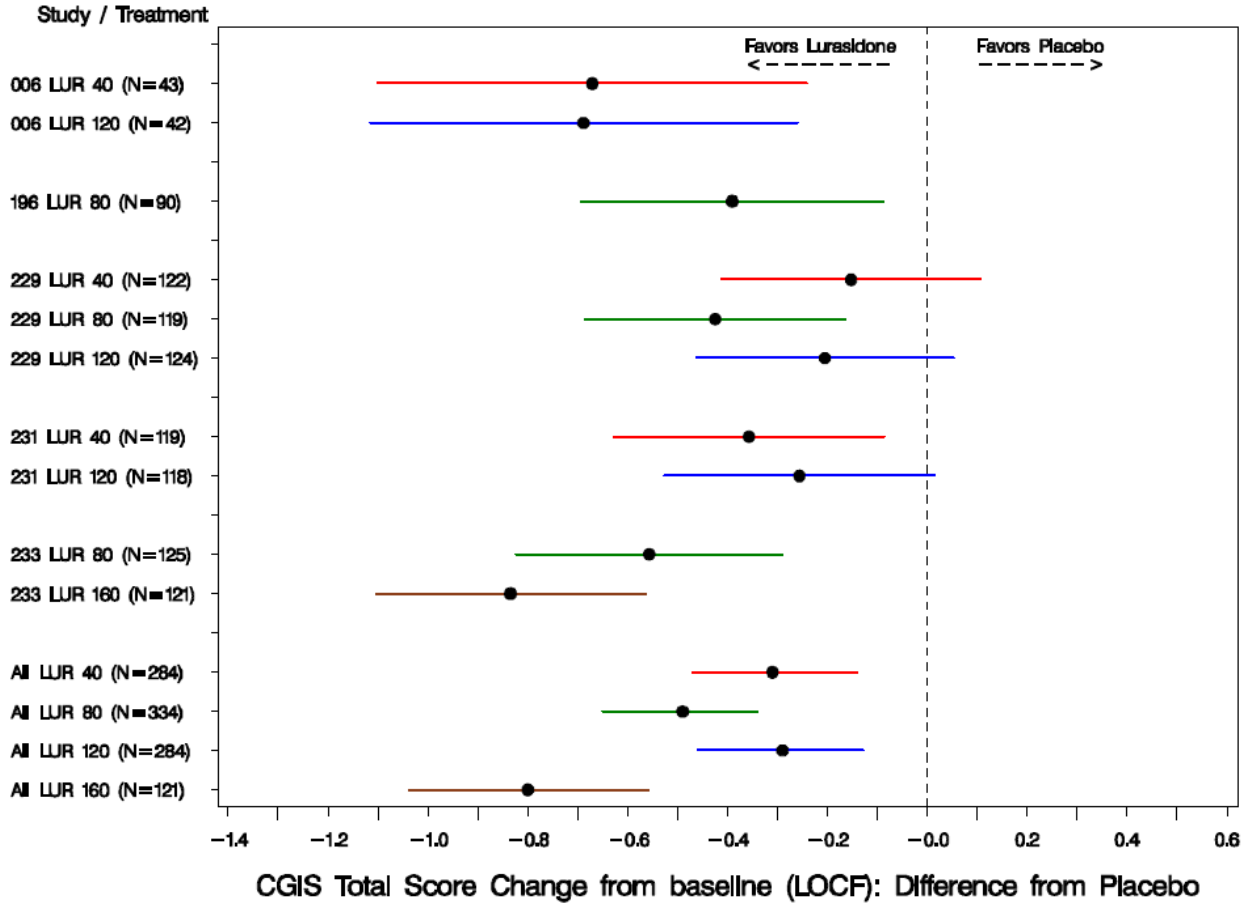


Figure 4. LS Mean Treatment Difference (95% CI) for CGI-S Score Change from Baseline to LOCF Endpoint: ANCOVA Analysis.



The results were supportive of the primary efficacy endpoints in Studies D1050229, D1050231 and D1050233 and the secondary efficacy endpoints in Studies D1050006 and D1050196.

Responder analyses

Moreover, the responder analyses were presented for the pivotal short-term clinical studies. Hereafter reported are the results of at least a 30% reduction on the PANSS total score compared with Baseline as being generally considered to be a clinically relevant and appropriate definition of responders in short term efficacy trials of patients with schizophrenia (CHMP guideline on clinical investigation of medicinal products in the treatment of schizophrenia).

Table 35. Proportion of Responders (≥30% Improvement from Baseline) at Day 42/LOCF Endpoint (Studies D1050229, D1050231, and D1050233).

Study		Lurasidone				Active Control (a)
Statistic	Placebo	40 mg	80 mg	120 mg	160 mg	
Study D1050229	N=124	N=121	N=118	N=123		
n (%) of responders (b)	47 (38)	56 (46)	61 (52)	61 (50)		
p-value (f)		0.181	0.028*	0.058		
Study D1050231	N=114	N=118		N=118		N=121
n (%) of responders (b)	43 (38)	63 (53)		55 (47)		78 (64)
p-value (f)		0.018*		0.206		<0.001**
Study D1050233	N=120		N=125		N=121	N=116
n (%) of responders (b)	36 (30)		62 (50)		76 (63)	82 (71)
p-value (c)			0.002**		<0.001**	<0.001**

The clinically relevant responder rate (≥30%) was observed for the 160 mg lurasidone dose. In addition, statistically significant results were seen for the 40 mg and 80 mg doses and while no significant effect was shown for the 120 mg dose in either of the 2 studies. Olanzapine and quetiapine at equipotent dosages showed a significant effect on the 30% responder rate.

When discontinuing patients were counted as nonresponders compared with the responder analysis without imputation, the proportion of responders in each treatment group (including placebo) demonstrating ≥30% improvement in PANSS total score decreased (table 36).

Table 36. Proportion of Responders (≥30% Improvement From Baseline in PANSS Total Score) at Day 42 with discontinued patients counted as nonresponders.

Study		Lurasidone				Active Control (a)
Statistic	Placebo	40 mg	80 mg	120 mg	160 mg	
D1050229	**N=124**	**N=121**	**N=118**	**N=123**		
Discontinuing patients as nonresponders					--	--
n (%) of responders	42 (34)	49 (41)	53 (45)	56 (46)	--	--
Odds ratio (95% CI)		1.3 (0.8, 2.2)	1.6 (1.0, 2.7)	1.6 (1.0, 2.7)	--	--
p-value (b)		0.282	0.076	0.059	--	--
D1050231	**N=114**	**N=118**		**N=118**		**N=121**
Discontinuing patients as nonresponders						
n (%) of responders	40 (35)	59 (50)	--	46 (39)	--	69 (57)
Odds ratio (95% CI)		1.8 (1.1, 3.1)	--	1.2 (0.7, 2.0)	--	2.4 (1.4, 4.1)
p-value (b)		0.023*	--	0.579	--	0.001**
D1050233	**N=120**		**N=125**		**N=121**	**N=116**
Discontinuing patients as nonresponders						
n (%) of responders	35 (29)	--	58 (46)	--	71 (59)	81 (70.0)
Odds ratio (95% CI)		--	2.1 (1.2, 3.6)	--	3.5 (2.0, 5.9)	5.7 (3.2, 9.9)
p-value (b)		--	0.005**	--	<0.001***	<0.001***

All doses of lurasidone therapy showed a numerically greater proportion of subjects having at least a 30% improvement in the PANSS total score compared with placebo regardless of the analysis used.

Subject discontinuation

Given the high discontinuation rate in the 5 pivotal short-term studies, information on subject disposition, including the number and percentage of subjects that discontinued overall and due to lack of efficacy was presented in the initial application. From the response by the applicant to D120 LoQ, this information have expanded to include reasons for discontinuation (Table 37), and time to discontinuation in pooled data from the 5 pivotal, short-term studies; D1050006, D1050196, D1050229, D1050231, and D1050233 (ITT Population), Figure 5.

Table 37. Subject Discontinuation (Randomised Population): D1050006, D1050196, D1050229, D1050231, and D1050233.

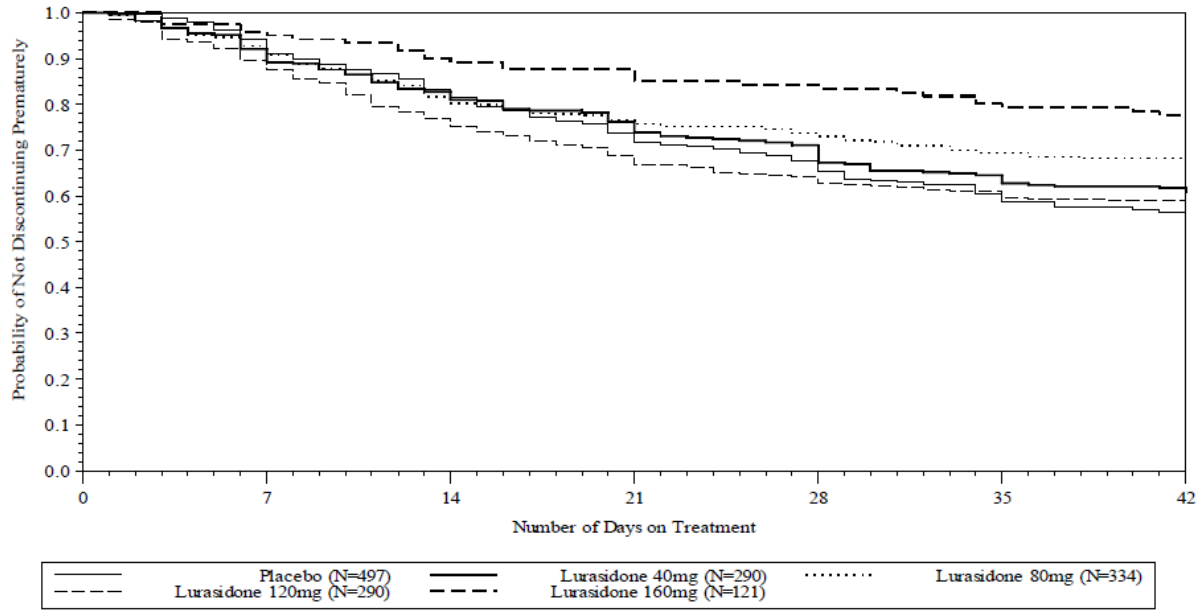
Study		Lurasidone					Active
Reason for Discontinuation	Statistic	Placebo	40 mg	80 mg	120 mg	160 mg	Control (a)
Pooled (D1050006, D1050196, D1050229, D1050231 and D1050233)		N=506	N=295	N=338	N=292	N=121	
Total subjects discontinued	n (%)	226 (45)	118 (40)	111 (33)	121 (41)	28 (23)	--
Lack of efficacy	n (%)	123 (24)	47 (16)	32 (9)	33 (11)	12 (10)	--
Withdrawal of consent	n (%)	59 (12)	38 (13)	48 (14)	53 (18)	9 (7)	--
AE	n (%)	21 (4)	20 (7)	19 (6)	27 (9)	4 (3)	--
Protocol violation	n (%)	3 (<1)	3 (1)	1 (<1)	0	0	--
Lost to follow-up	n (%)	12 (2)	7 (2)	4 (1)	4 (1)	1 (<1)	--
Other (Administrative)	n (%)	8 (2)	3 (1)	7 (2)	4 (1)	2 (2)	--

Source: D1050006 Post-text Table 2 (Initial MAA); D1050196 Post-text Table 2 (Initial MAA); D1050229 Table 14.1.1.1 (Initial MAA); D1050231 Table 14.1.1.1 (Initial MAA); D1050233 Table 14.1.1 (Initial MAA) and calculations.
AE=adverse event.
(a) Olanzapine 15 mg in D1050231, quetiapine XR 600 mg in D1050233.

The discontinuation rate was larger for the placebo than for the lurasidone treated patient group. This provides support for a lurasidone treatment effect. Lack of efficacy and withdrawal of consent were the two most common reasons for discontinuation among patients treated with placebo or lurasidone. Discontinuation due to lack of efficacy was a relatively more common than withdrawal of consent among patients treated with lurasidone 40 mg, 120 mg, 160 mg or placebo while the opposite for those treated with 80 mg daily dosage, although based on small numbers.

Additionally, discontinuation over time was displayed for pooled data from the 5 short-term clinical trials; D1050006, D1050196, D1050229, D1050231, and D1050233 (ITT Population). The probability of not discontinuing prematurely for the patient groups treated with placebo or lurasidone 40 mg, 80 mg, 120 mg or 160 mg, respectively, was plotted versus time, Figure 5.

Figure 5. Time to discontinuation: Pooled data from the pivotal short-term studies; D1050006, D1050196, D1050229, D1050231, and D1050233 (ITT Population).



Source: Integrated Summary of Efficacy (ISE) Figure 1.1.1 (Initial MAA).
ITT=intent-to-treat.

The least risk for discontinuation was shown among those treated with the 160 mg/d dose, followed by the 80 mg/d dose. There was no trend for a disproportional distribution of discontinuation over time for any of the 4 lurasidone daily doses, nor for placebo.

Long-term efficacy studies

During the procedure the CHMP requested a post hoc analysis of the secondary endpoints (PANSS total score, CGI-S, MADRS, and CogState) in D1050234 including all patients originally randomised into D1050233.

In response the analyses of the change from D1050233 core Baseline to endpoint in D1050234 based on MMRM have been presented (table 38).

Table 38. Change from D1050233 core Baseline to endpoint in D1050234 (MMRM).

Change From Core Baseline in Secondary Endpoints in D1050234 (Protocol-Specified and Post Hoc Analysis)

Parameter	LUR-LUR	QXR-QXR
Protocol-Specified Analysis		
MMRM		
PANSS total score (a)		
LS mean (SE)	-34.8 (1.5)	-26.3 (2.4)
95% CI	-37.7, -31.9	-31.1, -21.5
Treatment difference		
LS mean	-8.5 (2.8)	
95% CI	-14.1, -2.9	
CGI-S (a)		
LS mean (SE)	-1.9 (0.1)	-1.6 (0.1)
95% CI	-2.1, -1.7	-1.9, -1.4
Treatment difference		
LS mean	-0.3 (0.2)	
95% CI	-0.6, 0.0	
MADRS (a)		
LS mean (SE)	-6.0 (0.6)	-3.8 (0.9)
95% CI	-7.2, -4.8	-5.6, -2.1
Treatment difference		
LS mean	-2.2 (1.1)	
95% CI	-4.3, -0.1	
CogState (b)		
LS mean (SE)	0.38 (0.07)	0.15 (0.11)
95% CI	0.24, 0.52	-0.06, 0.36
Treatment difference		
LS mean	0.23 (0.12)	
95% CI	-0.01, 0.48	
Post Hoc Analysis	N=246	N=116
MMRM		
PANSS total score (c)		
LS mean (SE)	-30.39 (1.99)	-23.42 (2.81)
95% CI	-34.34, -26.45	-29.00, -17.84
Treatment difference		
LS mean	-6.97 (3.44)	
95% CI	-13.80, -0.15	
CGI-S (c)		
LS mean (SE)	-1.67 (0.10)	-1.58 (0.14)
95% CI	-1.87, -1.48	-1.86, -1.30
Treatment difference		
LS mean	-0.09 (0.17)	
95% CI	-0.44, 0.25	
MADRS (c)		
LS mean (SE)	-5.51 (0.60)	-3.59 (0.82)
95% CI	-6.69, -4.33	-5.22, -1.97
Treatment difference		
LS mean	-1.92 (1.01)	
95% CI	-3.92, 0.08	
CogState (d)		
LS mean (SE)	0.32 (0.07)	0.08 (0.10)
95% CI	0.18, 0.45	-0.11, 0.27
Treatment difference		
LS mean	0.23 (0.12)	
95% CI	0.00, 0.46	

Footnotes are on last table page.

Change from Core Baseline in Secondary Endpoints in Study D1050234 (Protocol-Specified and Post-Hoc Analysis) (continued)

Parameter	LUR-LUR	QXR-QXR
Post Hoc Analysis		
LOCF		
PANSS total score (e)		
LS mean (SE)	-23.56 (1.25)	-22.88 (1.81)
95% CI	-26.02, -21.10	-26.44, -19.32
Treatment difference		
LS mean	-0.68 (2.17)	
95% CI	-4.95, 3.60	
CGI-S (e)		
LS mean (SE)	-1.32 (0.07)	-1.35 (0.10)
95% CI	-1.45, -1.19	-1.54, -1.16
Treatment difference		
LS mean	0.03 (0.12)	
95% CI	-0.20, 0.26	
MADRS (e)		
LS mean (SE)	-4.83 (0.40)	-3.87 (0.54)
95% CI	-5.61, -4.05	-4.93, -2.80
Treatment difference		
LS mean	-0.96 (0.66)	
95% CI	-2.26, 0.34	
CogState (f)		
LS mean (SE)	0.18 (0.05)	0.03 (0.08)
95% CI	0.07, 0.28	-0.12, 0.18
Treatment difference		
LS mean	0.15 (0.09)	
95% CI	-0.03, 0.33	

Source: D1050234 Tables 14.2.2.1, 14.2.3.1, 14.2.4.1, and 14.2.5.1 (Initial MAA) and Ad hoc Table 28, 29, 30, 31, 32, 33, 34, and 35.
Lur=lurasidone, QXR=quetiapine XR.
(a) Change from core Baseline in D1050233 (Initial MAA) to Month 12 endpoint for the D1050234 ITT population.
(b) Change from core Baseline in D1050233 to Month 6 for the D1050234 ITT population.
(c) Change from core Baseline in D1050233 to Month 12 endpoint for the D1050233 ITT population.
(d) Change from core Baseline in D1050233 to Month 6 for the D1050233 ITT population.
(e) Change from core Baseline in D1050233 to Month 12 LOCF endpoint for the D1050233 ITT population.
(f) Change from core Baseline in D1050233 to Month 6 LOCF for the D1050233 ITT population.

The results were found to be supportive of a non-inferiority claim for lurasidone.

Clinical studies in special populations

No efficacy studies in special populations have been carried out yet. The PIP together with a deferral have been approved.

Supportive studies

Study D1050006 and Study D1050196

Both studies were double-blind, randomised, fixed-dose, placebo-controlled, parallel-group, 6-week, efficacy, safety, and tolerability studies of SM-13496 (lurasidone) in patients with schizophrenia.

Efficacy results from Study D1050006 suggested that lurasidone at doses of 40 mg and 120 mg daily demonstrated a statistically significant effect in the primary efficacy variable i.e. the mean change from Baseline to 6 weeks in BPRSd score for the ITT population. Significant results were also seen in a responder analysis defined as ≥20% decreases in BPRSd scores, as compared to placebo. Nonetheless, the study population was small (ITT subjects, N=149) and there was a high discontinuation rate (64%) leading to only 51 subjects completing the study (of which 36 subjects received lurasidone).

The results from the second short-term efficacy study (Study D1050196) reported a statistically significant mean change in the primary endpoint, BPRSd score, between Baseline and the Day 42 (0.012) using an ANCOVA model for lurasidone 80 mg compared to placebo. Also for the key

secondary endpoints (CGI-S, PANSS, and MADRS), there was a statistically significant difference favouring lurasidone 80 mg over placebo. Out of 180 ITT subjects, 90 subjects received lurasidone, however the discontinuation rate in this study was considerable, 99 subjects (55% of the randomised subjects) completed the study: 52 (58%) subjects in the lurasidone 80 mg group and 47 (52%) subjects in the placebo group. The time-course of discontinuation revealed that more than 50 % of patients in both treatment arms had discontinued from the study at study midpoint.

Initially the above described studies were submitted as pivotal short-term efficacy studies, however they were considered by the CHMP as supportive due to the observed high discontinuation rate.

Furthermore, twelve completed non placebo-controlled studies were conducted: 7 in the US and 5 in Japan. Of the 7 studies conducted in the US, one was an active-controlled study (D1050254) and 6 were uncontrolled, open-label studies (D1050174, D1050199, D1050229E, D1050289, and D1050231E, and D1050290). The 5 studies conducted in Japan were all uncontrolled, and included three 8-week studies (Studies D1001001, D1001016 and D1001017), one 52-week label extension study of D1001001 (D1001036) and one long-term study (Study D1001048).

Of the listed studies study D1050254 was active-controlled, randomised, multicenter, double-blind, fixed dose, parallel group study to estimate the tolerability profile of Lurasidone and an active comparator (ziprasidone) in clinically stable outpatients with chronic schizophrenia or schizoaffective disorder. On the first day after completion of the placebo run-in period, subjects were randomised in a 1:1 ratio to Lurasidone or ziprasidone in a double-blind fashion. The study duration was 3 weeks. 307 subjects were randomised, and 210 subjects completed the study. A total of 301 subjects were analysed for safety and efficacy. The analysis of the efficacy results (PANSS, CGI-S, CDSS, MATRICS, SCoRS and NAB) did not reveal any meaningful differences between the treatments.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

In the short term studies a positive effect of treatment was estimated, however in the view of the CHMP, discontinuation rates were considerable and methods selected for addressing the problem of missing data (LOCF, MMRM) appeared likely to favour active treatment. Hence, further analyses in line with the CHMP guideline on missing data were required to provide estimated treatment effects that would unlikely to be biased in favour of active treatment. Accordingly, in addition to the initially 2 performed analysis - ANCOVA based on last observation carried forward (LOCF) and Mixed-effect model repeated measure (MMRM), the more conservative analyses including ANCOVA based on observed cases (OC), baseline observation carried forward (BOCF) and Pattern-mixture modelling (PMM) with placebo-based multiple imputation have been applied to the data set. Disadvantages with each of these methods have been thoroughly and sufficiently discussed and ad hoc analyses using these methods have been presented for primary and key secondary endpoints and compared against the planned analyses submitted in the initial application. Though the point estimate was quite different from one method of analysis to the next, statistical significance was consistent in general with the initial analysis, therefore supporting the conclusion of a statistically significant treatment effect.

The reasons for, and timings of patients' withdrawal have been presented and discussed in detail following the committee's request. The most common reasons for discontinuation were withdrawal of consent and lack of efficacy. A listing containing patient-level information on the reason and timing for discontinuation in the 5 controlled short-term efficacy studies as well as listing of reasons for withdrawal of consent have not revealed any patterns or trends with regard to disposition or day of event from start of treatment. The results from the 2 active controlled short-term studies with olanzapine 15 mg and quetiapine XR 600 mg showed that overall discontinuation rates were slightly

higher in the placebo groups compared with the active comparators. The total percentage of subjects who discontinued from lurasidone treatment has been shown to be lower than for placebo in all dose groups in all 5 short-term studies with the exception of the 120 mg group in D1050231, which had a relatively high percentage of subject discontinuations due to withdrawal of consent. In general, the percentage of subjects who discontinued due to lack of efficacy or insufficient clinical response was lower in the lurasidone treatment groups than in placebo. However, the withdrawal of consent was reported at a slightly higher rate in lurasidone groups compared with placebo in D1050006, D1050196, and D1050231. The reasons provided for withdrawal of consent were similar between treatment groups. The pooled time to discontinuation data from the 5 placebo-controlled studies (ITT Population) was proportionately distributed within the studies (time-interval 0-42 days). In general the rate of discontinuation was comparable with the rate observed with other antipsychotic treatments, albeit somewhat higher for lurasidone than for the 2 active control treatments (olanzapine 15 mg, quetiapine XR 600 mg).

Responder analyses were included as tertiary endpoints in the phase 3 clinical studies and discussed in the initial application. Responder rates corresponding to ≥30% reduction on the PANSS total score compared to baseline have been presented including new analyses with patients that discontinued counted as non-responders as requested, providing reduced responder rate in most cases. The clinical relevance of the differences is discussed below.

In the short-term studies treatment effects of lurasidone were higher in the European patient population compared with the North American population, therefore the CHMP requested the applicant to comment on the representativeness of the study results to the EU-population given the small number of EU subjects in the short-term pooled database. The applicant provided a summary of results for geographic region by treatment interaction based on PANSS total score and CGI S change, using the MMRM and ANCOVA models. The results were not statistically significant, indicating that there was no treatment difference between the North America, Europe, and RoW regions. Furthermore, the applicant also discussed the potential influence of extrinsic factors such as standard/established medical practice (i.e., in- or outpatient care), treatment compliance, prevailing practice in the use of concomitant medications, and average length of time in relapse before the treatment between European and non-European trial populations. The applicant concluded that despite the possible differences in access to non-pharmacological interventions between European and non-European regions, the pivotal clinical trials implemented standard design and study methods to overcome any potential and differential confounding effects on study results thus the results provided an accurate representation of the treatment effects of lurasidone in the European population. The CHMP agreed with the provided argumentation.

Patients who received co-medication with an antipsychotic during the pivotal short-term studies were excluded from the per protocol population but included in the ITT and safety population. Therefore, the CHMP requested the applicant to specify which antipsychotic medication were used in each of the pivotal short- and long term efficacy studies in the active treatment arms and whether it could interfere with the results of each study. Concomitant antipsychotic usage during the short-term studies was numerically higher among risperidone-treated subjects (14% overall), compared with 9% among lurasidone-treated subjects and 8% among subjects receiving placebo. In the long-term study, D1050234, a double-blind extension of D1050233, only 1 subject in the lurasidone group (<1%) received a concomitant antipsychotic (haloperidol). No subject in the quetiapine XR treatment group received a concomitant antipsychotic medication. In D1050237, the proportion of patients using concomitant antipsychotics was similar in the lurasidone treatment group compared with the proportion in the risperidone treatment group. Subjects that received concomitant antipsychotic medications were excluded from the PP population but included in the ITT population with similar

efficacy results observed with the 2 populations. It was concluded that the co-administration of other antipsychotics did not affect the study results.

The proportion of patients who discontinued for any reason was similar across treatment groups in both pivotal long-term studies with the exception for the quetiapine XR patient group in study D1050234 which showed twice as high discontinuation rate due to insufficient clinical response. The applicant was requested to discuss how the high discontinuation rate in the quetiapine XR group in study D1050234 could have influenced the results. The applicant provided the proportion of patients who discontinued the study for any reason from the lurasidone and quetiapine XR treatment arms, which was 48% and 61% respectively. Withdrawal of consent was the most common reason for early discontinuation, with 20% of lurasidone-treated patients and 22% of quetiapine XR-treated patients withdrawing consent during the study. The proportion of patients who discontinued due to insufficient clinical response was 9% in the lurasidone-lurasidone group and 21% in the quetiapine XR group. However, the discontinuation pattern was not associated with the initial dosage. The discontinuation rates due to insufficient clinical response observed with quetiapine XR was similar to rates reported in other quetiapine XR studies. Therefore, the applicant considered that the discontinuation rate in the quetiapine XR group did not affect the final results of the study because the observed relapse rate of 27% for the quetiapine XR-quetiapine XR arm was similar to previous studies where the quetiapine relapse rates were 30% at 12 months (Stauffer et al. 2009), 31% over 2 years (Gaebel et al. 2010), and 14% at 6 months (Peuskens et al. 2007).

Efficacy data and additional analyses

The efficacy and safety of fixed doses of lurasidone 40, 80, 120, and 160 mg/day in the treatment of adult subjects with schizophrenia have been assessed in 5 short-term studies. In light of the heterogeneous responses to different doses in those studies the applicant was requested to discuss the clinical relevance of the findings taking into consideration additional analyses of missing data.

The applicant argued that the occasional failures of various doses in the short term studies were due to the heterogeneity of schizophrenia and the high and unpredictable placebo response rate. The results observed with lurasidone were comparable with those of the active comparators used in the development programme and with other antipsychotics in general. The CHMP agreed with the general assertion that presentations of schizophrenia vary substantially, and that this and the unpredictable and high placebo response may have played a role in some studies in the development programme. Comparison of the magnitude of the effect to that of the other antipsychotics however was considered to be more difficult and uncertain, in particular given that the development programme where active comparator was used was not designed to demonstrate superiority of one active treatment over the other. The CHMP noted that across the clinical development program, lurasidone has consistently shown superior efficacy compared with placebo. Furthermore, the magnitude of symptom reductions (change from Baseline in the primary efficacy endpoint) observed with lurasidone across the recommended therapeutic dose range of 40 to 160 mg/day and with the active comparators (olanzapine 15 mg/day and quetiapine XR 600 mg/day) were similar and the active comparators performed as seen in literature that was referred to in the response, thus ensuring assay sensitivity.

The CHMP concluded that the clinical relevance of the lurasidone 40 mg-160 mg dose range was supported by responder rates (≥30% improvement from Baseline in PANSS total score) based on more conservative analysis methods. Overall, it was concluded that the short term efficacy had been sufficiently justified and it would not differ by an important margin from that of the other antipsychotics. The additional analyses of the impact of missing data on study results were found by the committee to be reassuring.

As mentioned above, the CHMP noted the heterogeneous dose-response with the product. As a result the applicant was requested to justify the choice of the dose range and in particular the choice of the upper limit (160mg/day) and the dose of 80 mg/day given the statistically significant differences between the two doses. Furthermore, the justifications for doses 40mg/day and 120mg/day in view of their failure to differentiate from placebo in the study D1050229 and the dose-dependence of some of the AEs were also requested. Based on the applicant's responses, the CHMP concluded that it was plausible that heterogeneity of clinical presentations of schizophrenia and high placebo response rate might have influenced the dose response. The committee, however, saw as a concern that the highest dose (160 mg/day) appeared superior in terms of efficacy to the other doses as this could lead to the off-label use of doses higher than 160 mg/day in clinical practice. The applicant was requested to ensure that the risk of off-label use of doses higher than 160mg per day was addressed in the RMP. The applicant proposed to include high doses and off-label use assessment in the planned PASS/DUS.

Moreover, the CHMP requested further justification for recommendation of 40 mg per day as the starting dose. The applicant supported the choice of the 40 mg starting dose with the data from development programme, receptor occupancy studies, clinical guidelines and post-authorisation data. The CHMP accepted the justification and requested that this information be reflected in the product information. The committee was also of the opinion that there wasn't sufficient safety-driven evidence for restarting treatment with doses higher than 120 mg/day in case of discontinuation in treatment lasting longer than 3 days. The appropriate dosing recommendations following treatment discontinuation have been included in the SmPC.

The CHMP also noted that the proposed posology stipulated dose increases based on physician judgement and observed clinical responses in the absence of persuasive evidence that a dose increase will enhance the response. Therefore, further justification of posology was requested. The applicant acknowledged that there was no clear evidence from the clinical studies supporting the up-titration to the effective dose. The applicant stated that the proposed posology is in line with the usual clinical practice in psychiatry and therapeutic guidelines, and reflected in the product information the finding that in the short-term studies there was no consistent dose-response observed. This was accepted by the CHMP.

Long-term efficacy of lurasidone and non-inferiority in time to relapse was evaluated in 2 long-term studies D1050234 (extension of study D1050233) and D1050237, and compared to two active comparators, quetiapine XR and risperidone at fix followed by variable dosages over 12 months. As the extension study D1050234 was partly a non-randomised comparison, and in study D1050237 lurasidone failed to demonstrate non-inferiority to risperidone the CHMP felt that the long-term efficacy of lurasidone for the treatment of schizophrenia required further confirmation.

To address the concern that study D1050234 could only be accepted as an extension if it represented a non-inferiority comparison of truly random groups, a post hoc analysis was performed by the applicant. It included all subjects from the D1050233 ITT population, with the exception of subjects randomised to placebo. The upper bound of the 95% CI in this post hoc analysis was lower than the predefined non-inferiority margin and thus in the applicant's view supported non-inferiority of lurasidone compared with quetiapine XR and the validity of the results from the primary analysis. In addition, to include all patients originally randomised into D1050233, a post hoc analysis was also conducted on the secondary endpoints in D1050234. There was no relevant difference in the PANSS total score, CGI-S score or MADRS total score between the lurasidone group and the quetiapine XR group between the protocol-specified analysis and the post-hoc analysis. The CHMP agreed with the applicant's conclusion, that the results from the post-hoc analysis indicated non-inferiority between lurasidone and quetiapine XR in the prevention of relapse. However, the committee had concerns regarding the long term efficacy due to the methodological shortcomings of the extension study D1050234 and the fact that

the second long-term study (D1050237) did not demonstrate the non-inferiority in time-to-relapse for lurasidone versus risperidone.

Consequently, the applicant was requested to submit the results from the on-going long term randomised withdrawal efficacy study (D1050238) to sufficiently demonstrate long-term efficacy and maintenance of effect of lurasidone. The applicant provided a summary of the study results. In the view of the CHMP the study conformed well to the design suggested in the current EMA guideline on investigation of medicinal products for treatment of schizophrenia. The randomised withdrawal phase demonstrated a borderline statistically significant benefit of lurasidone when compared to placebo, however the CHMP noted the low number of events and loss of statistical significance if the patients censored due to informative censoring (i.e. patients who withdrew whilst the study was still running) were counted as events (p=0.070). Therefore the applicant was requested to comment on the narrow advantage of lurasidone over placebo in this study, the impact of informative censoring, and apparent convergence of the relapse rates between the treatment arms towards the end of the randomised period. The applicant re-discussed the initially submitted data and concluded that the totality of evidence from a variety of analyses applied indicated that study D1050238 demonstrated the maintenance of efficacy over placebo. The CHMP acknowledged the response and agreed that it was acceptable that lurasidone does seem to slow relapse when compared to placebo, given that the efficacy analysis together with the sensitivity analysis (which assumed all discontinuations not originally categorised as relapse events to be relapse) showed separation of the Kaplan-Meier curves, and results were close to the statistical significance. It was concluded that the non-significant p-value of 0.073 was most likely due to the study being underpowered for this sensitivity analysis. It was also accepted that the narrowing of relapse rates towards the end in the ITT analysis may have been due to the observed between-group differences in number of subjects at risk. The section 5.1 of the product information has been updated to reflect results of both analyses.

2.5.4. Conclusions on the clinical efficacy

Short-term efficacy

There were 5 short-term (6 week) and 3 long-term (52 weeks) clinical studies to demonstrate short- and long-term efficacy of lurasidone in the treatment of schizophrenia. In the short-term studies; D1050006, D1050196, D1050229, D1050231 and D1050233, the efficacy and safety of lurasidone was evaluated at a dose range of 40 mg to 160 mg oral daily doses for 6 weeks compared to placebo. In 2 of these studies, active comparators were used for comparison of efficacy and benefit/risk evaluations.

Given the high discontinuation rates observed in the short-term studies, more conservative analysis based on ANCOVA/BOCF, ANCOVA/OC and PPM analysis methods were performed. Hence, in addition to the initially performed ANCOVA/LOCF and ACOVA/MMRM analysis, it is concluded that the more conservative analysis results corroborate the initial results.

Taking the results from the 5 short-term studies together, a treatment effect has been demonstrated from each of the 40 mg, 80 mg, 120 mg and 160 mg lurasidone doses. However, this effect was not consistently demonstrated for each dose in all trials where it was included.

Overall, short-term efficacy of lurasidone has been sufficiently demonstrated at the proposed 40 mg/d-160 mg/d clinical dose range for the treatment of psychotic symptoms in adults with schizophrenia. However, no consistent dose-response relationship was observed.

Long-term efficacy studies

Maintenance of efficacy and non-inferiority to an active comparator was investigated for a time-period of 12 months in 2 pivotal long-term lurasidone clinical trials, Study D1050234 and D1050237. Non-

inferiority in time to relapse was supported by the results from a post-hoc sensitivity analysis for lurasidone in relation to quetiapine XR, including all ITT subjects from the previous short-term study D1050233, with the exception of those treated with placebo, and assigning a relapse event at the study D1050234 baseline for those who did not enter the extension study D1050234. The applicant was asked to justify that the upper bound of the observed confidence interval (1.490) does not imply an increased clinically relevant risk for treatment failure from the lurasidone treatment. This issue was addressed in the applicant's responses and was considered resolved. An additional finalised long-term study D1050237 provided support for maintenance of efficacy based on secondary efficacy endpoints, however it did not demonstrate statistically significant non-inferiority versus risperidone. For confirmation of long-term efficacy of lurasidone, the results from a randomised withdrawal-designed long-term study (D1050238) were submitted. In the primary analysis there was a statistically significant increase in the time to relapse for patients on lurasidone compared with patients on placebo, and overall the committee considered that the results supported the long-term efficacy in the claimed indication.

2.6. Clinical safety

Safety data from the 22 phase 2 and phase 3 clinical studies (controlled and uncontrolled studies - study grouping P23ALL) have been pooled for safety analyses. The P23ALL pool consists of short-term controlled (P23STC, P23STO), long-term controlled (P23LTC) and uncontrolled (P23AU) studies. Additionally, 31 clinical pharmacology studies in healthy subjects (P1NON) and in subjects with schizophrenia (P1SCH) provided supportive safety data.

Patient exposure

Clinical trials exposure

Lurasidone has been evaluated in 52 clinical studies (30 phase 1 clinical pharmacology studies [9 in schizophrenia]) and 22 phase 2/3 clinical studies) involving 5068 subjects with schizophrenia (3502 treated with lurasidone, 724 treated with placebo, 842 treated with other medications). The studies were 3 weeks to 22 months in duration and evaluated doses of lurasidone from 20 mg to 160 mg/day.

Among the lurasidone dose groups in the short-term, placebo-controlled studies (P23STC), 71 subjects received 20 mg, 487 received 40 mg, 538 received 80 mg, 291 received 120 mg, and 121 subjects received 160 mg. In the long-term, active-controlled studies (P23LTC), 624 subjects received flexible doses of lurasidone (40 mg to 160 mg) once daily, 199 received flexible doses of risperidone (2 mg to 6 mg) once daily and 85 subjects received flexible doses of quetiapine XR (200 mg to 800 mg) once daily. The most frequent daily doses for lurasidone, risperidone, and quetiapine XR were 80 mg, 4 mg, and 600 mg, respectively, in P23LTC. In the uncontrolled studies (P23AU), 1071 subjects were exposed to lurasidone.

Table 39. Source and number of subjects: All lurasidone phase 2/3 studies by individual study. P23ALL study grouping.

Study	Treatments										
Short-term Phase 2/3 Double-Blind Placebo-Controlled (P23STC)											
		Lurasidone									
	Placebo	20 mg	40 mg	80 mg	120 mg	160 mg	All	Haloperidol 10 mg	Olanzapine 15 mg	Quetiapine XR 600 mg	Risperidone 4 mg
D1001002	132	NA	127	131	NA	NA	258	NA	NA	NA	65
D1050006	50	NA	50	NA	49	NA	99	NA	NA	NA	NA
D1050049	72	71	67	71	NA	NA	209	72	NA	NA	NA
D1050196	90	NA	NA	90	NA	NA	90	NA	NA	NA	NA
D1050229	127	NA	124	121	124	NA	369	NA	NA	NA	NA
D1050231	116	NA	119	NA	118	NA	237	NA	122	NA	NA
D1050233	121	NA	NA	125	NA	121	246	NA	NA	119	NA
Total	708	71	487	538	291	121	1508	72	122	119	65

Short-term Double-Blind Active Comparator Controlled (P23STO)	Lurasidone 120 mg	Ziprasidone 160 mg
D1050254	150	151

Long-term Phase 3 Double-Blind Active Comparator Controlled (P23LTC)	Lurasidone Flex	Risperidone Flex	Quetiapine XR Flex
D1050237	417	199	
D1050234	207		85

Phase 2/3 Uncontrolled (P23AU)	New Exposure to Lurasidone (b)	Re-exposure to Lurasidone (c)	Total Lurasidone
D1001001	203	NA	203
D1001016	69	NA	69
D1001017	20	NA	20
D1001036 (a)			
D1001048	182	NA	182
D1050174	46	52	98
D1050199	31	28	59
D1050229E	59	191	250
D1050231E	133	115	248
D1050237E	87	136	223
D1050289	240	NA	240
D1050290	NA	149	149
Totals	1071		
Total number of Subjects Exposed to Lurasidone in Phase 2/3 Studies (P23ALL) (d)	**3202**		

Source: Table 1.1.1.0.
NA = not applicable.
(a) Subjects in Studies D1001036 (D1001001 extension) and D1050290 (D1050289 extension) are not included in the New exposure or Total Lurasidone columns since all subjects in these studies are counted under Studies D1001001 and D1050289 as 'New Exposures'.
(b) "New Exposures" refers to subjects who received placebo or a comparator in a previous study, or who entered an uncontrolled study directly without previous participation in a double-blind study.
(c) "Re-exposures" refers to subjects who received lurasidone in a previous study.
(d) Total number of subjects exposed to lurasidone in phase 2/3 studies equals all subjects who received lurasidone in the controlled studies plus all new exposures in the uncontrolled studies (1508 + 150 + 1071 + 473).

The total exposure to lurasidone in the phase 2/3 clinical database was 1212 person years.

The duration of exposure and the number of patients exposed to different doses of lurasidone in the P23ALL study grouping is shown in Table 40.

Table 40. Exposure to study medication, safety population: P23ALL study grouping.

Duration of Exposure	Persons		Person Years	
Cumulative Up to 1 Month	1003		38.8	
Cumulative Up to 3 Months	1960		168.2	
Cumulative Up to 6 Months	2239		273.4	
Cumulative Up to 12 Months	2841		703.5	
Cumulative Up to Maximum Duration	3201		1212.0	
Dose of Exposure				
Dose level >0 to <40 mg	159		20.0	
Dose level 40 mg	573		61.2	
Dose level 80 mg	644		59.2	
Dose level 120 mg	440		31.4	
Dose level 160 mg	121		12.0	
Flex Dose	1820		999.3	
Age Group and Gender	**Persons**		**Person Years**	
	M	**F**	**M**	**F**
18 - <40 years	1038	399	401.3	159.5
40 - <55 years	881	454	320.5	168.5
55 - <65 years	230	164	88.9	62.6
65- <75 years	14	21	1.3	9.6
>75	0	0	0	0
Ethnic Origin	**Persons**		**Person Years**	
Hispanic or Latino	239		128.2	
Not Hispanic or Latino	1606		775.9	
Unknown	1356		307.9	
Race	**Persons**		**Person Years**	
White	1033		447.5	
Black or African American	1044		345.7	
Other	1124		418.8	
Total Clinical Trial Exposure	**Persons**		**Person Years**	
Total exposure	3201		1212.0	

In the CHMP opinion the safety data submitted for all lurasidone subjects fulfilled the requirements of the guideline on population exposure (ICH E1). See also discussion on safety.

Adverse events

Treatment Emergent Adverse Events

P23STC population

Treatment Emergent AEs (TEAEs) were defined as AEs (newly occurring or an exacerbation of pre-existing conditions) with a start date on or after the date of the first dose of study medication through 7 days after study medication discontinuation.

Of the 1508 lurasidone-treated subjects in P23STC, 1150 (76.3%) reported 1 or more TEAEs. Subjects reporting 1 or more TEAEs were 503 (71.0%) of the 708 placebo-treated subjects, 63 (87.5%) of the 72 haloperidol-treated subjects, 101 (82.8%) of 122 olanzapine-treated subjects, 72 (60.5%) of 119 quetiapine XR-treated subjects, and 53 (81.5%) of 65 risperidone-treated. Among subjects receiving lurasidone, the proportion of subjects with 1 or more TEAE was 74.6% (n=53 of 71) of subjects in the 20 mg group, 79.9% (n=389 of 487) of subjects in the 40 mg group, 72.7% (n=391 of 538) in the 80 mg group, 82.8% (n=241 of 291) in the 120 mg group, and 62.8% (n=76 of 121) in the 160 mg group.

The most common TEAEs (with a frequency of ≥5%) for lurasidone were headache, akathisia, nausea, insomnia, somnolence, sedation, vomiting, schizophrenia, dyspepsia, agitation, anxiety, and constipation.

Headache was the most common TEAE in subjects receiving lurasidone and occurred with a frequency similar to placebo (14.5% for the all lurasidone-treated subjects, 15.0% for the placebo group, 19.4% for the haloperidol group, 14.8% for the olanzapine 15 mg group, 10.9% for the quetiapine XR 600 mg group, and 4.6% for the risperidone 4 mg group). The incidence of headache was not dose-related.

The incidence of akathisia, the second most common TEAE in subjects receiving lurasidone, increased with increasing lurasidone dose and was very common (over 20 %) in the 120 mg dose group (5.6 % of subjects in the 20 mg group, 10.7% of subjects in the 40 mg group, 12.3% of subjects in the 80 mg group, 22.0% of subjects in the 120 mg group, and 7.4% of subjects in the 160 mg group). Akathisia occurred in lurasidone-treated subjects with a frequency greater than placebo, olanzapine and quetiapine XR, but lower than for haloperidol and risperidone (12.9% for all lurasidone-treated subjects, 3.0% for the placebo group, 19.4% for the haloperidol group, 7.4% for the olanzapine group, 1.7% for the quetiapine XR group, and 13.8% for the risperidone group).

The incidences for all lurasidone-treated subjects reporting nausea (10.1%), the 3rd most common TEAE, and sedation (8.5%), were higher than placebo-treated subjects (5.2% and 3.8%, respectively), but did not in general increase with increasing dose of lurasidone.

Somnolence showed a dose-related increase for lurasidone with an incidence of 4.2 % in the 20 mg group, 7.6 % in the 40 mg group, 7.4 % in the 80 mg group and 14.4 % in the 120 mg group. Again, the incidence for the 160 mg group was lower (6.6 %). Somnolence occurred with a frequency greater than placebo but lower than for the active comparators with the exception of risperidone (8.6% for the all lurasidone-treated subjects, 3.4% for the placebo group, 12.5% for the haloperidol 10 mg group, 9.0% for the olanzapine 15 mg group, 13.4% for the quetiapine XR 600 mg group, and 0% for the risperidone 4 mg group).

At the preferred term (PT) level, akathisia, somnolence, and sedation were the 3 most frequent Treatment-Related Adverse Events (TRAEs with a frequency of ≥1%) for lurasidone-treated subjects.

Table 41. Incidence of treatment-related adverse events reported in ≥1% of subjects (and greater than placebo) at the Preferred Term level within any lurasidone dose group, safety population: Short-term placebo-controlled pool P23STC for lurasidone and placebo-treated subjects.

SOC/ PT (a)	Number (%) of Subjects						
	Placebo N = 708	Lurasidone 20 mg N = 71	Lurasidone 40 mg N = 487	Lurasidone 80 mg N = 538	Lurasidone 120 mg N = 291	Lurasidone 160 mg N = 121	All Lurasidone N = 1508
Number of subjects with At Least 1 TRAE	228 (32.2)	24 (33.8%)	208 (42.7)	229 (42.6)	169 (58.1)	45 (37.2)	675 (44.8)
Akathisia	19 (2.7)	3 (4.2)	49 (10.1)	61 (11.3)	62 (21.3)	9 (7.4)	184 (12.2)
Somnolence	19 (2.7)	2 (2.8)	31 (6.4)	38 (7.1)	41 (14.1)	7 (5.8)	119 (7.9)
Sedation	24 (3.4)	7 (9.9)	34 (7.0)	37 (6.9)	34 (11.7)	1 (0.8)	113 (7.5)
Nausea	26 (3.7)	6 (8.5)	32 (6.6)	39 (7.2)	25 (8.6)	7 (5.8)	109 (7.2)
Insomnia	29 (4.1)	2 (2.8)	22 (4.5)	36 (6.7)	15 (5.2)	4 (3.3)	79 (5.2)
Vomiting	26 (3.7)	2 (2.8)	14 (2.9)	36 (6.7)	17 (5.8)	6 (5.0)	75 (5.0)
Parkinsonism	3 (0.4)	0	19 (3.9)	12 (2.2)	25 (8.6)	7 (5.8)	63 (4.2)
Dizziness	8 (1.1)	2 (2.8)	13 (2.7)	18 (3.3)	14 (4.8)	6 (5.0)	53 (3.5)
Dystonia	3(0.4)	0	13 (2.7)	18 (3.3)	10 (3.4)	2 (1.7)	43 (2.9)
Tremor	14 (2.0)	1 (1.4)	11 (2.3)	13 (2.4)	13 (4.5)	4 (3.3)	42 (2.8)
Dyspepsia	18 (2.5)	1 (1.4)	14 (2.9)	11 (2.0)	12 (4.1)	2 (1.7)	40 (2.7)
Agitation	14 (2.0)	1 (1.4)	14 (2.9)	9 (1.7)	11 (3.8)	2 (1.7)	37 (2.5)
Anxiety	14 (2.0)	1 (1.4)	11 (2.3)	14 (2.6)	8 (2.7)	4 (3.3)	38 (2.5)
Fatigue	11 (1.6)	3 (4.2)	11 (2.3)	12 (2.2)	7 (2.4)	0	33 (2.2)
Salivary Hypersecretion	5 (0.7)	1 (1.4)	7 (1.4)	10 (1.9)	10 (3.4)	3 (2.5)	31 (2.1)
Musculoskeletal Stiffness	10 (1.4)	0	7 (1.4)	13 (2.4)	9 (3.1)	1 (0.8)	30 (2.0)
Weight Increased	10 (1.4)	0	10 (2.1)	9 (1.7)	7 (2.4)	2 (1.7)	28 (1.9)
Dyskinesia	9 (1.3)	2 (2.8)	10 (2.1)	7 (1.3)	4 (1.4)	2 (1.7)	25 (1.7)
Restlessness	7 (1.0)	1 (1.4)	9 (1.8)	5 (0.9)	7 (2.4)	2 (1.7)	24 (1.6)
Dry Mouth	7 (1.0)	0	6 (1.2)	11 (2.0)	5 (1.7)	2 (1.7)	24 (1.6)
Stomach Discomfort	8 (1.1)	1 (1.4)	5 (1.0)	7 (1.3)	3 (1.0)	2 (1.7)	18 (1.2)
Blood CPK Increased	5 (0.7)	0	5 (1.0)	7 (1.3)	6 (2.1)	0	18 (1.2)
Abdominal Pain Upper	1 (0.1)	0	3 (0.6)	6 (1.1)	6 (2.1)	2 (1.7)	17 (1.1)
Extrapyramidal Disorder	5 (0.7)	2 (2.8)	5 (1.0)	7 (1.3)	3 (1.0)	0	17 (1.1)

Source: ISS Table 6.1.10.1a and 6.1.10.1b.
(a) Adverse events are coded using MedDRA Version 11.1.
Note: Percentages are based on the number of subjects in the Safety Population. Subjects were counted in all applicable categories but only once within a category.
Note: TEAEs were defined as any adverse event (newly occurring or an exacerbation of a pre-existing condition) with a start date on or after the date of first dose and within 7 days after treatment discontinuation.
Note: P23STC grouping includes Studies D1050006, D1050049, D1050196, D1050229, D1050231, D1050233, and D1001002.

Table 42. Incidence of treatment-related adverse events reported in ≥1% of subjects (and greater than placebo) at the Preferred Term level within any lurasidone dose group, and active control-treated subjects (short term placebo - controlled pool P23STC).

SOC/ PT (a)	Number (%) of Subjects					
	Placebo N = 708	All Lurasidone N = 1508	Haloperidol 10 mg N = 72	Olanzapine 15 mg N = 122	Quetiapine XR 600 mg N = 119	Risperidone 4 mg N = 65
Number of Subjects with At Least 1 TRAE	228 (32.2)	675 (44.8)	42 (58.3)	67 (54.9)	45 (37.8)	25 (38.5)
Akathisia	19 (2.7)	184 (12.2)	14 (19.4)	9 (7.4)	2 (1.7)	7 (10.8)
Somnolence	19 (2.7)	119 (7.9)	8 (11.1)	11 (9.0)	15 (12.6)	0
Sedation	24 (3.4)	113 (7.5)	13 (18.1)	19 (15.6)	5 (4.2)	2 (3.1)
Nausea	26 (3.7)	109 (7.2)	4 (5.6)	5 (4.1)	4 (3.4)	2 (3.1)
Insomnia	29 (4.1)	79 (5.2)	5 (6.9)	6 (4.9)	3 (2.5)	3 (4.6)
Vomiting	26 (3.7)	75 (5.0)	1 (1.4)	2 (1.6)	4 (3.4)	2 (3.1)
Parkinsonism	3 (0.4)	63 (4.2)	0	7 (5.7)	4 (3.4)	0
Dizziness	8 (1.1)	53 (3.5)	2 (2.8)	3 (2.5)	14 (11.8)	0
Dystonia	3 (0.4)	43 (2.9)	9 (12.5)	1 (0.8)	1 (0.8)	2 (3.1)
Tremor	14 (2.0)	42 (2.8)	5 (6.9)	6 (4.9)	1 (0.8)	5 (7.7)
Dyspepsia	18 (2.5)	40 (2.7)	0	6 (4.9)	2 (1.7)	1 (1.5)
Agitation	14 (2.0)	37 (2.5)	3 (4.2)	1 (0.8)	3 (2.5)	0
Anxiety	14 (2.0)	38 (2.5)	5 (6.9)	4 (3.3)	0	1 (1.5)
Fatigue	11 (1.6)	33 (2.2)	6 (8.3)	2 (1.6)	0	0
Salivary Hypersecretion	5 (0.7)	31 (2.1)	3 (4.2)	0	0	2 (3.1)
Musculoskeletal Stiffness	10 (1.4)	30 (2.0)	3 (4.2)	3 (2.5)	0	0
Weight Increased	10 (1.4)	28 (1.9)	0	24 (19.7)	12 (10.1)	1(1.5)
Dyskinesia	9 (1.3)	25 (1.7)	3 (4.2)	2 (1.6)	1 (0.8)	1 (1.5)
Restlessness	7 (1.0)	24 (1.6)	3 (4.2)	4 (3.3)	0	0
Dry Mouth	7 (1.0)	24 (1.6)	2 (2.8)	12 (9.8)	7 (5.9)	1 (1.5)
Stomach Discomfort	8 (1.1)	18 (1.2)	2 (2.8)	2 (1.6)	0	0
Blood CPK Increased	5 (0.7)	18 (1.2)	0	1 (0.8)	0	0
Abdominal Pain Upper	1 (0.1)	17 (1.1)	1 (1.4)	2 (1.6)	0	1 (1.5)
Extrapyramidal Disorder	5 (0.7)	17 (1.1)	12 (16.7)	0	0	0

Source: Table 6.1.10.1 and 6.1.10.1b.
(a) Adverse events are coded using MedDRA Version 11.1.
Note: Percentages are based on the number of subjects in the Safety Population. Subjects were counted in all applicable categories but only once within a category.
Note: TEAEs were defined as any adverse event (newly occurring or an exacerbation of a pre-existing condition) with a start date on or after the date of first dose and within 7 days after treatment discontinuation.
Note: P23STC grouping includes D1050006, D1050049, D1050196, D1050229, D1050231, D1050233, and D1001002.

Only one study (D1050049) in safety pool P23STC evaluated a lurasidone dose of 20 mg. In that study, the safety profile was similar to the 40 mg dose in the same study. The highest lurasidone dose of 160 mg used in the placebo-controlled studies was also evaluated in only one study (Study D1050233). Adverse events occurred with a low frequency in the 160 mg dose group in this study.

Phase 2/3 long term, active comparator controlled studies (P23LTC) - Studies D1050234 and D1050237

Of the 624 subjects dosed with lurasidone, a similar percentage (77.9%) reported 1 or more TEAEs compared with quetiapine XR-treated subjects (70.6%) and risperidone-treated subjects (85.9%).

The most common TEAEs (with a frequency of ≥5%) in safety pool P23LTC were akathisia, nausea, insomnia, and somnolence.

Akathisia was reported with a higher incidence in subjects receiving lurasidone (13.6%) compared with 2.4% for quetiapine XR, and 8.0% for risperidone.

Nausea was the second most common TEAE and was reported with a higher incidence in subjects receiving lurasidone (13.3%) compared with 2.4% for quetiapine XR and 11.1% for risperidone.

Insomnia was reported in 12.8% lurasidone treated subjects, 9.4% quetiapine XR treated subjects, and 13.6% risperidone treated subjects.

Somnolence and sedation were reported with a higher frequency in lurasidone-treated subjects (10.1% and 9.9%, respectively), compared with the quetiapine XR group (4.7% and 1.2%, respectively) but at a lower frequency compared with the risperidone group (18.1% and 14.1%, respectively).

An overview of TEAEs reported in ≥ 2% of subjects in the safety pool P23LTC is provided in Table 43.

Table 43. Incidence of treatment-emergent adverse events reported in ≥ 2% of subjects at the SOC and PT level within any treatment group. Long term active comparator controlled studies (pool P23LTC) for lurasidone and active control-treated subjects.

System Organ Class/ Preferred term (a)	Number (%) of Subjects		
	Lurasidone Flex	Risperidone Flex	Quetiapine XR Flex
	N = 624	N = 199	N = 85
Number of Subjects with At Least 1 TEAE	441 (70.7)	158 (79.4)	51 (60.0)
Cardiac Disorders	4 (0.6)	2 (1.0)	2 (2.4)
Tachycardia	4 (0.6)	2 (1.0)	2 (2.4)
Gastrointestinal Disorders	153 (24.5)	50 (25.1)	14 (16.5)
Nausea	83 (13.3)	22 (11.1)	2 (2.4)
Vomiting	51 (8.2)	7 (3.5)	4 (4.7)
Diarrhea	23 (3.7)	8 (4.0)	4 (4.7)
Toothache	21 (3.4)	9 (4.5)	3 (3.5)
Dry Mouth	12 (1.9)	4 (2.0)	1 (1.2)
Constipation	9 (1.4)	14 (7.0)	2 (2.4)
Salivary Hypersecretion	8 (1.3)	4 (2.0)	0
Dyspepsia	6 (1.0)	8 (4.0)	0
General Disorders and Administration Site Conditions	22 (3.5)	8 (4.0)	3 (3.5)
Fatigue	17 (2.7)	8 (4.0)	0
Asthenia	6 (1.0)	0	3 (3.5)
Infections and Infestations	67 (10.7)	34 (17.1)	11 (12.9)
Nasopharyngitis	26 (4.2)	13 (6.5)	2 (2.4)
Urinary Tract Infection	18 (2.9)	9 (4.5)	0
Influenza	15 (2.4)	8 (4.0)	4 (4.7)
Upper Respiratory Tract Infection	11 (1.8)	6 (3.0)	2 (2.4)
Investigations	78 (12.5)	52 (26.1)	7 (8.2)
Weight Increased	46 (7.4)	40 (20.1)	4 (4.7)
Weight decreased	32 (5.1)	9 (4.5)	2 (2.4)
Metabolism and Nutrition Disorders	30 (4.8)	8 (4.0)	2 (2.4)
Decreased Appetite	23 (3.7)	3 (1.5)	2 (2.4)
Musculoskeletal and Connective Tissue Disorders	31 (5.0)	9 (4.5)	5 (5.9)
Back Pain	15 (2.4)	4 (2.0)	1 (1.2)
Pain in Extremity	8 (1.3)	1 (0.5)	2 (2.4)
Arthralgia	7 (1.1)	6 (3.0)	2 (2.4)
Nervous System Disorder	286 (45.8)	104 (52.3)	16 (18.8)
Akathisia	85 (13.6)	16 (8.0)	2 (2.4)
Somnolence	63 (10.1)	36 (18.1)	4 (4.7)
Sedation	62 (9.9)	28 (14.1)	1 (1.2)
Headache	61 (9.8)	30 (15.1)	8 (9.4)
Parkinsonism	36 (5.8)	11 (5.5)	0
Dizziness	29 (4.6)	8 (4.0)	2 (2.4)

Dystonia	21 (3.4)	13 (6.5)	1 (1.2)
Tremor	19 (3.0)	6 (3.0)	1 (1.2)
Dyskinesia	9 (1.4)	5 (2.5)	0
Psychiatric Disorders	167 (26.8)	54 (27.1)	31 (36.5)
Insomnia	80 (12.8)	27 (13.6)	8 (9.4)
Anxiety	49 (7.9)	17 (8.5)	3 (3.5)
Psychotic Disorder	29 (4.6)	15 (7.5)	7 (8.2)
Agitation	23 (3.7)	7 (3.5)	5 (5.9)
Schizophrenia	23 (3.7)	5 (2.5)	13 (15.3)
Restlessness	11 (1.8)	3 (1.5)	2 (2.4)
Respiratory, Thoracic and Mediastinal Disorders	21 (3.4)	14 (7.0)	6 (7.1)
Cough	10 (1.6)	9 (4.5)	4 (4.7)
Nasal Congestion	9 (1.4)	6 (3.0)	1 (1.2)
Skin and Subcutaneous Tissue Disorders	5 (0.8)	4 (2.0)	0
Pruritus	5 (0.8)	4 (2.0)	0
Vascular Disorders	8 (1.3)	3 (1.5)	3 (3.5)
Hypertension	8 (1.3)	3 (1.5)	3 (3.5)

Source: Table 6.1.2.4.a.
(a) Adverse events are coded using MedDRA Version 11.1.
Note: Percentages are based on the number of subjects in the Safety Population. Subjects were counted in all applicable categories but only once within a category.
Note: TEAEs were defined as any adverse event (newly occurring or an exacerbation of a pre-existing condition) with a start date on or after the date of first dose and within 7 days after treatment discontinuation.
Note: P23LTC grouping includes Studies D1050234 and D1050237.

The number of subjects reporting at least one TEAE was lower (approximately 68 %) in Study D1050234 than in Study D1050237 (approximately 85 %). Differences between the two studies were noted with a higher incidence of anxiety, insomnia and psychotic disorder in the lurasidone group in D1050237 than in D1050234. The incidence of nausea and vomiting for lurasidone was lower in D1050234 than in D1050237.

The safety profile was similar when all phase 2/3 controlled and uncontrolled studies were combined compared with the P23STC and P23TC Study Groups.

TEAEs of special interest

Further analyses for P23STC, P23LTC, and P23ALL were conducted on specific TEAEs, which were grouped into clusters for EPS events (and combined events), Metabolic events, and Hypersensitivity events, which were defined based on observations made during the clinical program or known effects of the drug class.

Additionally, a separate cluster was undertaken for analysis of grouped terms for somnolence, dystonia, and parkinsonism.

Extrapyramidal Symptoms (EPS)

In P23ALL, 820 (25.6%) of the “all lurasidone” treated subjects experienced at least 1 treatment-emergent EPS. The most common treatment-emergent EPS that occurred in this group of subjects were akathisia (13.6%), parkinsonism (4.4%), tremor (3.9%), dystonia (3.2%), and restlessness (2.5%). The rate of reporting of each of the EPS was similar between P23STC, P23LTC and P23ALL pools. The percentage of subjects with EPS-related TEAEs was 9.2% for the placebo group, 24.4% for the lurasidone-treated group, 54.2% in the haloperidol group, 23.0% in the olanzapine group, 7.6% in the quetiapine XR group, and 27.7% in the risperidone group.

Tardive dyskinesia and Neuroleptic Malignant Syndrome

In the P23STC, P23LTC and P23ALL tardive dyskinesia occurred in 1 (<0.1%), 4 (0.6%) and 11 (0.3%) lurasidone-treated subjects. In all phase 2/3 short and long-term studies (P23ALL), neuroleptic malignant syndrome occurred in 2 (< 0.1%) lurasidone-treated subjects.

Metabolic Parameters

In P23ALL, 6.5% (n=208) of all-lurasidone subjects had at least 1 metabolic TEAE of which 2 (<0.1%) led to study discontinuation. In P23STC, 3.2% (n=49) of lurasidone-treated subjects had at least 1 metabolic TEAE of which 1 (<0.1%) led to study discontinuation. In P23STC, compared to lurasidone, metabolic TEAEs occurred in 0 in haloperidol, 30 (24.6%) with olanzapine, 13(10.9%) quetiapine XR and 1(1.5%) risperidone.

In P23LTC, 8.8% (n=55) of flexible-lurasidone treated subjects had at least 1 metabolic TEAE of which 0 led to study discontinuation. In D1050234 metabolic TEAEs occurred in 13 (6.3%) of lurasidone treated subjects and 9 (10.6%) of quetiapine XR treated subjects. In D1050237, metabolic TEAEs occurred in 49 (11.7%) of lurasidone treated subjects and 42 (20.8%) of risperidone treated subjects

Weight Gain

In all phase 2/3 short and long-term studies (P23ALL), weight increased was reported in 134 (4.2%) all-lurasidone subjects. In pooled short-term (6-week) clinical trials (P23STC), TEAE of weight increased was reported in 12 (1.7%) placebo, 33 (2.2%) in all lurasidone, compared to 0 in haloperidol, 25 (20.5%) in olanzapine, 12 (10.1%) in quetiapine XR, and 1 (1.5%) in risperidone, treated subjects. In P23STC the mean change in weight was a 0.43 kg increase for lurasidone treated patients compared to a 0.02 kg decrease for placebo-treated patients. In P23STC a ≥ 7% weight increase occurred in 23 (3.3%) placebo, 71 (4.8%) in all lurasidone treated subjects, 3 (4.2) in haloperidol, 42 (34.4%) olanzapine, 17 (15.3%) in quetiapine XR and 4 (6.2%) in risperidone treated subjects.

In all phase 2/3 long-term studies (P23LTC), weight increased was reported in 46 (7.4%) flexible-lurasidone subjects. In D1050234, TEAE of weight increased in 4.8% of Lurasidone treated subjects versus 8.2% of quetiapine XR in D1050234. In D1050237 weight increase was reported in 39 (9.3%0 of lurasidone and 40 (19.8%) of risperidone, treated subjects.

Following 12 months treatment in D1050237 a ≥ 7% weight increase was observed in 30 (7%) lurasidone, compared to 27 (14%) risperidone, treated subjects. In D1050234, ≥ 7% weight increase was observed in 21 (11.5%) lurasidone versus 6 (8.2%) quetiapine XR treated subjects after 12 months treatment.

Dyslipidaemia

In the phase 2/3 short-term studies pool (P23STC), TEAEs coded to preferred MedDRA terms blood triglycerides increased, hypertriglyceridemia, and hyperlipidaemia occurred in 5 (0.3%), 0, and 0 lurasidone-treated subjects, respectively.

In the phase 2/3 long-term studies pool (P23LTC), TEAEs coded to preferred MedDRA terms blood triglycerides increased, hypertriglyceridemia, and hyperlipidaemia occurred in 3 (0.5%), 0, and 1 (0.2%), in flexible-lurasidone subjects, respectively.

In all phase 2/3 short and long-term studies (P23ALL), TEAEs coded to preferred MedDRA terms blood triglycerides increased, hypertriglyceridemia, and hyperlipidaemia occurred in 32 (1.0%), 3 (<0.1%), and 7 (0.2%) of all-lurasidone subjects, respectively.

In pooled short-term (6-week) clinical trials, the mean (SD) change in total fasting cholesterol from Baseline to LOCF for lurasidone-treated subjects was -0.15 (0.75) mmol/L compared to -0.16 (0.77) mmol/L for placebo treated subjects. For fasting low-density lipoprotein (LDL), the mean (SD) change

from Baseline to LOCF levels was -0.09 (0.60) mmol/L for lurasidone-treated subjects compared to 0.09 (0.64) mmol/L for placebo treated subjects. For high-density lipoprotein (HDL), the mean (SD) changes from Baseline to LOCF was -0.02 (0.24) mmol/L for lurasidone-treated subjects compared to --0.07 (0.21) mmol/L in placebo group. Mean change from Baseline to LOCF for triglyceride levels (fasting) was -0.15 (0.80) mmol/L for lurasidone-treated subjects and -0.17 (0.83) mmol/L for subjects in the placebo group.

Diabetes/hyperglycaemia

In P23ALL, the incidence of TEAEs that coded to MedDRA PTs suggestive of hyperglycaemia and diabetes mellitus (blood glucose increased (n=24, 0.7%), glycosylated haemoglobin increased (n=5, 0.2%), hyperglycaemia (n=8, 0.2%), impaired glucose tolerance (n=1, <0.1%), glycosuria (n=1, <0.1%), diabetes mellitus (n=4, 0.1%), and type 2 diabetes mellitus (n=2, <0.1%)) ranged from 0 to 0.7%.

Somnolence

In P23STC somnolence (defined as the combined PTs of hypersomnia, hypersomnolence, sedation and somnolence) was reported in 17.0% of All Lurasidone, and in 7.1% of Placebo-administered subjects. In P23LTC PT somnolence was attributed to 19.9% of Lurasidone, 31.7% of risperidone, 5.9% of Quetiapine XR-treated subjects.

Other TEAEs of special interest included: venous thromboembolism, seizures, cerebrovascular disorders/stroke, orthostatic hypotension, withdrawal syndrome, angioedema, leukopenia/agranulocytosis, bone fracture.

Venous Thromboembolism

There were no TEAEs of venous thromboembolism reported in the phase 2/3 clinical studies.

Seizures

In the all phase 2/3 short and long-term controlled and uncontrolled studies (P23ALL) pool, complex partial seizures occurred in 1 (<0.1%) lurasidone-treated subject and convulsion occurred in 5 (0.2%) lurasidone-treated subjects. There were no reports in either the placebo or active comparator treatment groups.

Cerebrovascular Disorders/Stroke

In P23ALL there were 3 reports of cerebrovascular accidents out of the total number of patients who received lurasidone.

Orthostatic Hypotension

In all phase 2/3 short and long-term studies (P23ALL), 11 (0.3%) lurasidone-treated subjects experienced orthostatic hypotension and 1 (<0.1%) experienced postural orthostatic tachycardia syndrome. In P23STC there were 2 (1.6%) subjects in the olanzapine treatment group, and 3 (2.5%) subjects in the quetiapine XR treatment group who experienced orthostatic hypotension.

Withdrawal syndrome

Based on the cumulative data in P23ALL, no safety signal has been identified following abrupt discontinuation of lurasidone treatment, nor has a withdrawal syndrome associated with lurasidone treatment cessation been observed. There have been no TEAEs of “drug withdrawal syndrome” (PT) reported to date in the phase 2/3 clinical database (IDB). There was 1 TEAE of “withdrawal syndrome” (PT).

Angioedema

There were no cases of angioedema reported in the P23STC pool. One case was reported in the P23LTC pool and 0 cases in the other studies resulting in 1 case reported in the P23ALL pool.

Thus, in all Phase 2/3 short and long-term studies (P23ALL), the TEAE of angioedema occurred in 1 (<0.1%) “all-lurasidone” subjects.

Bone Fracture

In the P23STC subjects, there was 1 (<0.1%) fracture reported in the lurasidone-treated subjects and in the P23LTC pool there were 8 (1.3%) subjects who received flexible dose lurasidone who reported fractures.

The incidence of TEAEs that coded to MedDRA PTs related to bone fractures was low (24 cases [0.7%]) in all-lurasidone subjects in the phase 2/3 studies (P23ALL).

QT prolongation

In safety pool P23STC the frequency of QTc prolongation (male > 450 msec, female > 470 msec) using Bazetts’s correction (QTcB) for the lurasidone-treated and placebo groups was 3.9 % for lurasidone and 3.5 % in the placebo group, respectively. With Fridericia’s correction, the incidence of QTc prolongation was 1.0 % and 3.0 %, respectively. For comparison, the frequency of QTcB prolongation in safety pool P23STC was 4.5 % in the haloperidol 10 mg group, 5.8 % in the olanzapine 15 mg treatment group, 4.7 % in the quetiapine XR 600 mg group, and 6.2 % in the risperidone 4 mg treatment group, and for QTcF prolongation 1.5 % in the haloperidol 10 mg group, 0 % in the olanzapine 15 mg group and the quetiapine XR 600 mg group, and 4.6 % in the risperidone 4 mg treatment group.

In the long-term phase 2/3 comparator controlled studies (P23LTC), the frequency of QTcB prolongation (male QTc >450 msec, female QTc >470 msec) for the flexible dose lurasidone, flexible risperidone and flexible quetiapine XR groups was 6.2%, 13.9%, and 4.6%, respectively. The incidence of prolongation for QTcF for the flexible dose lurasidone, flexible risperidone, and flexible quetiapine XR groups was 1.0%, 2.6%, and 0%, respectively.

ECG measurements taken at various time points during the lurasidone clinical programme did not show any QT prolongations exceeding 500 ms. There were no occurrences of Torsade de pointes, ventricular tachycardia, ventricular fibrillation, or flutter reported in any subjects treated with lurasidone in all short and long-term phase 2/3 studies (P23ALL).

In all short and long-term phase 2/3 studies (P23ALL), among lurasidone-treated subjects, 8 (0.2%) experienced syncope, 2 (< 0.1%) experienced loss of consciousness, 1 (< 0.1%) experienced complex partial seizures, and 5 (0.2%) experienced convulsion. There were no clinically meaningful increases in QTc noted for any of these subjects.

In the P23ALL group, 6 (0.2%) lurasidone-treated subjects experienced ventricular extrasystoles of whom 1 (<0.1%) lurasidone-treated subject in the P23STC group, experienced ventricular extrasystoles reported to be related to the study medication. There was no clinically meaningful increase in QTc duration in this subject.

Thorough QT study

A “Thorough QT” (TQT) study (Study D1050249) was conducted to characterise the potential effect of lurasidone on the QT interval. This study was a double-blind, double-dummy, randomized, three-arm, parallel study in male and female schizophrenic or schizoaffective subjects. A total of 87 subjects (67 male and 20 female) were enrolled in the study and received at least one dose of study drug. Of these, 73 subjects received all doses of study drug and completed all study procedures.

Subjects were administered either lurasidone 120 mg/day (standard dose, n=23) or 600 mg/day (supratherapeutic dose), n=20) over 11 days. A positive control arm was included where subjects were administered ziprasidone 160 mg/day (n=23) over the 11-day treatment period. No placebo arm was included.

Twelve-lead ECGs were obtained Day 0 (baseline) and Day 11 at protocol-specified time points (Day 0: at 1,2,4,6 and 8 hours after time zero. Day 11: at 1,2,4,6 and 8 hours after the AM dose of lurasidone or ziprasidone). To improve the chance to capture any peak effect on QTc, ECG replicates and corresponding means were also extracted at 4 additional time points pre-dose and at the 3-, 5- and 7-hour post dose time points on Day 11, and at matching time points on Day 0. Lurasidone serum concentrations were determined at the following time points: Day 2 to Day 11: trough concentrations; Day 11: 1, 2, 3, 4, 6, 8 and 24 hours post dose.

Pharmacodynamic variables included: ECG intervals (heart rate [HR], PR, RR, QRS, QT). QT interval corrected for heart rate using different approaches: Fridericia's: QTcF=QT/RR0.33, Bazett's: QTcB=QT/RR0.5, Individual: QTcI=QT/RRγi, Population based: QTcP=QT/RRψ and Model-based correction.

Table 44.

Statistical Assessment of Time-matched Change-from-baseline ECG Interval, Primary Analysis Including Protocol-specified Timepoints, ECG Population (Lurasidone Study Arms)

Interval	Nominal Time (h)	Lurasidone 120 mg			Lurasidone 600 mg		
		N	LS Mean	Two-sided 90% CI	N	LS Mean	Two-sided 90% CI
QTcF (ms)	1	23	5.7	(0.1, 11.2)	19	6.9	(1.0, 12.8)
	2	**23**	**10.8**	**(5.4, 16.3)**	20	7.1	(1.4, 12.8)
	4	23	9.3	(4.4, 14.2)	19	7.3	(2.1, 12.6)
	6	23	7.3	(2.5, 12.0)	19	7.2	(2.2, 12.2)
	8	21	7.4	(2.3, 12.5)	**19**	**8.4**	**(3.1, 13.8)**
QTcI (ms)	1	23	3.2	(-2.3, 8.7)	19	4.4	(-1.5, 10.2)
	2	**23**	**9.4**	**(4.2, 14.7)**	20	5.3	(-0.2, 10.9)
	4	23	8.0	(2.7, 13.3)	**19**	**5.8**	**(0.2, 11.5)**
	6	23	4.6	(-0.1, 9.4)	19	4.8	(-0.3, 9.8)
	8	21	4.5	(-0.4, 9.3)	19	6.4	(1.4, 11.4)
QTcP (ms)	1	23	3.7	(-1.6, 9.0)	19	5.5	(-0.2, 11.2)
	2	**23**	**9.7**	**(4.6, 14.9)**	20	6.9	(1.4, 12.3)
	4	23	8.3	(3.3, 13.2)	19	7.1	(1.8, 12.4)
	6	23	4.1	(-0.5, 8.7)	19	5.4	(0.4, 10.3)
	8	21	4.3	(-0.6, 9.1)	**19**	**7.8**	**(2.8, 12.9)**
QTcB (ms)	1	23	10.7	(2.5, 18.9)	19	9.7	(1.1, 18.3)
	2	23	13.9	(6.0, 21.8)	20	7.4	(-0.9, 15.7)
	4	23	11.3	(4.0, 18.5)	19	8.0	(0.3, 15.7)
	6	23	14.3	(7.3, 21.3)	**19**	**11.4**	**(3.9, 18.9)**
	8	**21**	**14.1**	**(6.3, 21.9)**	19	9.8	(1.7, 18.0)
HR (bpm)	1	23	5.2	(0.4, 9.9)	19	3.0	(-2.0, 8.0)
	2	23	2.5	(-1.9, 7.0)	20	0.1	(-4.6, 4.7)
	4	23	1.4	(-3.1, 6.0)	20	1.0	(-3.8, 5.8)
	6	23	6.7	(2.6, 10.9)	20	4.1	(-0.2, 8.5)
	8	21	6.7	(2.0, 11.5)	20	1.0	(-3.9, 5.9)

Note(s): LS=least-squares, CI=confidence interval.

Analyzed values were based on average of the replicates at each timepoint on Day 11 minus the average of the replicates of each corresponding timepoint on Day 0. Results are based on a linear mixed-effect model, with treatment, time, and interaction of treatment by time plus covariates for gender, time-matched baseline value, and prior exposure to aripiprazole with time as a repeated measure. Covariance structure: UN.

The maximum upper bound of the two-sided 90% CI and corresponding LS mean dQTc are presented in bold font.

Source: Table 14.2.5.

In the lurasidone 120-mg study arm, dQTcI increased between 1-hour to 2-hour post dose and declined between 2-hour to 8-hour post dose. The upper bound of the two-sided 90% CI was greater than 10 ms at 2-hour and 4-hour post dose (14.7 and 13.3 ms, respectively).

In the lurasidone 600 mg study arm, the dQTcI versus time profile remained relatively constant with small fluctuations during 8 hours post dose. The upper bound of the two-sided 90% CI was greater than 10 ms at 1-hour, 2-hour, 4-hour and 8-hour post dose (10.2, 10.9, 11.5 and 11.4 ms, respectively).

In the lurasidone 120-mg study arm, the maximum upper bound of the two-sided 90% CI dQTcI of 14.7 ms occurred at 2-hour post dose at which time the mean change from baseline was 9.4 ms.In the lurasidone 600-mg study arm, the maximum upper bound of the two-sided 90% CI of 11.5 ms occurred at 4-hour post dose at which time the mean change from baseline was 5.8 ms.

In the positive control ziprasidone 160-mg study arm, the maximum upper bound of the two-sided 90% CI dQTcI of 22.6 ms occurred at 4-hour post dose at which time the mean change from baseline was 17.7 ms.

There were no patients in the lurasidone arms in the study that experienced absolute QTcI > 450 ms or change from baseline dQTcI > 30 ms. For other correction factors (QTcB, QTcF and QTcP) in both lurasidone study arms, there were no absolute QTc values above 480 ms or change from baseline QTc more than 60 ms. According to the ICH E14 guideline, the thorough QT study (TQT) is to be considered inconclusive (drugs that prolong the mean QT/QTc interval by more than 5 and less than 20 ms; see clinical safety discussion on section 2.6).

Serious adverse event / deaths / other significant events

Overall, 19 deaths were reported during the lurasidone clinical development program. The data cut-off for the reporting was 30 June 2012. Of the 19 deaths, 17 were included in the integrated clinical database (IDB). Two events happened pre-treatment and were not included in the IDB. The following categories of deaths were identified:

- Thirteen lurasidone treatment-emergent deaths;

- Two pre-treatment deaths not included in the IDB;

- Two non-treatment emergent lurasidone deaths;

- Two deaths on comparator drugs.

Of the 13 deaths in lurasidone-treated subjects, there were 3 sudden deaths, 1 death due to hypertensive heart disease and 1 due to myocardial infarction. Five subjects exposed to lurasidone committed suicide. The remaining deaths were due to septic shock (1), thermal burn (1) and road traffic accident (1).

For the 3 subjects classified as ‘sudden deaths’ no autopsies were available. The death of one subject was confounded by administration of intramuscular haloperidol close to the event. One subject, a 73-year old woman with a possible diagnosis of heart infarction or pulmonary embolus as cause of death, had experienced a heart infarction in the past. Where the results of ECG investigations were available, there were no significant changes reported. With regard to concomitant medications, there was no initiation of CYP3A4 inhibitor treatment for any of the subjects. Considering the available data for these 3 subjects, a causal association with lurasidone is considered unlikely.

There were 5 reports of completed suicide in subjects exposed to lurasidone in the P23ALL lurasidone study grouping (n=3202, 0.16 %). These subjects had been on lurasidone for variable times before death (22 days, 24 days, 223 days, 182 days, and 78 days, respectively). The doses of lurasidone were 120 mg, 60 mg, 60 mg, 40 mg and 80 mg, respectively. There was no pattern evident regarding duration of treatment, dose of lurasidone, concomitant medications (e.g. CYP3A4 inhibitors) or demographic characteristics, except that all subjects were Asian. The 5 subjects were between 30-years old and 64-years old.

There was no particular signal from P23STC for suicide or suicidal ideation but the number of suicide attempts and episodes of self-harm appeared to be very low in comparison to the number of completed suicides.

A total of 69 lurasidone treated subjects reported serious adverse events (SAEs) in the double-blind, short-term controlled studies (P23STC). The proportion of subjects with SAEs in this group were the following: 40 of 708 (5.6%) in the placebo group, 69 of 1508 (4.6%) for all-lurasidone group, 5 of 72 (6.9%) in the haloperidol 10 mg, 6 of 122 (4.9%) in the olanzapine 15 mg, 3 of 119 (2.5%) in the quetiapine XR 600 mg, and 2 of 65 (3.1%) in the risperidone 4 mg group.

The 69 lurasidone-treated subjects with SAEs were distributed to the following lurasidone dosing groups: 4 of 71 (5.6%) lurasidone 20 mg, 25 of 487 (5.1%) lurasidone 40 mg, 17 of 538 (3.2%) lurasidone 80 mg, 18 of 291 (6.2%) lurasidone 120 mg, and 5 of 121 (4.1%) lurasidone 160 mg.

In lurasidone-treated subjects from the P23STC group, the most common SAEs were in the psychiatric disorders SOC and included schizophrenia (40 [2.7%] subjects), psychotic disorder (10 [0.7%] subjects), and suicidal ideation (4 [0.3%] subjects). All other SAEs in lurasidone-treated subjects occurred with an incidence of <0.1% (1 subject).

In the pooled long-term, double-blind, active comparator controlled studies (P23LTC), the proportion of subjects with SAEs were distributed as follows: 66 of 624 (10.6%) subjects in the lurasidone group, 17 of 85 (20.0%) subjects for quetiapine XR, and 20 of 199 (10.1%) subjects for risperidone treated subjects. Sixteen of 624 (2.6%) lurasidone-treated subjects, 6 of 199 (3.0%) risperidone treated subjects, and 8 of 85 (9.4%) quetiapine XR subjects experienced SAEs considered related to the study treatment.

The most frequent SAEs in the long-term studies (P23LTC) were in the psychiatric disorders and nervous system disorders SOCs. The most common SAEs in lurasidone-treated subjects in SOC psychiatric disorders included psychotic disorder (19 [3.0%] subjects), schizophrenia (13 [2.1%] subjects), suicidal ideation (2 [0.3%] subjects), schizophrenia, paranoid type (2 [0.3%] subjects), agitation (2 [0.3%] subjects), and anxiety (2 [0.3%] subjects). For nervous system disorders, SAEs were reported in 8 (1.3%) lurasidone-treated subjects, 2 (1.0%) risperidone-treated subjects, and 0 quetiapine XR-treated subjects. Parkinsonism was observed in 2 (0.3%) lurasidone-treated subjects but not in the other treatment groups.

One SAE of angioedema was reported in the P23ALL pool. This SAE was associated with partial airway obstruction and caused discontinuation from the study.

Laboratory findings

Haematology evaluations

For haematology evaluations, there were no changes that are considered to be clinically meaningful. In P23ALL, leukopenia occurred in 1 (<01 %) and neutropenia in 3 (<0.1 %) of lurasidone-treated subjects. No cases of agranulocytosis were reported.

Liver function tests

In short-term, placebo-controlled studies (pool P23STC) the proportion of subjects with normal to high shifts in AST, ALT, and alkaline phosphatase was 3.1%, 4.8%, and 1.0%, respectively for the lurasidone-treated subjects and 4.9%, 4.1%, and 0.7%, respectively for subjects in the placebo group. None of the lurasidone-treated subjects in pool P23STC had a markedly abnormal value (MAV) for liver function tests that met the criteria for Hy's Law.

In the long-term, active comparator-controlled studies (pool P23LTC) in the lurasidone flex group, the proportion of subjects with markedly abnormal laboratory values (MAVs) for AST and ALT (≥3 X upper limit of normal [ULN]) was 0.5% and 1.2%, respectively. No subject in any treatment group had an albumin, alkaline phosphatase, or lactate dehydrogenase (LDH) value that met the criteria for MAV.

In all clinical studies, for the parameters of ALT, AST, Alk phosphatase and LDH, the proportion of lurasidone-treated subjects with ≥ 3xULN post-baseline values was 1.1%, 0.8 %, <0.1 % and <0.1 %, respectively. A total of 0.6 % of subjects had markedly abnormal bilirubin levels (≥35 µmol/L).

Renal function tests

In the phase 3 short-term placebo-controlled studies (pool P23STC) no short-term or long-term adverse changes from baseline over time were observed with lurasidone for bicarbonate, blood urea nitrogen, calcium, chloride, potassium, or sodium.

Slight mean (SD) increases from baseline were observed for creatinine in lurasidone-treated subjects over time: 3.08 (11.76) µmol/L (Week 2), 3.94 (11.48) µmol/L (Week 4), 5.26 (11.84) µmol/L (Week 6), and 4.60 (11.77) µmol/L (LOCF endpoint). In addition, an effect of lurasidone dose on creatinine increase was also observed at each time point. At LOCF endpoint, mean (SD) changes in creatinine from Baseline in the lurasidone 20 mg, 40 mg, 80 mg, 120 mg, and 160 mg dose groups were: 2.86 (11.93) µmol/L, 3.20 (11.42) µmol/L, 4.28 (11.12) µmol/L, 6.23 (12.10) µmol/L, and 8.89 (13.61) µmol/L, respectively. A dose-related increase was observed for lurasidone in the proportion of subjects with shifts from normal/low creatinine at baseline to high creatinine at LOCF endpoint. The incidence of shifts to high creatinine at LOCF endpoint from normal/low at baseline in the lurasidone 20 mg, 40 mg, 80 mg, 120 mg, and 160 mg dose groups were 1.4%, 1.9%,2.2%, 5.0%, and 7.3%, respectively.

In the long-term, active comparator-controlled studies (P23LTC), mean (SD) changes in creatinine (from Baseline to LOCF endpoint) were observed in all treatment groups: 2.86 (17.98) µmol/L, 0.27 (13.15) µmol/L, and 3.03 (15.34) µmol/L for the lurasidone flex, risperidone flex, and quetiapine XR flex treatment groups, respectively.

Lipid parameters

In the short-term placebo-controlled studies (P23STC group), the mean change from baseline to LOCF endpoint for total fasting cholesterol and for fasting triglycerides were very close to the placebo group.

In the long-term, active comparator-controlled studies (P23LTC), mean (SD) change in total fasting cholesterol from baseline to LOCF for lurasidone flex was -0.08 (0.78) mmol/l, compared to -0.12 (0.89) mmol/l for risperidone treated subjects and - 0.21 (0.91) mmol/l for quetiapine XR.

Mean (SD) change in total fasting triglycerides from baseline to LOCF for lurasidone flex was -0.08 (0.84) mmol/l, compared to 0.10 (1.17) mmol/l for risperidone treated subjects and -0.19 (1.05) mmol/l for quetiapine XR.

Glucose levels

In short-term placebo-controlled studies (P23STC group), for fasting glucose, the mean (SD) change from baseline to LOCF endpoint for all lurasidone-treated subjects and subjects in the placebo group was 0.07 (1.19) mmol/L and 0.03 (1.17) mmol/L, respectively. The corresponding changes for the comparators were -0.19 (1.04) mmol/L (haloperidol 10mg), 0.49 (1.75) mmol/L (olanzapine 15 mg), 0.43 (1.19) mmol/L (quetiapine XR 600 mg), 0.06 (0.53) mmol/L (risperidone 4 mg).

In the long-term active controlled studies (P23LTC), there were small mean (SD) changes in fasting glucose across treatment groups from baseline to LOCF: 0.11 (1.21) mmol/L, 0.24 (1.03) mmol/L, and -0.10 (1.23) mmol/L for the lurasidone flex, risperidone flex, and quetiapine XR flex treatment groups, respectively.

Prolactin

In the short-term, placebo-controlled studies (P23STC), there was a trend for increase in prolactin with increasing lurasidone dose. The median values from baseline to LOCF endpoint were: -49.78 pmol/L

(20 mg), -61.00 pmol/L (40 mg), -6.52 pmol/L (80 mg), 143.00 pmol/L (120 mg), and 130.43 pmol/L (160 mg).

The incidence of markedly abnormally high (MAV) prolactin values (≥5xULN) in the P23STC grouping was 2.7 % in lurasidone-treated subjects and 1.0 % for placebo.

In the long-term, active comparator-controlled studies (P23LTC), median values from baseline to LOCF endpoint were -8.00 pmol/L (lurasidone flex), 385.00 pmol/L (risperidone flex), and -17.39 pmol/L (quetiapine XR flex). The incidence of markedly abnormally high prolactin values (≥5xULN) in the overall P23LTC study grouping was 2.0%, 4.0 % and 1.4 % in the lurasidone flex, risperidone flex and quetiapine XR flex groups, respectively. The proportion of male subjects that met the criteria for markedly abnormal prolactin was consistently lower than for female subjects.

In the 22 controlled and uncontrolled studies (P23ALL), treatment-emergent adverse events of "blood prolactin increased" and "blood prolactin abnormal" occurred in 100 (3.1 %) and 1 (<0.1%) of subjects treated with lurasidone, respectively.

Safety in special populations

Gender, race and geographic region

In general there were no important differences in the safety profile by gender or race. For geographic region, however, in the short-term placebo-controlled studies (P23STC), there was in general a lower rate of AEs in studies conducted in Europe compared with other regions. For some SOCs differences were substantial, for example 'gastrointestinal disorders' which occurred at a rate of 40.1 % in North America, 31.6 % in Asia, 27.0 % in South America and only 8.3 % in Europe. The corresponding rates for "musculosceletal disorders" were 18.2 %, 16.2 %, 10.3 % vs. only 0.9 % for Europe.

The reason for the low incidence of certain side effects in Europe compared with other geographical regions might have been related to extrinsic factors, such as medical practice, life style, including social or cultural environment, and disease definition.

Children

No children or adolescents were included in the lurasidone clinical studies.

Elderly

In the P23STC group, the total safety population comprised 2594 subjects. Of the lurasidone-treated subjects in P23STC, 2 % (n=29) were 65 years of age or older. In P23ALL, the subject age ranged from 18 to 74 years. The total number of subjects ≥ 65 years was 72 in the schizophrenia clinical program.

Out of the 72 elderly subjects, 51 (72%) subjects experienced a total of 175 TEAEs across the schizophrenia clinical program. Of those 175 AEs, 75 were considered lurasidone drug-related. The gastrointestinal disorders SOC was most frequently reported, followed by nervous system disorders and then investigations SOC. The most frequently reported lurasidone drug-related AEs included increased blood prolactin, vomiting, and somnolence. Mean (SD) time to onset for the most common nervous system disorders was 9.8 (10.9) days (range, 1-41 days) and they lasted 10.6 (19.1) days (range, 1-91 days).

There were no clinically significant ECG findings noted. No subject older than 65 years had a corrected QTc using Bazett's correction or Fridericia's correction value >500 msec.

Four SAEs were reported in elderly subjects. Three subjects were admitted to hospital due to exacerbation of psychiatric symptoms and the 4th SAE was a fatal case in a 73-year-old female

(lurasidone 80 mg) who died suddenly. The subject had suffered myocardial infarction years earlier. Possible causes of death included pulmonary embolus and myocardial infarction.

Pregnancy

There are no studies of lurasidone in pregnant woman. Six confirmed pregnancies were reported in the clinical studies as of the 30 June 2012 cut-off; all 6 subjects were known to have been treated with lurasidone. For two of the pregnancies, the outcome is unknown. One pregnancy ended in spontaneous abortion and one in elective abortion. One pregnant woman developed pre-eclampsia and this resulted in premature delivery. One child was delivered by C-section as per previous births, there were no complications.

The applicants proposed SmPC for lurasidone states in section 4.6 that there are no data from the use of lurasidone in pregnant women and that lurasidone should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. The proposed SmPC also includes the warning agreed by the PhVWP in September 2011 on the need to carefully monitor neonates following exposure to antipsychotics in the third trimester of pregnancy.

Hepatic impairment

Please see section on Pharmacokinetics.

Renal impairment

Please see section on Pharmacokinetics.

Safety related to drug-drug interactions and other interactions

The applicant conducted several clinical pharmacology and biopharmaceutical studies to examine the effect of extrinsic factors (e.g., food, other drugs) on the administration of lurasidone. Results of these studies showed that in the presence of food, lurasidone is associated with a 3.0-fold increase in mean Cmax and a 2.2-fold increase in mean AUC. In clinical studies, subjects were instructed to take their daily dose with food.

Lurasidone is not a substrate of CYP1A2, CYP2E1, CYP2D6, CYP2B6, CYP2C8, CYP2C9, and CYP2C19 enzymes, and an interaction of lurasidone with drugs that are inhibitors or inducers of these enzymes is unlikely. CYP3A4, however, is responsible for lurasidone metabolism, and an interaction of lurasidone with CYP3A4 inhibitors and inducers has been demonstrated. Lurasidone is contraindicated with strong CYP3A4 inhibitors (e.g. ketokonazole) or strong CYP3A4 inducers (e.g. rifampicin). When lurasidone is given in combination with a moderate CYP3A4 inhibitor like diltiazem, a lower starting dose (20 mg) should be used and the maximum dose of lurasidone should not exceed 80 mg once daily.

Discontinuation due to adverse events

In the short-term, phase 2/3, double-blind, placebo-controlled studies (P23STC), 240 subjects had TEAEs leading to discontinuation: 143 of 1508 (9.5%) lurasidone-treated subjects, 66 of 708 (9.3%) placebo-treated subjects, 8 of 72 (11.1%) haloperidol 10 mg-treated subjects, 12 of 122 (9.8%) olanzapine 15 mg-treated subjects, 4 of 119 (3.4%) quetiapine XR 600 mg-treated subjects, and 7 of 65 (10.8%) risperidone 4 mg treated subjects. The 143 lurasidone-treated subjects with TEAEs leading to withdrawal were distributed in the following lurasidone dosing groups: 0 lurasidone 20 mg; 48 (9.9%) lurasidone 40 mg; 47 (8.7%) lurasidone 80 mg; 40 (13.7%) lurasidone 120 mg; and 8 (6.6%) lurasidone 160 mg.

The most common TEAEs (occurring in ≥3 subjects) leading to discontinuation in lurasidone-treated subjects in study group P23STC were in the psychiatric disorders SOC (schizophrenia, 52 [3.4%] subjects; psychotic disorder, 13 [0.9%] subjects; agitation, 5 [0.3%] subjects; anxiety, 3 [0.2%] subjects; and insomnia, 3 [0.2%] subjects), nervous system disorders SOC (akathisia, 21 [1.4%] subjects; dystonia, 7 [0.5%] subjects; and dyskinesia, 3 [0.2%] subjects), investigations SOC (blood CPK increased, 4 [0.3%] subjects), and gastrointestinal disorders SOC (nausea, 4 [0.3%] subjects and vomiting, 4 [0.3%] subjects).

Schizophrenia, akathisia, psychotic disorder, dystonia, and agitation were the most frequent TEAEs that led to study discontinuation in lurasidone-treated subjects, with an incidence of ≥5 subjects. One subject treated with lurasidone 80 mg experienced a TEAE of increased weight gain that led to permanent discontinuation from the study.

In the long-term, phase 2/3, double-blind, active-comparator controlled studies (P23LTC), 115 subjects had TEAEs leading to discontinuation: 115 of 624 (18.4%) lurasidone flexible dose subjects, 19 of 85 (22.4%) flexible quetiapine XR, and 32 of 199 (16.1%) flexible risperidone treated subjects.

Eleven (1.8%) lurasidone flexible dose subjects, 5 (2.5%) flexible risperidone subjects, and 0 flexible quetiapine XR treated subjects experienced EPS-related TEAEs with the action taken of discontinuation of study medication. One subject only (taking flexible risperidone) experienced metabolic TEAEs with the action taken of discontinuation of study medication.

For the lurasidone flexible dose subjects, the most common TEAEs (occurring in ≥3 subjects) leading to discontinuation were in psychiatric disorders SOC (psychotic disorder, 23 [3.7%] subjects; schizophrenia, 19 [3.0%] subjects; hallucination, auditory, 4 [0.6%] subjects; suicidal ideation, 4 [0.6%] subjects), nervous system disorders SOC (akathisia, 6 [1.0%] subjects), and gastrointestinal disorders SOC (vomiting, 4 [0.6%] subjects).

The most common TEAEs (occurring in ≥3 subjects) leading to discontinuation in flexible dose risperidone subjects were in psychiatric disorders SOC (psychotic disorder, 8 [4.0%] subjects; schizophrenia, 5 [2.5%] subjects; insomnia, 3 [1.5%] subjects), nervous system disorders SOC (akathisia, 3 [1.5%] subjects), and investigations SOC (ECG QT prolonged, 3 [1.5%] subjects). In the flexible quetiapine XR group, the most common TEAEs (occurring in ≥3 subjects) leading to discontinuation were in the psychiatric disorders SOC (schizophrenia, 11 [12.9%] subjects and psychotic disorder, 6 [7.1%] subjects).

Post marketing experience

Lurasidone was approved by the FDA on 28 October 2010 for the treatment of schizophrenia and was launched on 07 February 2011 in the United States (US) using the trade name Latuda. Since launch, approximately 386,900 prescriptions were issued for Latuda in the US, up to and including 30 June 2012. Each prescription is assumed to represent a single patient. This represents an approximate exposure of 32,241 person-years, assuming 1 month supply per prescription. The total exposure number may be underestimated due to the data limitations with dispensed Latuda at institutions or hospitals.

The most commonly reported ADRs were nausea, akathisia, insomnia, rash and anxiety and the most commonly reported Serious ADRs were suicidal ideation, convulsion, death NOS, auditory hallucination and psychotic disorders.

There were two reports of QT interval prolongation but one of these reports does not include any other information. The other report concerned a 56-year-old male patient who was prescribed 40 mg bid. of lurasidone and his QTc interval increased from 472 ms at baseline to 504 ms. The attending physician

considered this to be related to lurasidone and the drug was discontinued. His QT interval returned to 476 ms. This patient was concurrently receiving unspecified cardiac medications.

Forty-six reports of angioedema-related terms were reported in the postmarketing setting up to 31 December 2012, whereby approximately 312,300 patients were exposed to lurasidone in the United States, and 607 patients were exposed to lurasidone in Canada. Of the 46 postmarketing reports, 11 reports were serious, which included 1 report of angioedema, and 35 were nonserious, and included 2 reports of angioedema.

In the post-marketing experience up to 30 June 2012, there were no reports identified that were associated with a drug interaction.

Safety data from study D1050238

Adverse events

An overall summary of TEAEs in the open-label phase is provided in Table 45.

Table 45. Overview of TEAEs, Open-Label Phase.

	Number (%) of Subjects	
	Nonrandomized	Total
Number of Subjects With:	N=391	N=676
At least 1 TEAE	286 (73.1)	495 (73.2)
Drug-related TEAE	193 (49.4)	345 (51.0)
EPS-related TEAE (a)	80 (20.5)	141 (20.9)
Hypersensitivity-related TEAE (b)	25 (6.4)	39 (5.8)
Metabolic TEAE (c)	7 (1.8)	22 (3.3)
Serious TEAE	53 (13.6)	59 (8.7)
Serious drug-related TEAE	16 (4.1)	16 (2.4)
Discontinuation due to TEAE	84 (21.5)	84 (12.4)
Treatment-emergent death	1 (0.3)	1 (0.1)

EPS=extrapyramidal symptoms.

Note: EPS and metabolic TEAEs were identified by medical review of PTs prior to database lock.

(a) EPS TEAEs included the following PTs: Akathisia, Dystonia, Parkinsonism, Restlessness, Tremor, Drooling, Muscle rigidity, Oromandibular Dystonia.

(b) Hypersensitivity TEAEs included the following PTs: Rash, Pruritus, Asthma, Pruritus generalised, Dermatitis contact, Hypersensitivity, Hypotension, Oedema peripheral, Urticaria, Allergic oedema, Conjunctivitis allergic, Food allergy.

(c) Metabolic TEAEs included the following PTs: Weight increased, Glycosuria, Blood glucose increased, Blood triglycerides increased, Hypercholesterolaemia, Hyperglycaemia, Hyperlipidaemia, Hypoglycaemia Impaired fasting glucose and Type II Diabetes Mellitus.

The most frequently affected SOCs were nervous system disorders 150 (38.4%), then psychiatric disorders 108 (27.6%), and gastrointestinal disorders 95 (24.3%). Within nervous system disorders SOC, the most frequently reported TEAEs were headache (12.8%), akathisia (12%), followed by somnolence (3.6%) and sedation (2.8%). The most frequently reported events in psychiatric SOC were insomnia (7.4%) and anxiety (4.3%). Nausea (9.5%) and vomiting (5.4%) were the most frequently reported TEAEs in gastrointestinal SOC. These were consistent with previous studies, both short-term and long-term.

Table 46. Overview of TEAEs, Double-Blind Phase.

	Number (%) of Subjects	
	Lurasidone	Placebo
Number of Subjects With:	N=144	N=141
At least 1 TEAE	77 (53.5)	77 (54.6)
Drug-related TEAE	47 (32.6)	36 (25.5)
EPS-related TEAE (a)	6 (4.2)	6 (4.3)
Hypersensitivity-related TEAE (b)	1 (0.7)	2 (1.4)
Metabolic TEAE (c)	8 (5.6)	7 (5.0)
Serious TEAE	6 (4.2)	11 (7.8)
Serious drug-related TEAE	2 (1.4)	4 (2.8)
Discontinuation due to TEAE (d)	20 (13.9)	22 (15.6)
Treatment-emergent death	0	0

EPS=extrapyramidal symptoms.

Note: EPS and metabolic TEAEs were identified by medical review of PTs prior to database lock.

(a) EPS TEAEs included the following PTs: Akathisia, Dystonia, Parkinsonism, Restlessness, Tremor, Drooling, Muscle rigidity, Oromandibular Dystonia.

(b) Hypersensitivity TEAEs included the following PTs: Rash, Pruritus, Asthma, Pruritus generalised, Dermatitis contact, Hypersensitivity, Hypotension, Oedema peripheral, Urticaria, Allergic oedema, Conjunctivitis allergic, Food allergy.

(c) Metabolic TEAEs included the following PTs: Weight increased, Glycosuria, Blood glucose increased, Blood triglycerides increased, Hypercholesterolaemia, Hyperglycaemia, Hyperlipidaemia, Hypoglycaemia Impaired fasting glucose and Type II Diabetes Mellitus.

(d) Discontinuation due to TEAE also includes TEAEs that are associated with relapse event of worsening of schizophrenia.

The incidence of TEAEs occurring in the double-blind safety population was similar between lurasidone and placebo-treated subjects, 53.5% and 54.6% respectively. The incidence of EPS-related TEAEs and metabolic TEAEs were similar between the 2 treatment groups. The incidence of drug related TEAEs was higher in lurasidone-treated subjects 32.6% compared to 25.5% in placebo-treated subjects. SAEs and serious drug-related AEs were higher in the placebo-treated subjects. Discontinuation due to TEAEs was slightly higher in placebo-treated subjects.

The most commonly reported TEAEs in this SOC were schizophrenia (7.6%) and insomnia (6.3%). The next most frequently affected SOC was nervous system disorders with an incidence of 17 (11.8%), with headache (3.5%) and akathisia (2.1%) the most commonly reported TEAEs in this SOC. Gastrointestinal disorders was the third most frequently affected SOC (11.1%).

Serious adverse event / deaths / other significant events

Table 47. Summary of Serious TEAEs by SOC and PT: Open-Label Phase.

SOC/ PT	Number (%) of Subjects	
	Nonrandomized	Total
	N=391	N=676
Number of subjects with at least 1 serious TEAE (a)	53 (13.6)	59 (8.7)
Gastrointestinal disorders disorders	1 (0.3)	1 (0.1)
Gastrooesophageal reflux disease	1 (0.3)	1 (0.1)
General disorders and administration site conditions	3 (0.8)	3 (0.4)
Drug ineffective	1 (0.3)	1 (0.1)
Sudden cardiac death	1 (0.3)	1 (0.1)
Therapeutic response delayed	1 (0.3)	1 (0.1)
Hepatobiliary disorders	0	1 (0.1)
Cholelithiasis	0	1 (0.1)
Injury, poisoning and procedural complications	2 (0.5)	4 (0.6)
Facial bones fracture	0	1 (0.1)
Intentional overdose	1 (0.3)	1 (0.1)
Overdose	1 (0.3)	1 (0.1)
Radius fracture	0	1 (0.1)
Metabolism and nutrition disorders	2 (0.5)	2 (0.3)
Hypoglycaemia	1 (0.3)	1 (0.1)
Hyponatraemia	1 (0.3)	1 (0.1)
Nervous system disorders	1 (0.3)	1 (0.1)
Akathisia	1 (0.3)	1 (0.1)
Psychiatric disorders	42 (10.7)	44 (6.5)
Psychiatric disorder	20 (5.1)	20 (3.0)
Psychotic disorder	11 (2.8)	11 (1.6)
Suicidal ideation	3 (0.8)	3 (0.4)
Anxiety	0	2 (0.3)
Depression	2 (0.5)	2 (0.3)
Acute pyschosis	1 (0.3)	1 (0.1)
Aggression	1 (0.3)	1 (0.1)
Agitation	1 (0.3)	1 (0.1)
Hallucination, auditory	1 (0.3)	1 (0.1)
Homicidal ideation	1 (0.3)	1 (0.1)
Hostility	1 (0.3)	1 (0.1)
Psychiatric decomposition	1 (0.3)	1 (0.1)
Substance-induced psychotic disorder	1 (0.3)	1 (0.1)
Suicide attempt	1 (0.3)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	2 (0.5)	3 (0.4)
Acute respiratory failure	1 (0.3)	1 (0.1)
Asthma	0	1 (0.1)
Respiratory failure	1 (0.3)	1 (0.1)

(a) A subject might have had 2 or more AEs, the subject is counted only once in a category.

Table 48. Summary of Serious TEAEs by SOC and PT: Double-Blind Phase.

SOC/ PT (a)	Number (%) of Subjects	
	Lurasidone	Placebo
	N=144	N=141
Number of subjects with at least 1 serious TEAE	6 (4.2)	11 (7.8)
Cardiac disorders	0	2 (1.4)
Angina pectoris	0	1 (0.7)
Atrial fibrillation	0	1 (0.7)
General disorders and administration site conditions	0	1 (0.7)
Non-cardiac chest pain	0	1 (0.7)
Injury, poisoning and procedural complications	1 (0.7)	1 (0.7)
Toxicity to various agents	1 (0.7)	0
Road traffic accident	0	1 (0.7)
Musckoskeletal and connective tissue disorders	1 (0.7)	0
Pain in extremity	1 (0.7)	0
Nervous system disorders	1 (0.7)	0
Headache	1 (0.7)	0
Transient ischaemic attack	1 (0.7)	0
Psychiatric disorders	3 (2.1)	7 (5.0)
Psychiatric disorder	2 (1.4)	2 (1.4)
Schizophrenia	1 (0.7)	4 (2.8)
Suicide attempt	0	1 (0.7)
Respiratory, thoracic and mediastinal disorders	1 (0.7)	0
Dyspnoea	1 (0.7)	0

(a) Although a subject may have had 2 or more AEs, the subject is counted only once in a category.

The incidence of SAEs was higher in the placebo-treated subjects, with a rate of 7.8% compared with 4.2% in lurasidone-treated subjects. The most frequent SAEs occurred in psychiatric disorders SOC, with the most frequently reported PTs of schizophrenia and psychiatric disorders, 2.8% and 1.4% respectively.

A single subject, a 48-year-old black female, suffered a fatal event during the open-label phase of the study. Cause of death was recorded as sudden cardiac death. The investigator considered the event to be not related to lurasidone.

Other safety findings

Additionally, metabolic laboratory parameters, prolactin and weight increase were comparable to placebo. No abnormal QTc signal was observed with lurasidone treatment. No signal was noted for suicidality with lurasidone treatment.

2.6.1. Discussion on clinical safety

The clinical development program for lurasidone included 31 clinical pharmacology studies and 22 phase 2/3 clinical studies involving 5068 subjects with schizophrenia (3502 treated with lurasidone, 724 with placebo and 842 treated with other medications). The total exposure to lurasidone in the phase 2/3 clinical database was 1,212 person years. The number of patients and the duration of treatment for which safety data are available in the all lurasidone treated group fulfils the requirements in the guideline on population exposure (ICH E1). However, the number of exposed patients for the highest dose group 160 mg/day in the short-term placebo controlled studies was considered to be limited. The applicant was therefore asked to provide additional exposure data for subjects treated with lurasidone 160 mg/day. In the response the data on exposure in the short-term placebo-controlled studies (40 mg dose- 61.2 PY, 60 mg dose -59.2 PY, 120 mg dose -31.4 PY and 160 mg -12

PY) and in the 12-month flexible dose study D1050234 (46.59 PY to 160 mg/day) were provided. The total exposure for the 160 mg dose in patients with schizophrenia across all phase I and phase 3 studies was 58.78 person-years. With the additional information provided by the applicant, the total exposure to the 160 mg dose in the lurasidone clinical program was considered acceptable.

The clinical development did not include paediatric population; however a Paediatric Investigation Plan (PIP) for lurasidone in the treatment of schizophrenia, including a waiver for subsets of the paediatric population and deferral of planned studies, has been approved.

Certain patient groups including patients with clinically significant cardiovascular disease, active epilepsy or Parkinson's disease were excluded from the clinical studies. However, the postmarketing experience for lurasidone in the US is considerable and represents approximately 32,241 person years.

The CHMP noted also that the exposure in the elderly was limited. The applicant was requested to discuss the safety of lurasidone in this population based on the pharmacodynamic data and occurrence of adverse events. In the response, the applicant clarified that 72 elderly subjects (≥65 years) were exposed to lurasidone with 72 % experiencing 175 TEAEs. The results obtained with elderly subjects showed that there was no apparent relationship between the incidence of adverse events and the dose of lurasidone. The elderly subjects received mainly low doses of lurasidone in the clinical studies. Despite receiving lower doses of lurasidone the elderly experienced a higher rate of adverse events. Although generally the safety profile observed for the elderly subjects was similar to that seen in the younger population asthenia was prominent at the maximum administered dose of 120 mg, however the number of patients exposed was very low (n=5). In conclusion, the applicant acknowledged that limited safety information was available for the elderly. This is reflected in the RMP and the product information. The evaluation of the lurasidone effects in the elderly will be included in the PASS.

Overall, the spectrum of adverse drug reactions was similar to that for other approved atypical antipsychotic drugs. The most common treatment related adverse drug reactions (with an incidence higher than placebo) in the placebo-controlled studies were akathisia, somnolence, sedation, nausea, insomnia and vomiting. For akathisia and somnolence as well as dizziness (another common TRAE) the incidence was dose-related. The CHMP noted that in the highest dose group of lurasidone (160 mg/day), adverse drug reactions occurred with an unexpected low frequency in study D1050233. In this study lurasidone was administered in the evening which may have lowered the incidence of some ADRs. Nausea and vomiting occurred more frequently for lurasidone than for the comparators both in the short-term and the long-term controlled studies.

A thorough QTc (TQT) study was conducted, which was considered inconclusive according to the ICH E14 guideline (drugs that prolong the mean QT/QTc interval by more than 5 and less than 20 ms). There were no patients treated with lurasidone in the TQT study who experienced QTc increase > 60 ms from baseline or with a QTc > 480 ms. In the clinical development, there were no adverse events that could be linked to QT prolongation in the lurasidone short-term or long-term phase 2/3 studies. ECG measurements taken at various time points during the lurasidone phase 2/3 clinical programme did not show any QTc prolongations exceeding 500 ms. However, post marketing there were two reports of QT prolongation exceeding 500 ms. The applicant was requested to discuss the risk of QT prolongation when using lurasidone in renal impairment, when drug interactions may occur and when lurasidone is co-prescribed with other antipsychotics. In the response, the applicant provided data from PBPK modelling for renal impairment and drug interactions, and proposed amendments to the product information regarding dosing in renal impairment, warnings on co-administration with antipsychotics and in patients with risk factors for QT prolongation. Furthermore, following the CHMP recommendation the planned PASS protocol was amended to include all cardiovascular events.

The applicant was requested to discuss the safety of Lurasidone use when additional antipsychotic medication is required, particularly parenteral antipsychotics, in the acute management of psychosis.

The applicant described in more detail the three deaths in patients who received concomitant medication, i.e. one death was due to septicaemia, whereas the other two deaths were sudden and the causes were not clear. The applicant proposed the appropriate wording in the product information and included the evaluation of lurasidone/antipsychotic combination therapy in relation to each safety outcome of interest in the PASS protocol.

During the assessment the CHMP expressed concerns regarding suicidality in lurasidone-treated patients. The applicant was asked to discuss the suicidality signal and its relationship to the lurasidone safety profile, together with the reasons for the observed low rates of suicide attempt and self-harm in relation to the completed suicide rate. The applicant clarified that five of 3202 subjects in the lurasidone arms were confirmed to have died as a result of suicide (0,41 per 100 PY). There were 2 additional deaths in the lurasidone arm for which suicide could not be completely excluded thereby increasing the suicide rate to 0.57 per 100 PY. This compared favourably with the suicide rates reported for other second generation antipsychotics (SGAs). Regarding the reasons for the low observed rates of suicide attempt and self-harm in relation to the completed suicide rate in the lurasidone studies, the applicant argued that due to the very small completed suicide prevalence estimate (0.16% to 0.22%) in the lurasidone clinical program, extrapolation to the ratio of completed to attempted sucide/self-harm cited in the literature may be unreliable. One additional factor referred to by the applicant was the fact that lurasidone studies excluded subjects with an imminent risk of suicide, history of deliberate self-harm and those with personality disorders such as borderline personality disorder who have high reported rates of suicidal behaviour. The applicant argued that this may further explain the low observed number of suicide attempts compared to number of completed suicides. In conclusion, the clinical trial population is likely to have a lower risk of suicidality. The applicant will include suicidality as an important potential risk in the RMP. This is considered appropriate to address the issue, combined with the proposed warning in the SmPC.

A moderate dose dependant increase of prolactin was observed for lurasidone, however lower than for risperidone 4 mg and haloperidol 10 mg. The increase in prolactin was more pronounced in female than in male patients. Endocrinological side effects including galactorrhoea, amenorrhea and erectile dysfunction occurred with a low incidence.

In the short-term placebo-controlled studies increases in creatinine correlated to dose and duration of lurasidone treatment were observed. A higher proportion of lurasidone-treated subjects (48.1 %; 726/1508) than placebo-treated subjects (37.3 %; 264/708) had >10 % increase in serum creatinine (S-Cr) at any time point during those studies. The applicant clarified that the increases in creatinine in the short term studies were isolated and not accompanied by any other indicators of renal damage. The review of the outcomes for those subjects who had a change in creatinine above 10 % of their baseline value revealed that in 691/726 subjects the value remained within the reference interval for S-Cr, whereas 35 lurasidone-treated subjects had a value greater than the ULN at any time point. In most of these 35 subjects where follow-up data are available S-Cr returned to normal with continued lurasidone treatment. Additional laboratory investigations in subjects with creatinine increase have not indicated any associated renal parenchymal damage, and there were no clinically relevant changes from baseline in the urinalysis parameters. Increased serum creatinine has been added as an important potential risk to the RMP, and serum creatinine, renal impairment and renal failure has been included as outcomes in the proposed PASS. In addition, the applicant included “serum creatinine increased” in the section 4.8 of the SmPC.

Lurasidone had small effects on blood lipids and blood glucose, and produced moderate weight increase.

In response to a question related to orthostatic hypotension during lurasidone treatment the applicant provided data from three phase I studies in healthy male volunteers and 2 studies in subjects with

schizophrenia. Three of these studies recorded orthostatic measurements, whilst the other 2 studies recorded supine and sitting BP measurements. Incidences of orthostatic hypotension were observed in the 3 phase 1 studies that collected orthostatic BP measurements. The magnitude of the drop in systolic and diastolic pressures was in the range of 20-30mm Hg systolic and 10-16mmHg diastolic. No apparent relationship was observed between the dose of lurasidone administered and the occurrences of orthostatic hypotension reported. Appropriate warnings are proposed in the SmPC.

There was one SAE of angioedema in the clinical studies, and additional 4 SAEs and 14 non-serious AEs of angioedema and related terms reported post-marketing at the time of initial MAA filing. The applicant was asked to review all reports of angioedema and related terms in the clinical studies and the post-marketing period. The applicant performed a search using Standard MedDRA Query (SMQ) Angioedema from MedDRA (version15.1). A total of 68 reports of angioedema-related SMQ terms were received in the phase 2/3 clinical development program, 10 of which were related to the comparator antipsychotic groups and 5 related to placebo. The events occurred most frequently at lurasidone doses of 80 mg and 120 mg. Forty-six reports of angioedema-related terms were reported in the postmarketing setting up to 31 December 2012, whereby approximately 312,300 patients were exposed to lurasidone in the United States, and 607 patients were exposed to lurasidone in Canada. Of the 46 postmarketing reports, 11 reports were serious, which included 1 report of angioedema, and 35 were nonserious, and included 2 reports of angioedema. For some of the reports there were possible confounding concomitant medications. Angioedema is included as an important potential risk in the RMP and is listed in the section 4.8 of the proposed SmPC. Hypersensitivity to lurasidone and the excipients is included as a contraindication in section 4.3 of the SmPC.

The occurrence of seizures and convulsions in the clinical studies and post-marketing was also reviewed by the applicant in response to the committee's request. For the P23ALL group, convulsions occurred in 4 lurasidone-treated subjects between 10-419 days of administration with a dose range of 20-120 mg/day. All 4 reports were serious and considered related to lurasidone treatment. A total of 16 post-marketing reports were received of which five reports were not well documented. Four cases reported suspect concomitant medications. Two reports were considered life-threatening, and several of the events occurred within a relatively short time following initiation of treatment which suggests a causal relationship to lurasidone. The applicant has added a statement to the section 4.4 of the lurasidone SmPC in line with information for other antipsychotic medications: "… should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold." In addition, the applicant included convulsions in section 4.8 of the SmPC and seizures in the RMP as an important potential risk.

In conclusion, from the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Lurasidone has a spectrum of side effects that is similar to that for other atypical antipsychotic drugs. The most common treatment related side effects (with an incidence higher than placebo) in the short-term placebo-controlled studies were akathisia, somnolence, sedation, nausea, insomnia and vomiting. For akathisia, somnolence and another common TRAE dizziness the incidence was dose related. Also for extrapyramidal symptoms (EPS) such as dystonia, tremor, Parkinsonism and salivary hypersecretion there was a trend for dose relation and these AEs occurred with the highest frequency in the lurasidone 120 mg/day dose group. The incidence of EPS was in general lower for lurasidone than for haloperidol 10 mg. Nausea and vomiting occurred with a higher incidence for lurasidone than for the comparators. Effects of lurasidone on blood lipids, glucose and HbA1c were limited, and the

effect on weight increase moderate, which is considered to indicate a relatively favourable metabolic profile.

The CHMP considers the following measures necessary to address issues related to safety:

1. MEA: PASS "Characterising the safety profile of lurasidone in clinical practice: A drug utilisation and safety study using a United Kingdom primary care database" (included in RMP as Category 3).

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

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

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 1.0, the PRAC considers by consensus that the risk management system for Lurasidone hydrochloride (Latuda) in the treatment of schizophrenia in adults aged 18 years and over is acceptable.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

Table 49. Summary of the Safety Concerns.

Summary of Safety Concerns	
Important identified risks	Extrapyramidal symptoms Drug interactions with strong cytochrome P-450 3A4 inhibitors or inducers
Important potential risks	Angioedema Neuroleptic malignant syndrome Tardive dyskinesia Metabolic profile (Hyperglycaemia, Weight increased, Dyslipdemia) Rhabdomyolysis Suicidality (suicidal ideation, suicidal behaviour, suicide attempt, self-harm and completed suicide) Agranulocytosis Seizure Increased serum creatinine Use in patients with moderate or severe renal impairment Use in patients with moderate or severe hepatic impairment Off-label use: • Bipolar disorder • Elderly with dementia • Doses higher than 148 mg/day Third trimester exposure during pregnancy and risk to neonates
Missing information	Elderly patients Patients with cardiac impairment Pregnant or lactating women

Summary of Safety Concerns	
	Children and adolescents Long-term safety Potential drug-drug interactions with drug metabolising enzymes and transporters

Pharmacovigilance plans

Table 50. Ongoing and planned studies in the PhV development plan.

Study / Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
PASS/ Characterising the safety profile of lurasidone in clinical practice: A longitudinal cohort study using a UK primary care database	1) To measure incidence rates and rate ratios of selected safety outcomes in patients with schizophrenia prescribed lurasidone and other second generation antipsychotics in a real world setting. 2) To describe patterns of utilisation of lurasidone that might be related to its safety including off-label use in children and use in patients identified to be at risk or potential risk in the Risk Management Plan.	To further characterise the identified and potential risks and missing information	Planned	Planned post-authorisation (estimated date of completion 2021)
D1001057/ A long-term extension study of SM-13496 (lurasidone HCl)	To evaluate the long-term safety and efficacy of lurasidone (40 and 80 mg per day) in patients with schizophrenia.	Long-term safety	Ongoing	Estimated completion date February 2016
D1050298/ A long-term, multicentre, open-label, flexible dose continuation study of lurasidone	To evaluate long-term safety, tolerability, and effectiveness of lurasidone in eligible subjects who have completed a prior lurasidone extension study.	Long-term safety	Ongoing	Estimated completion date August 2016
D1050307/ An open-label extension study of lurasidone in clinically stable outpatients	To evaluate long-term safety, tolerability, and effectiveness of lurasidone in eligible subjects who have completed a prior lurasidone extension study.	Long-term safety	Ongoing	Estimated completion date April 2014
D1050300/ pharmacokinetic, safety and tolerability study in subjects from 6 to 17 years of age with schizophrenia, bipolar, autistic spectrum disorder, or any other psychiatric disorders	To characterize the pharmacokinetics and assess safety and tolerability of single and multiple oral doses of 20, 40, or 80 mg/day lurasidone in subjects 6 to 17 years old with schizophrenia spectrum, bipolar spectrum, autistic spectrum disorder, or other psychiatric disorders.	Use in children and adolescents	Clinically complete; final clinical study report pending submissio n	Estimated completion date November 2013
In Vitro Study	To assess if the active lurasidone metabolite ID-14823 is a substrate of the liver uptake transporters (OATP1B1 and OATP1B3).	Potential drug-drug interactions with drug metabolising enzymes and transporters	Planned	Estimated End 2014
In Vitro Study	To investigate if lurasidone causes time-dependent inhibition of CYP2C8 and CYP2B6.	Potential drug-drug interactions with drug metabolising enzymes and	Planned	Estimated End 2014

Study / Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
		transporters		
In Vitro Study	An in vitro solubility study of lurasidone in FESSIF (fed state simulated intestinal fluid) to estimate the maximum intestinal lurasidone concentration and consequently the clinical relevance of P-gp and BCRP inhibition	Potential drug-drug interactions with transporters	Planned	Estimated End 2014

Risk minimisation measures

Table 51. Summary table of Risk Minimisation Measures.

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risks		
Extrapyramidal movement disorders: akathisia, parkinsonism and dystonia	As part of routine risk minimisation text is included in section 4.4 (Special warnings and precautions for use) of the SmPC: and is included in section 4.8 (Undesirable effects) of the SmPC:	None
Drug interactions with strong CYP4A inhibitors or inducers	As part of routine risk minimisation text is included in sections 4.2 (Posology and method of administration) of the SmPC: 4.3 (Contraindications)of the SmPC: Section 4.5 (Interaction with other medicinal products and other forms of interaction) of the SmPC:	None
Important Potential Risks		
Angioedema	As part of routine risk minimisation information on hypersensitivity reactions is included in section 4.3	None
Neuroleptic Malignant syndrome	As part of routine risk minimisation text is included in section 4.4	None
Tardive dyskinesia	As part of routine risk minimisation text is included in section 4.4	None
Metabolic profile (Hyperglycemia, Weight increased, dyslipidemia)	As part of routine risk minimisation text is included in section 4.4 *"Blood glucose increased"* is included as an uncommon ADR in section 4.8	None
Rhabdomyolysis	*"Rhabdomyolysis"* is included as a rare ADR in section 4.8	None
Suicidality (suicidal ideation, suicidal behaviour, suicide attempt, self-harm and completed suicide)	As part of routine risk minimisation text is included in section 4.4 *"Suicidal behaviour"* is included as an ADR (frequency unknown) in section 4.8	None
Agranulocytosis	As part of routine risk minimisation "*Leukopenia"*	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	and *"Neutropenia"* are included as ADRs (frequency unknown) in section 4.8	
Seizure	As part of routine risk minimisation text is included in section 4.4 *"Convulsion"* is included as an ADR (frequency unknown) in section 4.8	None
Increased serum creatinine	"*Renal failure"* is included as an ADR (frequency unknown) in section 4.8	None
Patients with moderate or severe renal impairment	As part of routine risk minimisation information text is included in section 4.2 and section 4.4	None
Patients with moderate or severe hepatic impairment	As part of routine risk minimisation text is included in section 4.2 and section 4.4	None
Off-label use: • Bipolar disorder	Section 4.1	None
• Elderly with dementia	section 4.4	None
• Doses higher than 148 mg/day	Section 4.2	None
Third trimester exposure and risk to neonates	As part of routine risk minimisation information around the use of lurasidone in pregnancy is included in section 4.6	None
Missing Information		
Elderly patients (≥65 years)	As part of routine risk minimisation text is included in section 4.2 and section 4.4	None
Patients with cardiac impairment	As part of routine risk minimisation information around the use of lurasidone in patients with cardiovascular disorders is included in section 4.4	None
Pregnant or lactating women	As part of routine risk minimisation information on the use of lurasidone in pregnancy and breastfeeding is included in section 4.6 .	None
Children and adolescents	As part of routine risk minimisation information on the use of lurasidone in children and adolescents is included in section 4.2	None
Long-term safety	None required at this time.	None
Potential drug-drug interactions with drug metabolising enzymes and transporters	None required at this time.	None

The CHMP endorsed this advice without changes.

2.9. 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

In acute studies differences of about 10 points in PANSS-T change from baseline were shown for lurasidone at a dose range of 40 to 120 mg while the highest treatment effect (~15 points) was achieved at the highest dose of 160 mg, demonstrated in one clinical study. The short-term treatment effect observed based on PANSS-T scores was supported by the congruency in CGI-S results. Treatment differences in CGI-scores between baseline and week 6 in study D1050231 comparing the efficacy of lurasidone 40 and 120 mg respectively and olanzapine 15 mg to placebo were: LUR 40 mg, LS mean (SE) -0.3 (0.1), p=0.012; 120 mg, LS mean (SE) -0.2 (0.1), p=0.075, OLA 15 mg, LS mean (SE) -0.5 (0.1), p=<0.001. In the other pivotal placebo- and active controlled short-term study D1050233 comparing the effect of lurasidone 80 mg, 160 mg and quetiapine XR 600 mg to placebo, CGI-S scores similarly decreased from baseline to end of study, namely LUR 80 mg mean (SE) -0.6 (0.1), p<0.001; 160 mg mean (SE) -0.8 (0.1), p<0.001 and QUE XR 600 mg -0.8 (0.1), p<0.001.

In addition, responder rates (≥20%), i.e. improvement in efficacy outcome measures (PANSS-T) between baseline and study endpoint were demonstrated at each lurasidone dose (Study D1050231; LUR 40 mg, 120 mg and OLA 15 mg: 62% (p=0.054), 60% (p=0.108) and 74% (p=<0.001), respectively. In study D1050233, the corresponding ≥20% PANSS-T score reduction from baseline to study endpoint at week 6 for the 80 mg and 160 mg lurasidone doses were 65% (p=<0.001), and 79% (p=<0.001), respectively compared to 79% (p=<0.001) for quetiapine XR and 30% for the placebo group. The corresponding response rates calculated as ≥30%, PANSS-T score reduction from baseline to study endpoint at week 6 for the 80 mg and 160 mg lurasidone doses were 50% (p=0.002), and 63% (p=<0.001), respectively compared to 71% (p=<0.001) for quetiapine XR and 30% for the placebo group. It was concluded that efficacy of lurasidone at a dose-range of 40 mg to 160 mg was supported by the pivotal acute placebo- and active comparator trials as well as by the complementary more conservative analyses.

In the long-term lurasidone maintenance of effect studies, PANSS scores declined progressively during 52 weeks and non-inferiority for time to relapse was supported from post-hoc sensitivity analysis of lurasidone (mean dose 125 ±25 mg) compared to quetiapine XR (mean dose 630 ±112 mg) in one study. In a second long-term study, non-inferiority was not demonstrated compared to risperidone but the study provided support for maintenance of effect based on secondary efficacy endpoints.

The results from an additional recently finalised randomised withdrawal study demonstrated a statistically significant benefit of lurasidone when compared to placebo. Overall, 35% of subjects relapsed at some point during the randomised or double-blind phase of the study, with 30% of lurasidone subjects and 41% of placebo subjects experiencing a relapse. The Kaplan-Meier estimates of relapse at Week 28 were 0.422 and 0.512 for lurasidone and placebo, respectively, and overall there was a statistically significant increase in the time to relapse for lurasidone compared with placebo (p=0.039). A sensitivity analysis performed using the Cox proportional hazard model for lurasidone vs. placebo produced a HR estimate of 0.66 (0.45, 098) and was statistically significant (p=0.041). Other efficacy measures demonstrated congruence in trends. Overall, taking the results from all three long-term studies into account, it was concluded that long-term efficacy for lurasidone has been sufficiently demonstrated.

Uncertainty in the knowledge about the beneficial effects

Discontinuation rates were high in both short- and long-term studies and it is questionable if any of the analysis (LOCF and MMRM) is conservative enough to address the missing values and even more so in studies with small numbers of subjects in the ITT population. The small numbers of subjects completing the short-term efficacy study D1050196 questions the validity of the results. In 3 of the pivotal short-term studies however, (D1050229, D1050231 and D1050233) the proportion of subjects who completed the study was sufficiently large and provided support for the claimed efficacy. Notably, there was an inconsistency between studies for each dose group. Furthermore, no dose-dependency in treatment effect could be demonstrated although the most prominent effect was shown for the 160 mg dose, however shown in one study only. As maximum tolerated dose in patients is not clearly defined and doses higher than 160 mg per day were well tolerated the dossier does not present the rationale for selecting 160 mg per day as the maximum dose.

While there is acceptable statistical differentiation from the placebo in the short term studies, the clinical relevance of the results was not sufficiently documented in the initial dossier. In two of the short term studies (D1050231 and D1050233), an active comparator (Olanzapine and Quetiapine XR respectively) was used but the studies were not designed to directly compare the efficacy of these comparators with lurasidone. Also the responder analyses in D1050006 and D1050196 did not differentiate lurasidone from placebo. In summary, the initially presented information did not allow conclusion regarding the clinical relevance of the results either independently or in comparison with known treatments and thus additional more conservative analyses were requested. The results presented from these analyses were considered acceptable and support the short-term efficacy.

The initially submitted documentation on long term efficacy included one extension study and one safety study with additional efficacy measures. The dedicated long term non-randomised efficacy study (D1050234) was found to be subject to bias in patient selection to a degree that the results could not be regarded as sufficiently robust. The efficacy results from the active controlled safety study (D1050237) did support maintenance of effect although non-inferiority to the comparator was not shown.

Consequently, the results from an ongoing randomised withdrawal long term efficacy study D1050238 were requested, since these data were considered necessary to sufficiently demonstrate long-term efficacy of lurasidone. The study demonstrated a statistically significant increase in the time to relapse for lurasidone compared with placebo (p=0.039) in the overall population. Other efficacy measures in this study also demonstrated congruence in trends. The results were, however, not very robust; the number of events was quite low and the statistical significance was lost if the patients censored due to informative censoring (i.e. patients that withdrew whilst the study was still running) were counted as events (p=0.070). Of the 676 patients that entered the open-label phase of the study, 285 (42%) were randomised. In regional subgroup analyses on efficacy in this study there was a statistically significant effect demonstrated for EU- but not for US-located patient populations. An explanation for this finding was discussed by the applicant. Overall, it was considered that the results from the total ITT study population were more relevant than the results for subgroups as purely geographically based subgroups might not be biologically distinct, and social factors, such as the healthcare system could play a role. In this regard, the overall ITT population based results were considered to be relevant.

Risks

Unfavourable effects

The spectrum of adverse drug reactions for lurasidone is similar to that for other atypical antipsychotic drugs. The most common treatment-related AEs (with an incidence higher than placebo) in the

placebo-controlled studies were akathisia, somnolence, sedation, nausea, insomnia, vomiting, Parkinsonism and dizziness. For akathisia, somnolence and dizziness (another common TRAE) the incidence was dose related. Also for extrapyramidal symptoms (EPS) such as dystonia, tremor, Parkinsonism and salivary hypersecretion there was a trend for dose relation. The incidence of EPS was in general lower for lurasidone than for haloperidol 10 mg. Nausea and vomiting occurred more frequently for lurasidone than for the comparators both in the short-term and the long-term studies. A moderate dose dependant increase in prolactin was observed for lurasidone, however lower than for risperidone 4 mg and haloperidol 10 mg.

Five completed suicides occurred during the development programme and there were 2 other deaths where suicide could not have been excluded. The risk for suicide with lurasidone treatment has been adequately analysed by the applicant and it was concluded that the suicide rate for lurasidone is of similar magnitude as for other second generation antipsychotics. Appropriate warnings have been included in the product information.

A moderate weight-gain was reported from lurasidone treatment, but there were small changes in HbA1c, glucose or blood lipids as additional indicators of an increased risk for metabolic effects. Hypersensitivity reactions included one SAE of angioedema in the clinical studies, and additional 4 SAEs and 14 non-serious AEs of angioedema and related terms post-marketing. A thorough QT (TQT) study was conducted according to the ICH E14 guideline. No lurasidone-treated subject in this study experienced an absolute QTc value above 480 ms or change from baseline QTc more than 60 ms.

Uncertainty in the knowledge about the unfavourable effects

The total number of patients and treatment duration for which safety data for lurasidone are available fulfil the requirements in the guideline on population exposure (ICH E1). There was an unexpected low incidence of adverse drug reactions in the 160 mg/day dose group of lurasidone in one of the short-term placebo-controlled studies (D1050234) which can be at least partly explained by the fact that this study was the only study where lurasidone was administered in the evening.

The number of elderly subjects (>65 years) in the clinical program was low, and certain patient groups including patients with clinically significant cardiovascular disease, active epilepsy or Parkinson's disease were excluded from the clinical studies which limits the generalisability of the results.

In the lurasidone short-term studies there were slight dose-related increases in serum creatinine. The increases in creatinine were isolated and not accompanied by other indicators of renal parenchymal damage. The results of in vitro studies performed by the applicant clarified that the increase in serum creatinine levels was not attributable to the inhibition of the renal transporters involved in creatinine clearance. The applicant's clinical data review has indicated that the observed serum creatinine values were not sustained and in the majority returned to within normal limits even when subjects were continuing to receive lurasidone. Increased serum creatinine is added as an important potential risk to the RMP, and serum creatinine, renal impairment and renal failure are included as outcomes in a proposed PASS.

There were no clear differences by gender or race with regard to tolerability or safety in the clinical studies. Of note however, exposure to lurasidone was 1.5 times higher in the Asian population and 1.7 times higher in Asian females than in White males suggesting a possible need for dose adjustments in the Asian population. However, supplementary information provided showed that there is no need for dose adjustments in Asian females.

Benefit-risk balance

Importance of favourable and unfavourable effects

The results of the clinical short-term studies support an effect of lurasidone at the 40-160 mg dose range proposed for the treatment of psychotic symptoms in patients with schizophrenia. No consistent dose-response relationship was observed. Responder rates (≥20% and ≥30%) showed a statistically significant effect of lurasidone treatment however with some inconsistency for the 120 mg dose. Given the high discontinuation rates in the acute treatment trials complementary more conservative analyses were asked for to support the acute treatment results. These post-hoc analyses have provided support to the efficacy results seen in the initial analyses.

To support long-term efficacy, the results from three studies have been submitted. Based on the results from these studies, it was concluded that long-term efficacy for lurasidone has been sufficiently demonstrated.

The spectrum of adverse drug reactions for lurasidone is similar to that for other atypical antipsychotic drugs and includes extrapyramidal symptoms, nausea, sedation/somnolence, a moderate increase for prolactin and weight, and hypersensitivity reactions. The relatively low potential for metabolic effects and the absence of profound effects on QTc prolongation are considered as clinically relevant given the need for alternative antipsychotic agents with lower propensity to induce such side effects.

Benefit-risk balance

Discussion on the benefit-risk balance

The quality of the drug substance lurasidone hydrochloride and the film-coated tablets is considered acceptable and adequate.

The presented clinical efficacy data show a short-term effect which is modest. A dose-effect relationship has not been clearly demonstrated, however, within the suggested clinical dose-range 40 mg-160 mg the highest effect has been demonstrated in one study at the maximal daily dose of 160 mg. Long-term efficacy has been supported by the results from post hoc analyses providing supportive evidence, and a recently reported randomised withdrawal study D1050238 which showed an advantage of lurasidone over placebo.

Lurasidone has a spectrum of side effects which is similar to that for other atypical antipsychotic drugs, but the safety profile for lurasidone shows some potential advantages with a low tendency for metabolic effects and a low propensity to induce QTc prolongation. The most common treatment related side effects (with an incidence higher than placebo) in the short-term placebo-controlled studies were akathisia, somnolence, sedation, nausea, insomnia and vomiting. For akathisia, somnolence and dizziness the incidence was dose related. Also for extrapyramidal symptoms (EPS) such as dystonia, tremor, Parkinsonism and salivary hypersecretion there was a trend for dose relation. The incidence of EPS was in general lower for lurasidone than for haloperidol 10 mg. Nausea and vomiting occurred with a higher incidence for lurasidone than for the comparators. Effects of lurasidone on blood lipids, glucose and HbA1c were limited, and the effect on weight increase moderate, which is considered to indicate a relatively favourable metabolic profile. There were no profound effects on QTc prolongation.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Latuda in the treatment of schizophrenia in adults aged 18 years and over 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 medical prescription.

Other 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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **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 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that lurasidone hydrochloride is qualified as a new active substance.