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SCIENCE MEDICINES HEALTH

23 July 2020
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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Latuda

International non-proprietary name: lurasidone

Procedure No. EMEA/H/C/002713/II/0029

Note

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

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List of abbreviations

ADR	adverse drug reaction
AE	adverse event
AERS	adverse event reporting system
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BARS	Barnes Akathisia Rating Scale
BID	twice daily
BMI	body mass index
BP	blood pressure
bpm	beats per minute
C-CASA	Columbia Classification Algorithm of Suicidal Assessment
CIOMS	Council for International Organization of Medical Sciences
CK	creatine kinase
C-SSRS	Columbia Suicide Severity Rating Scale
DB	double-blind
DBP	diastolic blood pressure
ECG	electrocardiogram
EPS	extrapyramidal symptoms
FDA	Food and Drug Administration
GGT	gamma-glutamyltransferase
HbA1c	glycosylated hemoglobin
HDL	high-density lipoprotein
HR	heart rate
ICH	International Conference on Harmonization
LDL	low-density lipoprotein
LFT	liver function test
LOCF	last observation carried forward
MAPLV	Markedly Abnormal Post-Baseline Laboratory Values
MAPVS	Markedly Abnormal Post-Baseline Vital Signs
MedDRA	Medical Dictionary for Regulatory Activities
OL	open-label
PT	Preferred Term
QD	once daily
QTc	corrected QT
QTcF	QTc using Fridericia's correction
RAUC	Accumulation ratio calculated for AUC
RCmax	Accumulation ratio for Cmax
SAE	serious adverse event
SAS	Simpson-Angus Rating Scale
SBP	systolic blood pressure
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent SAEs
TQT	thorough QT
US	United States
WBC	white blood cell

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Aziende Chimiche Riunite Angelini Francesco S.p.A. submitted to the European Medicines Agency on 19 November 2019 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication for the treatment of schizophrenia in adolescent from 13 years and over; as a consequence, sections 4.1, 4.2, 4.7, 4.8, 5.1, 5.2, 5.3 of the SmPC are updated. The Package Leaflet is updated accordingly. Version 8 of the RMP has also been submitted.

In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest excipient guideline.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0359/2019 on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP P/0359/2019 was completed. The PDCO issued an opinion on compliance for the PIP P/0359/2019.

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.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The MAH received scientific advice from EMA on 23 of February 2017.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson Co-Rapporteur: Martina Weise

Timetable	Actual dates
Submission date	19 November 2019
Start of procedure:	28 December 2019
CHMP Co-Rapporteur Assessment Report	n/a
CHMP Rapporteur Assessment Report	28 February 2020
PRAC Rapporteur Assessment Report	28 February 2020
PRAC Outcome	12 March 2020
CHMP members comments	16 March 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	20 March 2020
Request for supplementary information (RSI)	26 March 2020
PRAC Rapporteur Assessment Report	28 May 2020
CHMP Rapporteur Assessment Report	10 June 2020
PRAC Outcome	11 June 2020
CHMP members comments	15 June 2020
Updated CHMP Rapporteur Assessment Report	18 June 2020
Request for supplementary information (RSI)	25 June 2020
PRAC Rapporteur Assessment Report	8 July 2020
CHMP Rapporteur Assessment Report	8 July 2020
PRAC members comments	n/a
CHMP members comments	n/a
Updated PRAC Rapporteur Assessment Report	15 July 2020
Updated CHMP Rapporteur Assessment Report	15 July 2020
Opinion	23 July 2020

2. Scientific discussion

2.1. Introduction

Lurasidone is an atypical antipsychotic agent approved for the treatment of adult patients with Schizophrenia on the 21 March 2014 in EU (EU/1/14/913/008-014)

Lurasidone is a selective blocking agent of dopamine and monoamine effects. Lurasidone binds strongly to dopaminergic D2- and to serotonergic 5-HT2A and 5-HT7- receptors with high 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 partial agonism at the 5HT-1A receptor with a binding affinity of 6.38 nM. Lurasidone does not bind to histaminergic or muscarinic receptors.

Schizophrenia is very rare in pre-pubertal children. According to the DSM IV-TR, diagnostic criteria for schizophrenia apply similarly to both adult and paediatric populations. Schizophrenia is a chronic and debilitating illness that has an estimated lifetime adult prevalence of 0.5 to 1% (APA, 2000). Within the paediatric age group, a diagnosis of schizophrenia is most commonly made in adolescents, and the symptoms in this age group are generally similar to those in adults (APA, 1997).

The applicant is submitting this application to establish the efficacy and safety of lurasidone hydrochloride (lurasidone) for the treatment of schizophrenia in adolescent patients (aged 13 to 17 years).

A modification of an agreed paediatric investigation plan for lurasidone (hydrochloride) (Latuda) (EMEA-001230-PIP01-11-M05) was accepted on 4 November 2019.

Three studies were outlined in the current paediatric investigation plan.

This variation does not include any specific quality variation application and the already approved formulations, 18.5 mg, 37 mg and 74 mg film-coated tablets for adults, are proposed for the paediatric population from 13 years of age.

The 18.5 mg and 37 mg film-coated tablets are round 6 mm and 8 mm, respectively in diameter. The 74 mg strength is an oval film-coated tablet with a size of 12 mm x 7 mm. The tablet cores contain the excipients mannitol, starch pregelatinised, croscarmellose sodium, hypromellose and magnesium stearate. The tablets are coated with a mixture of hypromellose, titan dioxide and macrogol. The coating of the 74 mg strengths tablets also contains the colouring agents iron oxide yellow and indigo carmine.

Suitability of the formulation for the paediatric population from 13 years of age.

Since the variation concerns introduction of a paediatric population, the suitability of the proposed formulation in the proposed age group should be addressed, in line with the Guideline on pharmaceutical development of medicines for paediatric use EMA/CHMP/QWP/805880/2012 Rev.2. No such justification has been provided but this can be accepted since the proposed adult formulations only contain commonly used excipients in amounts for which no safety issues are foreseen in the proposed target age group. The proposed adult formulation is considered acceptable from a quality point of view.

2.2. Non-clinical aspects

2.2.1. Introduction

The non-clinical study package submitted in the initial MAA (EMEA/H/C/002713/0000, 2014) was considered adequate to support administration of lurasidone in adult patients up to a maximum dose of 148 mg lurasidone free base/day (equivalent to 160 mg lurasidone hydrochloride/day).

This variation concerns introduction of a paediatric population from 13 years of age. Two new juvenile studies have been submitted that are presented and assessed in this procedure.

The recommended maximum dose in the paediatric population is 74 mg lurasidone free base/day (equivalent to 80 mg lurasidone hydrochloride/day).

Of note, the doses presented throughout the non-clinical parts of this assessment report are expressed as lurasidone hydrochloride (M_w 529.14 g/mol) whereas in the SmPC, dose levels are expressed as lurasidone free base (M_w 492.68 g/mol). Lurasidone is denoted SM-13496 in the study reports.

2.2.2. Pharmacology

No new pharmacology studies have been submitted in this variation. A very brief summary on the main characteristics of lurasidone is included below.

Lurasidone is a selective blocking agent of dopamine and monoamine effects. Lurasidone binds strongly to dopaminergic D2- and to serotonergic 5-HT2A and 5-HT7- receptors with high 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 partial agonism at the 5HT-1A receptor with a binding affinity of 6.38 nM. Lurasidone does not bind to histaminergic or muscarinic receptors.

The mechanism of action of the minor active metabolite of lurasidone ID-14283 is similar to that of lurasidone.

2.2.3. Pharmacokinetics

No new pharmacokinetic studies have been submitted in this variation. A very brief summary on the metabolism of lurasidone is included below.

Lurasidone is extensively metabolized and the receptor binding profiles of 13 metabolites have been determined. Of these, 2 metabolites (ID-14283 and ID-14326) are pharmacologically active with affinity similar to lurasidone for dopamine, serotonin, and α-adrenergic receptors. Functional assay results confirm this binding profile as lurasidone, ID-14283 and ID-14326 are potent antagonists for human D2L and 5-HT7 receptors and partial agonists for human 5-HT1A receptors. The 2 major metabolites of lurasidone (ID-20219 and ID-20220) are not pharmacologically active.

2.2.4. Toxicology

From SmPC:

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.

In rats, lurasidone had no effect on male and female reproduction at oral doses of 150 and 0.1 mg/kg/day lurasidone hydrochloride, respectively, or on early embryonic development at an oral dose of 15 mg/kg/day lurasidone hydrochloride.

A fertility study in female rats resulted in prolonged oestrous cycle and delayed copulation at ≥1.5 mg/kg/day lurasidone hydrochloride, whilst the copulation and fertility indices, and the numbers of corpora lutea, implantations and live foetuses were decreased at 150 mg/kg/day lurasidone hydrochloride. These effects were due to the hyperprolactinemia following lurasidone treatment, affecting the oestrous cycle and copulatory behaviour as well as the maintenance of corpus luteum of the female rats, resulting in a decrease in implantation and the number of live foetuses. These prolactin-related effects are not considered to be relevant to human reproduction.

A single dose of 10 mg/kg lurasidone hydrochloride to pregnant rats resulted in fetal exposure. In a dose range finding study in pregnant rats, 150 mg/kg/day lurasidone hydrochloride caused fetal growth retardation without signs of teratogenicity. Lurasidone was not teratogenic in rats or rabbits at an exposure similar to or below the maximum recommended human dose (148 mg lurasidone).

Lurasidone was excreted in milk of rats during lactation.

Lurasidone was not genotoxic in a battery of tests. Mammary gland and/or pituitary gland tumours were observed in the mouse and rat carcinogenicity studies and are most likely due to the increased blood prolactin levels. These findings are common in rodents treated with antipsychotic medicinal products with dopamine D2 blocking activity and are considered to be rodent-specific.

Juvenile toxicity

Two juvenile toxicity studies in rats were submitted in this variation; one non-GLP 28-day dose-range finding study where lurasidone hydrochloride was administered from post-natal day (PND) 21 to 48, and one GLP study where lurasidone was administered from PND 21 to 91. The primary objective of the GLP study was to evaluate the potential effects of lurasidone on growth and development in juvenile male and female rats covering the period of development corresponding to childhood, adolescence, and young adulthood. Lurasidone hydrochloride (also denoted SM-13496) was administered once daily by oral gavage.

The juvenile studies are summarised below.

Table 1 Summary of juvenile dose-finding study performed with lurasidone hydrochloride in rats.

Study ID/GLP/ Duration	Species/Sex/Number/Group	Dose/Route	NOAEL
WIL-312359/non-GLP Dosing: PND 21 to 48 (28 days)	CD rat 6/sex/group + satellites for hormone analysis (estradiol in F, and prolactin in M+F)	0 (vehicle), 0.3, 3, 30 and 150/300 (M/F) mg/kg/day Oral gavage Vehicle/formulation: Suspension in aqueous 0.5% methylcellulose	NA

Special features
Hormone analysis; estradiol in females and prolactin in males and females, all measured at 1 and 24 h following the last study dose on PND 48.

Noteworthy findings

Mortality: None.

Clinical signs:
≥ 30 mg/kg/day (M/F): Half-closed or shut eyelids and yellow material around the urogenital and ventral abdominal areas, commonly seen at 1 to 4 h post-dose and mainly during the first 2 weeks of dosing.
150/300 mg/kg/day (M/F): Sporadic occurrences of hypoactivity.

Body weight and food consumption:
150/300 mg/kg/day (M/F): ↓ mean body weight gains with corresponding ↓ mean food consumption resulting in ↓ mean body weights of up to 20% (M) and 21% (F) at termination.

Balanopreputial separation: The mean age of attainment of balanopreputial separation was delayed at 150 mg/kg/day when compared with controls; 44.5, 44.4, 45.7, 45.5 and **47.0 days** at 0, 0.3, 3, 30 and 150 mg/kg/day, respectively. The difference was not statistically significant. However, 3 of the 6 males at 150 mg/kg/day did not exhibit balanopreputial separation by the end of the study (PND 49). Therefore, data from only 3 males in this group were evaluated. The mean body weights at the age of attainment were 238.3, 253.7, 243.4, 235.2 and 234.0 g at 0, 0.3, 3, 30 and 150 mg/kg/day, respectively.

Vaginal patency: The mean age of attainment of vaginal patency was delayed at 300 mg/kg/day when compared with controls; 33.3, 31.8, 32.8, 32.3 and **35.5 days** at 0, 0.3, 3, 30 and 300 mg/kg/day, respectively. The difference was not statistically significant. In 1 of the 6 females in the 300 mg/kg/day group, the age of attainment of vaginal patency was 42 days. The mean body weights at the age of attainment were 120.0, 110.0, 116.4, 104.7 and 110.6 g at 0, 0.3, 3, 30 and 300 mg/kg/day, respectively.

Hematology and coagulation:
300 mg/kg/day (F): ↓ mean corpuscular haemoglobin, unclear relation to treatment.

Hormone analysis on PND 48:
≥0.3 mg/kg/day (M/F): ↑ mean prolactin at 1 h post-dose.
≥0.3 mg/kg/day (F): ↓ mean estradiol at 1 h post-dose.

Dose level (mg/kg/day)	Prolactin (ng/mL)				Estradiol (ng/mL)	
	1 h		24 h		1 h	24 h
	M	F	M	F	F	F
0	11.8	19.2	14.4	18.9	34.45	27.60
0.3	22.9	239.5	17.7	2.6	18.50	27.60
3	86.3	430.1	1.9	12.4	22.55	17.15
30	94.5	270.4	18.3	14.6	18.70	19.70
150/300 (M/F)	44.7	75.6	1.1	16.7	16.23	22.77

Gross pathology: No test article-related findings.

Organ weights:
≥30 mg/kg/day (F): ↓ mean **uterine** weights (with cervix and oviducts) (22.2% and 24.4% lower than controls)
300 mg/kg/day (F): ↓ mean absolute **ovarian** weight (24.2% lower than controls). Potentially related to ↓ estradiol levels.

No microscopic pathology was evaluated in the study.

In this study, there was no mortality or moribundity at any dose level evaluated. The most notable clinical findings were half-closed or completely shut eyelids, which were observed in males and/or females at dose levels of 30 and 150/300mg/kg/day. In addition, lower mean body weights and body weight gains corresponding to lower food consumption were observed at 150 mg/kg/day in males and at 300 mg/kg/day in females. Vaginal patency was delayed in females at 300 mg/kg/day, and balanopreputial separation was delayed in males at 150 mg/kg/day. Lower mean uterine weights at 30 and 300 mg/kg/day and lower mean ovarian weight at 300 mg/kg/day were also noted. In addition, 1 hour following the last dose, mean prolactin levels were higher in all lurasidone-treated groups and mean estradiol levels were lower in the females at all dose levels.

Based on these results, dose levels of 150 mg/kg/day in males and 300 mg/kg/day in females were selected as the high dose levels in the definitive juvenile study. Dose levels of 3 and 30 mg/kg/day were selected as the low and mid doses in both sexes. The dose levels seem justified based on findings above.

In the GLP juvenile study, main study animals (40/sex/group) were treated daily during PND 21 to PND 91. Study animals were further divided in the subsets as illustrated below. The duration of the post-dosing period was as follows; PND 92 through PND 160-177 (males) or PND 14, post-cohabitation Day 35, or post-mating Day 35 (females). Additional satellite animals were included for hormone analysis and toxicokinetics.

Figure 1

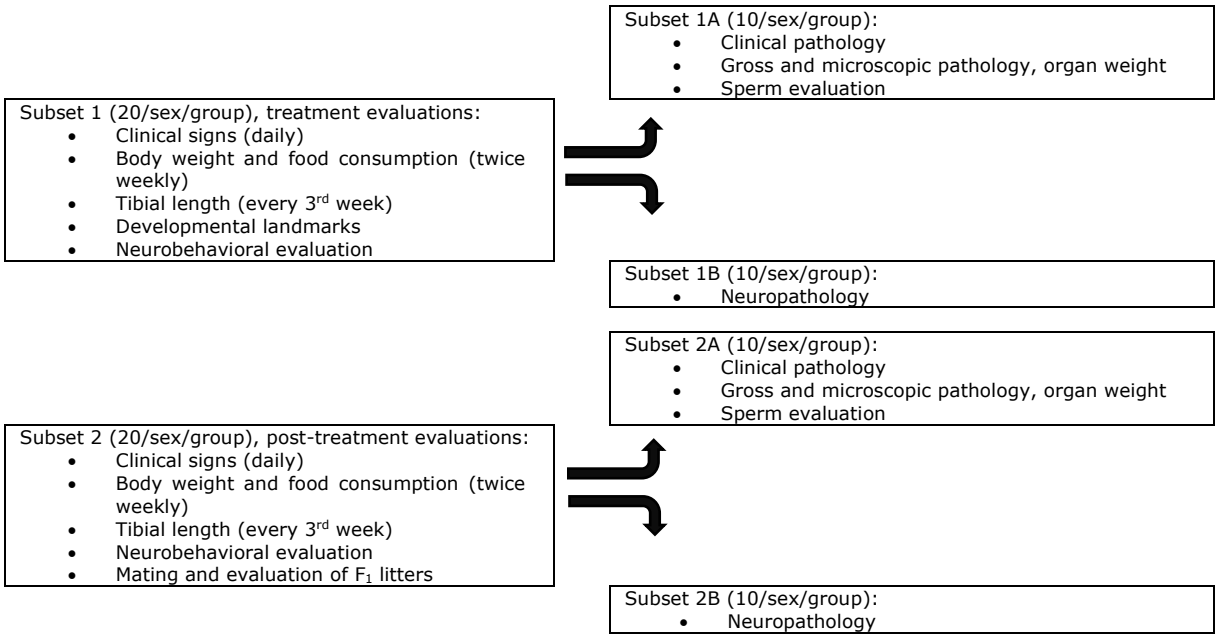


Table 2 Summary of juvenile toxicity study performed with lurasidone hydrochloride in rats.

Study ID/GLP/ Duration	Species/Sex/Number/ Group	Dose/Route	NOAEL
WIL-312361/GLP Dosing: PND 21 to 91 (70 days) Post-dose: PND 92 to 160-177 (M) and post-partum Day 14, post-cohabitation period Day 35 or post-mating Day 35 (F)	CD rat 40/sex/group + satellites for TK and hormone analysis (estradiol in F, and prolactin in M+F)	0 (vehicle), 3, 30 and 150/300 (M/F) mg/kg/day Oral gavage Vehicle/formulation: Suspension in aqueous 0.5% methylcellulose	F_0 physical growth and development: 3 mg/kg/day in both genders F_0 neurobehavioural development: 3 mg/kg/day in males and <3 mg/kg/day in females F_0 reproductive performance: 150 mg/kg/day in males and 300 mg/kg/day in females F_1 neonatal toxicity: 3 mg/kg/day in both genders

Special features
Toxicokinetics; Lurasidone and its major human metabolites, ID-20219, ID-20220, ID-14283 and ID-14326 were analysed on PND 21 and 91.
Hormone analysis; estradiol in females and prolactin in males and females, all measured at 1 and 24 h following the last study dose on PND 91.
Bone densitometry; the right femur (4 regions: whole femur, distal femur, midshaft femur and proximal femur) and lumbar vertebrae (L3-L5) were subjected to dual energy X-ray absorptiometry (DXA) analysis. Femur length, bone mineral content, area and density of each sample were determined. For the lumbar vertebrae (L3-L5), bone mineral content, area and density of the entire column was determined at the end of the treatment and post-treatment phase.

Noteworthy findings

Toxicokinetics: see Toxicokinetics section below and Table 3.

Mortality: 7 animals were found dead or euthanized in extremis, considered test article-related.

30 mg/kg/day:	1M was euthanized in extremis prior to dosing on PND 22.
150 mg/kg/day:	1M was euthanized in extremis prior to dosing on PND 22, and 2M were euthanized in extremis on PND 23.
300 mg/kg/day:	1F was found dead prior to dosing on PND 24, and 2F were euthanized in extremis.

Common clinical findings noted prior to death/euthanasia included prostrate posture, cool, and pale body, half-closed eyelids, cool limbs, hypoactivity, laboured and ↓ respiration, splayed hindlimbs, red material around the nose, yellow material around the urogenital area, and clear nasal discharge. In addition, the mean body weight at the start of dosing (PND 21) for male no. 65839-03 in the 30 mg/kg/day group (26 g) was 43% lower than the group mean body weight on this day (46 g), which may have contributed to the moribund condition of this animal. The causes of mortality/moribundity were not determined microscopically; however, as the majority of the deaths occurred in the high-dose groups and the proximity to the initiation of dose administration, they are considered to be test article-related.

Clinical signs:
≥30 mg/kg/day (M/F): half-closed or slightly drooping eyelids at ≈1 and 4 hours post dose observed sporadically during the first 4 weeks (PND 21-50).

150/300 mg/kg/day (M/F): ↓ defecation and small feces during the treatment period (PND 37-65), corresponding to ↓ food consumption, and sporadic ↑ incidences of yellow material around the urogenital and red material around the nose. During the post-treatment period, no remarkable clinical signs were noted.

Body weight and food consumption:
30 mg/kg/day (M/F): ↓ mean body weight gains with corresponding ↓ mean food consumption in M (throughout the treatment period) and in F (during PND 21-35), resulting in ↓ mean body weights up to 12.9% (M) and 8.5% (F) at the end of the treatment period. During the post-treatment period, the body weight effects were ameliorated after PND 126 (M) or PND 77 (F) due to mean body weight gains that were similar to or slightly higher than controls throughout the later part of the treatment and during the post-treatment period.

150/300 mg/kg/day (M/F): ↓ mean body weight gains with corresponding ↓ mean food consumption throughout the treatment period, resulting in ↓ mean body weights up to 20.2% (M) and 17.0% (F) at the end of the treatment period. During the post-treatment period, compensatory ↑ in body weight gains and/or food consumption were generally noted, but ↓ mean body weights persisted through post-partum Day 14 (F) or PND 161 (M).

Tibial length:
30 mg/kg/day (M/F): ↓ tibial lengths on PND 42. In M ↓ tibial lengths continued during the remainder of the treatment period (PND 63, 84, and 92) and continuing into the post-treatment period (PND 105), while in F mean tibial lengths in females at 30 mg/kg/day were similar to the control group thereafter. On PND 147 and on the day of the post-treatment necropsy, tibial lengths were comparable to controls.

150/300 mg/kg/day (M/F): ↓ tibial lengths on PND 42 and throughout the treatment and post-treatment period (PND147). At the day of post-treatment necropsy, tibial lengths were comparable to controls.

Developmental landmarks

Balanopreputial separation: The mean age of attainment of balanopreputial separation was delayed at 150 mg/kg/day ($p<0.01$) when compared with controls; **44.9**, 44.8, 45.7 and **47.8 days** at 0, 3, 30 and 150 mg/kg/day, respectively. The delay occurred in the presence of a significantly ($p<0.01$) lower (10.9%) mean body weight on the day of attainment, and mean body weights that were up to 21.4% lower than controls during PND 24-91.

Vaginal patency: The mean age of attainment of vaginal patency was delayed at 30 ($p<0.05$) and 300 mg/kg/day ($p<0.01$) when compared with controls; 32.1, 33.4, 33.8 and **38.1 days** at 0, 3, 30 and 300 mg/kg/day, respectively.

Neurobehavioural parameters

Home cage, handling, open field, sensory and neuromuscular observations: No test article-related effects on PND 80 or 105.

Physiological observations: Significantly ($p<0.01$) ↓ mean body weights in M at ≥30 mg/kg/day and in F at 300 mg/kg/day on PND 80 and 105.

Locomotor activity: Locomotor activity (total activity as well as ambulatory activity counts) were unaffected by test article administration at all dose levels at PND 81. During the post-treatment period (PND 106 and at end of post-treatment period testing sessions), ↑ mean total and ambulatory activity counts were observed in F at ≥3 mg/kg/day and in M ≥30 mg/kg/day. While the higher activity at 30 and 150/300 mg/kg/day was clearly test article-related, the relationship to test article administration for the higher activity counts in the 3 mg/kg/day group females was less certain because activity counts in this group during the first post-treatment period (PND 106) were comparable to the activity counts noted in this group during the treatment period. However, given the dose-related nature of the higher counts, the higher activity counts in the 3 mg/kg/day group females were attributed to the test article

Auditory startle response: No test article-related effects at the end of the treatment period and post-treatment period.

Biel maize swimming trials: No test article-related effects at the end of the treatment period and post-treatment period.

Reproductive parameters

Spermatogenic evaluation (testicular and epididymal sperm numbers and sperm production rate, motility, and morphology): No test article-related effects.

Reproductive performance (mating, fertility, copulation and conception indices): No test article-related effects.

Gestation length and parturition: No test article-related effects. The mean gestation lengths were 21.9, 22.0, 21.8 and 21.8 days at 0, 3, 30, and 300 mg/kg/day, respectively, and 21.8 days in the WIL historical control data.

F1 litter data: No test article-related effects were noted on mean number of pups born, live litter size, percentage of males per litter at birth, and post-natal survival between birth and PND 0, PND 0-1, 1-4, 4-7, from birth to PND 7 or on general physical condition. Pups (litters) found dead numbered 14(6), 10(6), 6(5), and 9(6) at 0, 3, 30, and 150/300 mg/kg/day, respectively. Six (2), 10(6), 10(4), and 15(7) pups (litters) in the same respective groups were missing and presumed to have
been cannibalised.

Slightly ↓ mean F_1 birth weights and pup body weights were noted during PND 4 to 7 at ≥30 mg/kg/day (dose-related), considered treatment-related (but within the performing laboratory's historical control data range), see below:

	0		3		30		150/300		Historical controls[a]	
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
PND 1	7.8	7.4	7.1*	6.8	6.6**	6.2**	6.6**	6.1**	7.1 (6.6-7.5)	6.7 (6.1-7.0)
PND 4	10.4	9.9	10.0	9.7	9.2*	8.5*	8.7**	8.3**	9.7 (8.7-10.8)	9.2 (8.1-10.4)
PND 7	14.9	14.1	14.4	14.0	12.9**	12.0**	12.3**	11.7**	15.1 (12.9-17.4)	14.3 (12.1-16.5)

*Significantly different from controls at 0.05; **Significantly different from controls at 0.01
[a]Presented as mean (min - max) n=38-48

Hormone analysis on PND 91 (n= 5-6/group):
≥3 mg/kg/day (M/F): ↑ mean prolactin at 1 h post-dose.
3 and mg/kg/day (F): ↓ mean estradiol at 1 h post-dose.

Dose level (mg/kg/day)	**Mean prolactin (ng/mL)**				**Mean estradiol (pg/mL)**	
	1 h		**24 h**		**1 h**	**24 h**
	M	**F**	**M**	**F**	**F**	**F**
0	12.8	99.4	16.0	13.5	27.7	20.0
3	100.4**	637.3**	9.8	62.1	23.8	24.5
30	85.1**	282.4	14.7	18.0	15.4	20.8
150/300 (M/F)	74.6*	166.9	19.4	47.9	28.0	24.8

*Significantly different from controls at 0.05; **Significantly different from controls at 0.01

Clinical pathology and pathology

Haematology and coagulation:
150 mg/kg/day (M): ↑ mean corpuscular volume, ↑ prothrombin time, and ↓ lymphocyte count.
300 mg/kg/day (F): ↑ red cell distribution widths, and ↓ lymphocyte count.
No effects at the end of the post-treatment phase.

Serum chemistry and urinalysis: No test article-related effects.

Gross pathology: No test article-related effects.

Organs weights:
↓ final body weights were noted in M at ≥30 mg/kg/day and in F at 300 mg/kg/day, and consequently numerous organ weights relative to body weight in these groups were therefore higher than controls.

≥30 mg/kg/day (M): ↓ **thyroid/parathyroid gland**, correlating with ↑ colloid (decreased number of follicles)
≥30 mg/kg/day (F): ↓ **pituitary gland**

Microscopic pathology:
≥3 mg/kg/day (F): **Mammary gland**, minimal to moderate hyperplasia of glandular epithelium; **Ovaries**, minimal to mild ↑ atretic follicles; and **vagina**, minimal to mild mucification of luminal epithelium.
150 mg/kg/day (M): **Thyroid gland**, minimal to mild ↑ colloid, and **prostate**, ↑ severity of background inflammation (minimal to moderate; moderate in one animal)
No findings following the post-treatment period.

Neuropathology

Gross pathology: No test article-related effects.

Brain weight and size:
≥30 mg/kg/day (M): ↓ mean brain length at the end of treatment (Subset IB), not observed at 30 mg/kg/day following the post-treatment period but at 150 mg/kg/day (to a lesser degree).
150 mg/kg/day (M): ↓ mean absolute brain weight (↑ mean relative weight) at the end of treatment (Subset IB), not observed following the post-treatment period. However, mean brain weights of Subset IA males were not statistically significantly different to controls.

Microscopic pathology (brain, spinal cord, spinal ganglia or nerve roots, trigeminal ganglia or nerve, peripheral nerves, optic nerves, or eyes: No test article-related effects.

Bone densitometry
Femur:
30 mg/kg/day (M): ↓ bone mineral content at the whole, proximal and distal femur and ↓ bone area at the proximal femur.
≥30 mg/kg/day (M): ↓ femoral length, not observed following the post-treatment period.
150 mg/kg/day (M): ↓ bone mineral density, content and area at the whole, proximal, midshaft and distal femur. Following the post-treatment period, ↓ bone mineral content at the whole, proximal and midshaft femur and ↓ bone area at the distal femur were observed.
300 mg/kg/day (F): ↓ bone mineral density at the whole, proximal and distal femur, and ↓ bone mineral content at the distal femur. Following the post-treatment period, ↓ bone mineral content at the proximal and midshaft femur, ↓ bone area at the whole, proximal and distal femur, and ↓ femoral length were observed.

Vertebral column:
≥30 mg/kg/day (M): ↓ bone mineral content and area.
150 mg/kg/day (M): ↓ bone mineral density.
300 mg/kg/day (F): ↓ bone mineral density, content and area.
Following the post-treatment period lower values were noted but not statistically significant.

Toxicokinetic data

In the juvenile toxicity study, blood samples for determination of lurasidone and its metabolites ID-20219, ID-20220, ID-14283, and ID-14326 in serum were collected from 3 satellite animals/sex/group at approximately 0.5, 1, 2, 4, 8, and/or 24 hours following dose administration on PND 21 (first day of dosing) and 91 (last day of dosing). The concentrations of lurasidone and its metabolites were determined by HPLC with MS/MS detection.

As shown below, all juvenile rats dosed with lurasidone were exposed to the parent and its metabolites, ID-20219, ID-20220, ID-14283, and ID-14326. Exposure to lurasidone and the metabolites increased as dose level increased.

On PND 21, the increase in exposure to lurasidone ($AUC_{0.5\text{-}24h}$) was more than dose-proportional over the 3 to 150/300 mg/kg/day range; on PND 91, increase in exposure to lurasidone ($AUC_{0.5\text{-}24h}$) was more than dose-proportional from 3 to 30 mg/kg/day and less than dose-proportional from 30 to 150/300 mg/kg/day. On PND 21, the increase in exposure to lurasidone (C_{max}) was nearly dose-proportional over

the 3 to 150/300 mg/kg/day range; on PND 91, increase in exposure to lurasidone (C_{max}) was more than dose-proportional from 3 to 30 mg/kg/day and less than dose-proportional from 30 to 150/300 mg/kg/day. The increase in exposure to lurasidone metabolites, in terms of $AUC_{0.5\text{-}24h}$ and C_{max}, was generally less than or nearly dose-proportional over the 3 to 150/300 mg/kg/day range.

Exposure to lurasidone, in terms of $AUC_{0.5\text{-}24h}$, increased from PND 21 to PND 91 up to approximately 3-fold in animals dosed at 3 and 30 mg/kg/day, but was similar on the 2 evaluation days in the males dosed at 150 mg/kg/day and the females dosed at 300 mg/kg/day. Exposure to the metabolites generally was similar or decreased from PND 21 to PND 91.

At 3 and 30 mg/kg/day, exposure to lurasidone and the metabolites was similar between the genders, except for ID-20219 and ID-20220 on PND 91, where exposure was higher in males than in females. The t_{max} for lurasidone and metabolites ranged from 0.5 to 4 hours for males and 0.5 to 8 hours for females, and generally increased at higher dose levels.

Table 3 Toxicokinetic results in juvenile rat study.

	PND 21		PND 91	
SM-13496 Dose (mg/kg/day)	$AUC_{0.5\text{-}24h}$ [$AUC_{0.5\text{-}t}$]* (ng·h/mL)	C_{max} (ng/mL)	$AUC_{0.5\text{-}24h}$ [$AUC_{0.5\text{-}t}$]* (ng·h/mL)	C_{max} (ng/mL)
		SM-13496		
		Males		
3	85.8	41.0	287	42.5
30	1500	269	4120	800
150	10200	1150	8530	946
		Females		
3	65.3 [56.5]	20.2	215	62.1
30	2030	367	5310	1080
300	24500	1980	24500	1950
		ID-20219		
		Males		
3	206	49.4	118 [94.5]	33.8
30	5630	575	1090	211
150	20200	1580	2980	323
		Females		
3	237 [204]	49.7	44.4 [34.1]	18.9
30	3390	705	512	82.8
300	18700	1380	6070	549
		ID-20220		
		Males		
3	210	37.9	125 [106]	41.8
30	2830	343	622	113
150	5340	529	1550	199
		Females		
3	223 [180]	51.0	33.5	12.1
30	1920	347	181	34.4
300	4610	461	1260	135

	PND 21		PND 91	
SM-13496 Dose (mg/kg/day)	$AUC_{0.5\text{-}24h}$ [$AUC_{0.5\text{-}t}$]* (ng·h/mL)	C_{max} (ng/mL)	$AUC_{0.5\text{-}24h}$ [$AUC_{0.5\text{-}t}$]* (ng·h/mL)	C_{max} (ng/mL)
		ID-14283		
		Males		
3	76.1 [71.0]	17.3	88.2 [71.5]	22.5
30	1020	132	1050	142
150	3810	348	1770	169
		Females		
3	72.8 [62.9]	18.9	229 [167]	55.3
30	1970 [918]	173	1700	222
300	6950	508	3170	206
		ID-14326		
		Males		
3	7.63 [5.79]	2.01	34.9 [27.5]	8.33
30	218 [124]	25.8	504	58.0
150	698	63.7	639	58.0
		Females		
3	6.54 [4.51]	1.87	81.5 [59.5]	18.6
30	527 [209]	39.8	742	76.0
300	1190	84.1	1180	75.8

*Where not listed, $AUC_{0.5\text{-}t} = AUC_{0.5\text{-}24h}$

The metabolites ID-20219 and ID-20220 are major human metabolites. Neither of these 2 metabolites is pharmacologically active. In contrast, metabolites ID-14283 and ID-14326 were determined to be pharmacologically active, with D_2 binding affinities similar to that of lurasidone. In the initial MAA of Latuda, the non-clinical qualification of these metabolites was discussed (EMEA/H/C/002713/0000, 2014), and considered adequately addressed.

2.2.5. Ecotoxicity/environmental risk assessment

An environmental risk assessment was submitted in the initial MAA for Latuda (EMEA/H/C/002713/0000). In this variation, no updates to the ERA has been provided but the applicant has provided a justification included below.

The outcome of this ERA report concluded that no relevant environmental concerns are apparent from the use of lurasidone hydrochloride as a drug with a maximum recommended daily dose (MDD) of 160 mg/day/patient by the use of the default market penetration factor (Fpen) of 0.01. The conclusion in this ERA report are also valid for the treatment of schizophrenia for adolescents since the MDD of Lurasidone hydrochloride for this treatment will be 80 mg/day/patient, which is lower dose than the MDD used in the previous ERA report. In addition, the default Fpen (0.01) is considered to be a conservative value and could be considered to be included the market penetrations of both adults and adolescents. Based on these rationales, the extension of indication would not provoke a relevant adverse effect to the environment, and therefore, no updates to the ERA report is provided.

The applicant´s position that the previously submitted ERA can be considered to include the market penetrations of both adults and adolescents is agreed. Thus, no further updates are required.

2.2.6. Discussion on non-clinical aspects

Assessment of paediatric data on non-clinical aspects

In support of the paediatric clinical development program, a non-clinical juvenile toxicity study in rats was performed. In this study, dosing was initiated at an age of 22 days and continued until PND 91. A 22-day-old rat corresponds (approximately) to a 2-year infant based on overall CNS and reproductive development whereas a 91-day-old rat corresponds (approximately) to a 16-year adolescent. Thus, the study covers the periods of development corresponding to childhood, adolescence and young adulthood in rats.

The main target organs of toxicity identified in juvenile rats include mammary gland, ovary and vagina. Additionally, mild effects in prostate and thyroid gland were also observed.

Mortality
There were 7 unscheduled deaths noted at ≥30 mg/kg/day during PND 22 to 24. Adverse clinical signs noted in these animals prior to death included prostrate posture, cool, and pale body, half-closed eyelids, cool limbs, hypoactivity, laboured and decreased respiration, splayed hindlimbs, red material around the nose, yellow material around the urogenital area, and clear nasal discharge. The causes of moribundity were not determined. As most of the deaths occurred in the high-dose groups and in proximity to initiation of dosing, they are considered to be test article-related. All deaths occurred between PND 22 and 24, a discrete time within the post-weaning period, when animals are particularly sensitive to perturbations in body weight and food consumption. Thus, the moribund condition is considered likely to be secondary to effects on food consumption and body weight observed at these dose levels.

Clinical signs
The main clinical signs in juvenile rats at dose levels ≥30 mg/kg/day were half-closed and/or slightly drooping eyelids, red material around nose and yellow material around urogenital area. Similar observations were made in adult rats where in addition decreased motor activity was commonly observed. Somnolence (the term includes hypersomnia sedation, and somnolence) is described as a common adverse reaction noted in adult and paediatric patients (section 4.8 of the SmPC).

Body weight and growth parameters
Reductions in body weight gain/mean body weight correlating with reduced food consumption and decreased defecation/small feces were noted at dose levels ≥30 mg/kg/day. Although compensatory increases in body weight gains and/or food consumption were generally noted in males at 150 mg/kg/day and in females at 300 mg/kg/day during the post-treatment period, lower mean body weights in the high dose groups persisted through post-partum Day 14 (females) or PND 161 (males). Likely as a result of

the lower mean body weights, delays in growth and development were observed in both genders at ≥30 mg/kg/day, lower femoral length and bone mineral content at ≥30 mg/kg/day in males and at 300 mg/kg/day in females; reduced brain length at ≥30 mg/kg/day and decreased brain weight at 150 mg/kg/day in males (persisting in the post-treatment period), shorter tibial lengths in both genders at ≥30 mg/kg/day and delays in the mean age of attainment of balanopreputial separation at 150 mg/kg/day. The mean age of attainment of vaginal patency was also delayed at ≥30 mg/kg/day; this effect may have been exacerbated by the effects on body weight gain but is likely secondary to the test article-related lower serum estradiol observed at these dose levels. Systemic exposures at the lowest effect level for these findings (30 mg/kg/day) in male and female rats were approximately 11- to 14-fold in paediatric/adolescent patients receiving the MRHD of 80 mg/day based upon total exposure. At the NOAEL, exposure margins were less than 1.

Lurasidone-related effects on body weight and food consumption were also noted in adult rat toxicology studies; there does not appear to be an increased sensitivity of juvenile animals to these effects. In contrast, increased body weight is reported as common (SmPC 4.8) in adult patients and is also observed in adolescents.

Central nervous system

Potential effects of long-term treatment with lurasidone on the developing brain were assessed by detailed CNS histopathology as well as FOB assessments (i.e. home cage, handling, open field, sensory, neuromuscular and physiological observations) and evaluation of locomotor activity, auditory startle response and biel maze swimming trials.

As discussed above, test article-related effects on brain weight and/or length were observed and considered likely secondary to the reduced body weight. Additionally, since dosing began on PND21, about the height of brain myelination, lurasidone may have caused decreased myelination as has been noted with undernutrition in the growing rat pup.

The microscopic evaluation revealed no lurasidone-related alterations in brains, spinal cords, spinal ganglia or nerve roots, trigeminal ganglia or nerve, peripheral nerves, optic nerves, or eyes. Test article-related FOB findings noted in males at ≥30 mg/kg/day and in females at 300 mg/kg/day were limited to lower mean body weights. No lurasidone-related effects on auditory startle responsiveness and learning and memory (Biel maze) were observed. Mean total and ambulatory activity counts for males at ≥30 mg/kg/day and for females at ≥3 mg/kg/day during both post-treatment period assessments (PND 106 and the end of the post-treatment period) were higher than in the control group. Similar observations of hyperactivity during the post-treatment period has also been reported for other D_2 antagonists (e.g. asenapine, haloperiodol and risperidone). Post-treatment hyperactivity-related adverse events were assessed in two clinical studies in adolescent patients (D1050301 and D1050325). No post-treatment hyperactivity related adverse events have been observed in the small number of patients (n=55) that discontinued or did not rollover into the long-term extension study D1050302.

Hormone analysis
Mean prolactin levels were higher in males and females at ≥3 mg/kg/day than in the control group. Mean estradiol levels were slightly lower in females at 3 and 30 mg/kg/day and were similar to controls at 300 mg/kg/day. Elevated prolactin levels were also observed in adult rats, dogs and monkeys. In adult female rats, high prolactin levels were associated with effects on bones, adrenal glands and reproductive tissues. In dogs, high prolactin levels were associated with effects on male and female reproductive tissues. Elevated prolactin levels are commonly seen in rodents treated with antipsychotic drugs with dopamine D_2 blocking activity. In study D105301 changes from baseline in prolactin levels were significant different in the lurasidone treatment groups compared to placebo.

Alterations in males; thyroid gland and prostate
Lower thyroid/parathyroid gland weights were seen at ≥30 mg/kg/day. At 150 mg/kg/day, microscopic examination revealed increased colloid (minimal to mild) in the thyroid glands and increased severity in inflammation of the prostate (minimal and one rat with moderate severity). Both findings were reversible.

Increased colloid in the thyroid gland has not been previously noted in adult rats. Increased colloid and lower thyroid epithelial height are consistent with decreased responsiveness to thyroid stimulating hormone (TSH) as would occur with endocrine disruption. Regarding the increased severity in inflammation of the prostate, the study pathologist speculate that this may be associated by elevated prolactin as is has been reported that prepubertal exposure to compounds that induce prolactin secretion can increase inflammation in the rat prostate gland (Ref). This finding was not observed in adult rats. A NOEL was established for findings in thyroid and prostate at exposures 11-fold higher than those anticipated in paediatric/adolescent patients.

Alterations in females; mammary gland, vagina and ovaries
Lower pituitary gland weights were seen at ≥30 mg/kg/day. Mammary glandular hyperplasia (minimal to moderate), increased mucification of the vagina (minimal to mild), and increased atretic follicles in the ovaries (minimal to mild) were observed at all dose levels. All findings were reversible following the recovery period. These findings were all attributable to the elevated prolactin levels and are similar to that previously seen in adult rats.

The findings in juvenile females were similar to those noted in adult female rats where effects on the bones and adrenal glands, pituitary gland and reproductive tissues were observed. Mammary gland and/or pituitary gland tumors were observed in mouse and rat carcinogenicity studies. These findings are common in rodents treated with antipsychotic drugs with dopamine D2 blocking activity. Tumor development is most likely related to increased blood prolactin.

Reproductive parameters
No lurasidone-related effects were observed on spermatogenesis, mating, fertility, copulation, and conception indices at any dose level. Slightly lower F_1 birth weights and pup body weights were noted during PND 4 to 7 at ≥30 mg/kg/day. Although these lower weights were considered to be treatment-related, the pup weights at 30 and 300 mg/kg/day were within the performing laboratory's historical control data range, and thus, these changes were slight and considered to be within the biological variation range. Because of the lower birth weights and body weight gains seen in the ≥30 mg/kg/day groups, the NOEL for neonatal toxicity was considered to be 3 mg/kg/day. The NOEL exposures for neonatal toxicity (effects on birth weight and body weight gains) are approximately equal to those anticipated clinically, while the exposures at the LOEL (30 mg/kg/day) are approximately 11-fold and 14-fold higher in males and females, respectively, than the anticipated clinical exposure. Similar effects on pup birth weight and body weight gain were not noted in a pre- and post-natal development (PPND) study conducted following administration of lurasidone to adult rats (EPAR, EMEA/H/C/002713/0000, 2014). However, lower dose levels were employed in the PPND study (0.3, 1, 3, and 10 mg/kg/day). Because of the different dose levels evaluated and differences in study design, it cannot be concluded

that the lower pup birth weights and body weight gains seen in pups of rats that had been dosed with lurasidone from PND 21 to PND 91 is a finding that is unique to juvenile rats.

Exposure margins

The exposure margins (C_{max} and AUC) calculated versus the maximum human recommended dose in paediatric patients, 80 mg/day lurasidone hydrochloride (74 mg/day lurasidone free base), are presented below. However further clarification on the exposure of lurasidone and metabolites in the paediatric population was requested. Based on the outcome of these clarifications, an updated exposure margin table was requested, i.e. C_{max} and AUC at NOAELs in juvenile rat study versus exposure at the maximum clinical dose of 80 mg/day.

Table 4 Exposure margins at NOAELs in juvenile rat study versus the maximum clinical dose of 80 mg/day.

Study	NOAEL (mg/kg/day)	Exposure at NOAEL (ng/mL or ng·hr/mL)		Exposure Margin at 80 mg/day (d)	
		Cmax	AUC	Cmax	AUC
Juvenile toxicity	F_0 physical growth and development: 3 F_0 neurobehavioral development: M, 3; F, <3 F_0 reproductive toxicity: M, 150; F, 300 F_1 neonatal toxicity: 3	3 mg/kg M: 42.5 F: 62.1	3 mg/kg M: 287 F: 215	3 mg/kg M: 0.53 F: 0.78	3 mg/kg M: 0.74 F: 0.56
		150 mg/kg M: 946	150 mg/kg M: 8530	150 mg/kg M: 12	150 mg/kg M: 22
		300 mg/kg F: 1950	300 mg/kg F: 24500	300 mg/kg F: 24	300 mg/kg F: 63

AUC(0-24hr)=area under the drug concentration-time curve from time 0 to 24 hours, F=female, M=male
(d) Based on human Cmax and AUC(0-24hr) values of 80 ng/mL and 387 ng·hr/mL, respectively.

As previously observed in adult animals (mouse, rat and monkey), exposure margins obtained in the juvenile toxicity study were below 1. The first adverse effects noted above the NOAEL were predominantly mild effects on the CNS and completely reversible within some hours. Also, reductions in body weight gain/mean body weight correlating with reduced food consumption were observed likely causing a slightly delayed overall development as a secondary consequence. Additionally, elevated prolactin levels associated with effects on reproductive tissues were seen, as previously observed in adult animals. Elevated prolactin levels are common in rodents treated with antipsychotic drugs with dopamine D_2 blocking activity. Most treatment-related effects were completely reversible within a 4-week recovery period. There are no functional or histopathological findings indicating any age-dependent lurasidone-related effects or effects specifically on developmental parameters.

The Applicant was requested to add appropriate wording regarding the juvenile toxicity studies in section 5.3, of the SmPC which was done satisfactorily.

The clarifications on the exposure of lurasidone and metabolites in the paediatric population were deemed satisfactory.

Based on Report M1050005 and Study D1050300, Table 1 for exposure margins of Lurasidone and its metabolites at NOAELs as described above was updated accordingly.

Table 5

Table 1: Exposure margins at NOAELs in juvenile rat study on postnatal day 91 versus the maximum clinical dose of 80 mg/day

Lurasidone Dose (mg/kg/day)	3				150/300 [b]			
	C_{max} (ng/mL)		$AUC_{(0-24)}$ (ng·hr/mL)		C_{max} (ng/mL)		$AUC_{(0-24)}$ (ng·hr/mL)	
Analyte/Sex	Male	Female	Male	Female	Male	Female	Male	Female
Lurasidone[a]	0.7	1.0	0.7	0.45	15.5	30	21	51
ID-20219[c]	0.47	0.26	0.43	0.16	4.5	7.6	11	22
ID-20220[c]	1.2	0.34	0.82	0.22	5.5	3.7	10	8.2
ID-14283[c]	1.1	2.8	0.79	2.0	8.5	10	16	28
ID-14236[c]	4.8	11	2.7	6.3	33	43	49	91

Risk management plan

The age span studied in the rat studies is considered relevant for the application. Overall, most study findings are expected based on the pharmacology of lurasidone. The data from the new non-clinical juvenile toxicity studies have not identified any new or unique risks with regard to the safety of lurasidone in a juvenile population.

No significant new findings were observed in the performed studies.

2.2.7. Conclusion on the non-clinical aspects

Two new juvenile studies have been submitted and assessed in this procedure; the labelling of the product has been updated accordingly.

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of lurasidone.

- Considering the above data, lurasidone is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

Three studies were outlined in the current paediatric investigation plan:

Study 1
Open-label, multicentre, single and multiple fixed ascending dose study to evaluate pharmacokinetics, safety, and tolerability of lurasidone in the paediatric population (D1050300).

Study 2
Randomised, parallel, double-blind, placebo-controlled, fixed-dose regimen, multicentre, study to evaluate the efficacy and safety of lurasidone in adolescent patients with schizophrenia (D1050301).

Study 3
A 104-week, flexible-dose, open-label multicentre extension study to evaluate the long-term safety and effectiveness of lurasidone in adolescent patients with schizophrenia (D1050302).

Study 4
Deleted in procedure EMEA-001230-PIP01-11-M04

2.3.2. Pharmacokinetics

Background

The Pharmacokinetics of Lurasidone and its metabolites have previously been established in adults. This extension of indication is for the treatment of schizophrenia in adolescent from 13 to 17 years old. Adults and adolescent 13-17 years are not expected to have major differences in PK except for influence of body weight (lower body weight in adolescents).

Lurasidone is metabolized mainly by the cytochrome P450 system. The major biotransformation pathways are oxidative N-dealkylation, hydroxylation of the norbornane ring, S-oxidation, reductive cleavage of the isothiazole ring followed by S-methylation, and a combination of two or more of these pathways.

Five metabolites were assessed in clinical studies: two major non-active metabolites (ID-20219, ID-20220); two active metabolites (ID-14283, ID-14326); and one non-major, non-active metabolite (ID-11614).

The applicant states that PK for lurasidone and its metabolites are similar between adults and adolescents/paediatric population. As a result of similar PK of lurasidone, no difference would be expected in paediatrics as those observed in adults in studies such as drug-drug interactions, intrinsic/extrinsic factors and renal/hepatic impairment.

popPK model (M1050005)

The PK profiles for lurasidone were characterized by a population PK analysis (M1050005). This population PK analysis consists of data from 22 Phase 1 through Phase 3 clinical studies. To date, 14605 measurable lurasidone concentrations from 1623 healthy subjects and subjects with schizophrenia were included in the population PK analysis. Intrinsic factors such as age, body weight, gender, and race and extrinsic factor such as food were evaluated. The following are important covariates with respect to population PK parameters were tested: race and food for absorption dissociation constant (Ka), race and gender for apparent oral clearance (CL/F); body weight for volume of distribution for the second peripheral compartment (V2/F); and food for relative BA.
The PopPK analysis suggest that the exposure to lurasidone is dose-proportional and extends from healthy subjects to subjects with schizophrenia. The observed geometric Cmax, AUC and Ctrough generally fell within the fifth and 95th percentile of the geometric mean simulated distribution for both healthy subjects and subjects with schizophrenia. Therefore, there is no difference in PK between healthy subjects and patients. No age effect was noted based on these modelling results. The current final popPk model found is *Final model Update 3* from an addendum to the M105005 report. The model does not appear to have an effect of body weight on clearance (see parameter estimates in table below).

Table 6

Table 4: Parameter Estimates for the Final Update 3 Model

Parameter	Update 3 Model (MVOF=73093)	
	Estimate (SE)	IIV Estimate (SE) [% CV][a]
Absorption Rate Constant (ka) (1/hr)	1.13 (0.0819)	1.00 (0.117) [100][b]
Proportional Change in ka for Asian Race	-0.309 (0.0759)	NE
Proportional Change in ka for Fasted Meal Status	1.31 (0.918)	NE
Proportional Change in ka for Non-High-Fat Meal Status	0.372 (0.195)	NE
Proportional Change in ka for Study D1050-233	-0.431 (0.0685)	NE
Apparent Clearance (CL/F) (L/hr)	196 (5.08)	0.151 (0.0185) [38.9]
Proportional Change in CL/F for Asian Race	-0.320 (0.0351)	NE
Proportional Change in CL/F for Females	-0.155 (0.0293)	NE
Proportional Change in CL/F for Study D1050-233	-0.274 (0.0704)	NE
Apparent Central Volume of Distribution (V2/F) (L)	794 (33.3)	0.120 (0.0445) [34.6]
Change in log V2/F per unit change in log BWT (L/kg)	0.355 (0.118)	NE
Difference between k_{32} and k_{42} (DK32) (1/hr)	0.0676 (0.00627)	NE
Apparent Peripheral Volume of Distribution 1 (V3/F) (L)	827 (92.6)	NE
Apparent Intercompartmental Clearance 2 (Q4/F) (L/hr)	101 (4.53)	NE
Apparent Peripheral Volume of Distribution 2 (V4/F) (L)	13300 (1230)	0.867 (0.117) [93.1]
Absorption Lag Time (ALAG1) (hr)	0.424 (0.00749)	NE
Relative Bioavailability (F1)	1 FIX	0.286 (0.0315) [53.5]
Proportional Change in F1 for Fasted Meal Status	-0.535 (0.0270)	NE
Proportional Change in F1 for Study D1050-233	-0.206 (0.0952)	NE
Residual Variability (σ) for Extensive Sampling Designs	0.367 (0.0077)	NE
Residual Variability (σ) for Phase 2 Studies	0.479 (0.0306)	NE
Residual Variability (σ) for Phase 3 Study D1050-229	0.521 (0.0199)	NE
Residual Variability (σ) for Phase 3 Study D1050-231	0.540 (0.0218)	NE
Residual Variability (σ) for Phase 3 Study D1050-233	0.426 (0.0209)	NE
Residual Variability (σ) for Phase 3 Study D1050-237	0.597 (0.0243)	NE

NE = Not estimated
$Q3/F = [(((Q4/F)/(V4/F)) + DK32) \cdot V3/F] = 62.2$ L/hr

Three additional population PK analyses were completed (M1050001, M1050002 and M1050003) early in the program. These three reports contained less than half of the data included in Report M1050005. Report M1050005 is more robust and provides a more complete characterization of lurasidone PK according to the applicant.

Simulations comparing exposure between adolescents and adults

As there is no observed adult lurasidone exposure following the dosing schemes as described in the pediatric PK study (D1050300), the exposure in adults were simulated through the previously established population PK model (Report M1050005). A subset of 240 adult patients were randomly sampled as a representative of adult patients. Simulations were subsequently carried out for these adult patients according to the dosing schemes the 20, 40, 80, 120 and 160 mg cohorts to predict the serum lurasidone concentrations per the PK sample collection times in Study D1050300.

No differences in PK between adults and adolescents are expected, except for influence of body weight (lower body weight in adolescent population). The applicant has however been requested to show that the exposures are similar in adults and adolescent/paediatric population. As there is no observed adult lurasidone exposure following the dosing schemes as described in the paediatric PK study (D1050300), the exposure in adults were simulated, which was acceptable.

A number of questions were raised during the assessment on the PoPK model which were satisfactorily addressed by the company.

The assumed final popPK model found in the documentation is the Final model Update 3 from addendum to M1050005 report. The model does not appear to have an effect of body weight on clearance. Body weight based allometric scaling with fixed exponents of 0.75 for Clearance/ Inter-compartmental clearance and 1 for distribution volumes should be included in the model unless otherwise justified. Further justifications on the final model from report M1050021 was provided to support that this is the appropriate model for adolescent and pediatric predictions.

Regarding the popPk model, the applicant mentions two reports. Differences between M1050005 and M1050021 model should be explained, and the use of the appropriate model for PK comparison of adults/adolescents exposure should be justified. For the appropriate model, VPCs stratified on body weight, age and adult/paediatric as well as pcVPCs was requested and provided. Prediction-corrected visual predictive checks for diagnosing nonlinear mixed-effects models. The AAPS journal, 2011, 13.2: 143-151. Justification of the adequacy of the model based on VPC/pcVPCs and parameter estimates (RSE% and CI) was requested and provided.

The CHMP requested to use the appropriate popPK model to simulate Lurasidone exposure in adults and in paediatric population for different doses and to further support the statement that exposure is similar between adults and adolescents based on the simulations from the popPK model.

The final model from report M1050021 was considered as the appropriate model for adolescent and paediatric predictions. Subjects included in the model were used for a population PK prediction at doses of 40 mg, 80 mg, 120 mg, and 160 mg. Individual covariates, meal status, study, and ETA values were kept constant during each simulation. The 90% prediction interval (PI) and the mean of the adult population (1623 subjects) were calculated for each dose and plotted in the background. Paediatric subjects (281 subjects) were grouped into weight bins from study D1050300 and D1050301. All doses show predicted AUC0-24,ss values within the 90% PI of the adult reference value. Based on these predictions there does not seem to be a strong correlation between exposure and body weight, consistent with the PK model parameter estimate of 0.218 as the exponent describing the relationship of body weight with the volume of distribution (i.e., where V2/F is the apparent central volume of distribution, θ3 is the population estimate of V2/F and WT is the subject body weight centered on the median value of 80 kg (Figure 11). In addition, there does not seem to be a correlation between predicted AUC0-24,ss values and age.

Having reviewed the data provided by the applicant, it was concluded that exposure is similar between adults and adolescents based on the simulations from the population PK model and paediatric/adolescent data from Study D1050300 and Study D1050301.The metabolites have not been modelled, however as the applicant could show that exposure in adults and adolescent are similar for Lurasidone, then the similar Lurasidane exposure are expected to provide similar metabolite exposures, as the metabolic capacity is not expected to differ between the adult and adolescent population.

Since body weight is expected to influence exposure, the adolescent population is expected to have slightly higher exposure compared to adults given the same dose. Since only 40 and 80 mg dose are proposed for adolescents, this is expected to fall within the range of adult exposure (40-160 mg doses). The questions regarding the popPK model are mainly in relation to support the information in the SmPC as the Exposure-response analysis (described further down in this report) is only considered supportive. This was adequately reflected in section 5.2 in the SmPC.

2.3.3. 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 and 5-HT7- receptors with high binding affinity of 0.994, 0.47 and 0.495nM, 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 partial agonism at the 5HT-1A receptor with a binding affinity of 6.38 nM. Lurasidone does not bind to histaminergic or muscarinic receptors.

Primary and secondary pharmacology

No new data on primary and secondary pharmacology has been submitted by the applicant in this procedure.

2.3.4. PK/PD modelling

Population Exposure Response (ER) Analysis of PANSS Total Scores after Short and Long Term Treatment in Adult and Adolescent Patients with Schizophrenia.

Short term

Observed and LOCF PANSS change from baseline at end of treatment versus individual predictions of luras-idone Css,av for the (acute) six-week studies that had plasma concentration measurements, on a semi-logarithmic scale are shown in the figure below. Overall, there is a trend of increasing response (lower PANSS scores) with higher exposures.

Figure 2

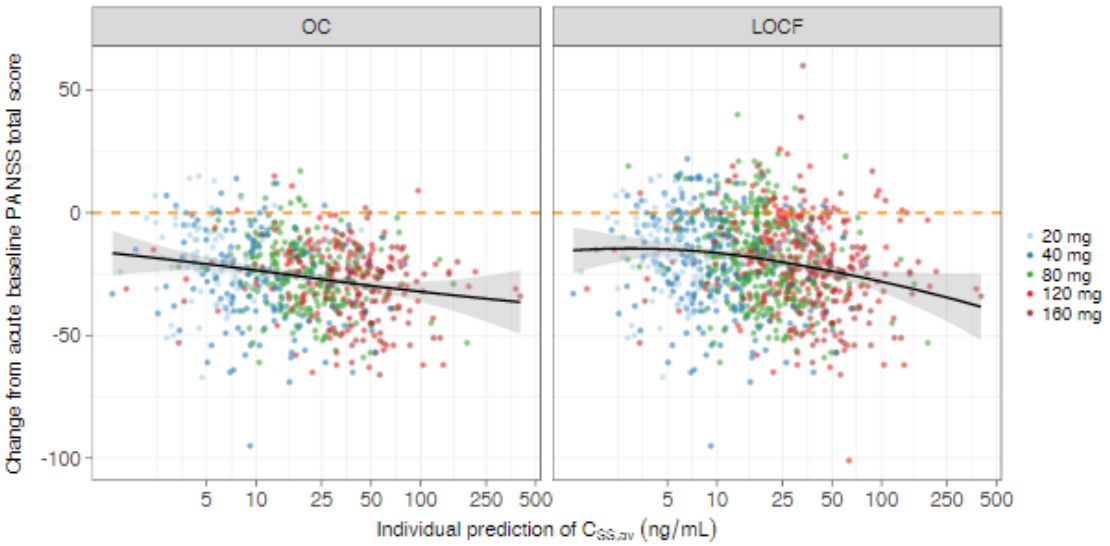


Figure 18: Observed and LOCF PANSS change from baseline at end of treatment versus individual predictions of lurasidone $C_{ss,av}$ for the (acute) six-week studies that had plasma concentration measurements, on a semi-logarithmic scale, based on the final analysis data set and stratified by imputation method: OC (no imputation) versus LOCF. Subjects assigned to placebo have been omitted, and only PANSS observations 38.5-49 days after the first dose have been included. The black line is a smooth with the grey area representing the 99% CI. The dots represent the individual data, coloured by the dose (daily dose assigned the day before the PANSS measurement). The dashed, horizontal orange line is a visual support line at zero change from baseline. PANSS: Positive and Negative Syndrome Scale; $C_{ss,av}$: average concentration, at steady-state; CI: confidence interval; OC: observed cases; LOCF: last observation carried forward.

The exposure-response relationship after long-term lurasidone treatment in adolescent subjects has been extrapolated from a model incorporating short-term and long-term data from adults and adolescents. The data used in this analysis originated from, as follows:

- Clinical studies in adults with acute schizophrenia (8 studies): D1050006, D1050196, D1050229, D1050231, D1050233, D1050303, D1070004, and D1001056 (of which two studies were in Asian subjects).
- Clinical studies of maintenance treatment in adults with schizophrenia (3 studies): D1050234, D1050238, and D1001057 (of which one study was in Asian patients).
- Clinical studies in adolescent subjects (ages 13 to 17 years-old) with acute schizophrenia (1 study): D1050301.
- Clinical studies of maintenance treatment in adolescents with schizophrenia (1 study): D1050302

A total of 34542 PANSS observations in 3603 patients were included in the analysis.
Non-linear mixed-effects models using the software NONMEM were used to update previously developed models for PANSS total score and dropout. The models were then used to extrapolate to maintenance treatment with lurasidone in adolescent patients. The last observation carried forward (LOCF) approach was used for PANSS total score after the simulated dropout. In the extrapolation, two scenarios were simulated. The first scenario represented a simulated randomized withdrawal study and was based only on the subjects that received active treatment in Study D1050301. These subjects were used three times over so that all original trial subjects received placebo, lurasidone 40 mg once daily, and lurasidone 80 mg once daily during the maintenance study. In the second scenario "maintained treatment", the subjects maintained their treatment from the acute phase, so that subjects on placebo in the acute phase also received placebo in the maintenance phase. Subjects on active treatment in the acute phase were simulated to receive

active treatment in the maintenance phase, but these subjects were used two times over, so that two active arms (40 mg and 80 mg lurasidone once daily) were simulated in the maintenance phase.

The PANSS total score model submitted to the previous lurasidone NDA, consisting of a placebo component, a spike component (ie, used to evaluate/model any sudden rise in PANSS total scores during the study for an individual subject), and a drug effect component, was updated after inclusion of data from maintenance treatment in adolescent subjects, low-dose acute treatment in adult subjects (Study D1050303), and acute and maintenance treatment in Asian subjects (Studies D1001056 and D1001057). Adolescent subjects were found to have a later spike time in PANSS total score and a larger placebo effect in the maintenance phase than adult subjects. The drug effect on PANSS total score was found to increase log-linearly with increased average concentration at steady-state (Css,av). Final model parameter estimates are shown in the table below.

Table 7

Table 7: Parameter estimates for the final PANSS model

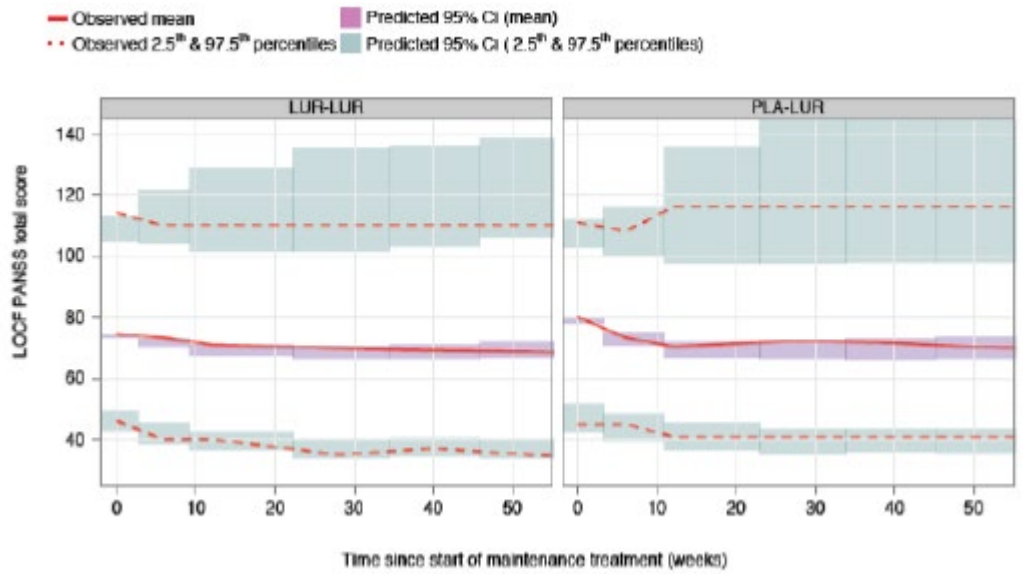
	Final PANSS model in adults and adolescents
Run	535
OFV	173275
Condition number	3954

	Final PANSS model in adults and adolescents			
	Unit	**Value**	**RSE (%)**	**SHR (%)**
log(Baseline)*	log(PANSS)	4.57	0.0718	
logit(P_{max})†		-0.161	23.1	
log(TD)*	log(weeks)	1.06	3.56	
POW	exponent	1.98	4.82	
logit(E_{20})		-1.45	3.82	
$Height_{Spike}$		0.690	4.11	
$Steep_{Spike}$		3.00	(FIX)	
$Time_{Spike}$	weeks	62.2	0.544	
$\theta_{RelPrev}$	mL/ng	0.00394	9.04	
logit($MaintP_{max}$)†		-1.48	4.96	
LBP_{max}		-0.157	5.82	
TD_{Maint}	weeks	2.20	12.8	
USA-Baseline		-0.0315	14.2	
NHOP-$Time_{Spike}$		-0.143	5.18	
USA-$Time_{Spike}$		-0.447	0.708	
D1050238-Baseline		-0.0465	10.2	
BTANS-Baseline		0.0179	17.7	
Adolescent-TD		0.601	17.0	
Adolescent-E_{20}		0.386	27.0	
Adolescent-$Time_{Spike}$		1.72	0.743	
Adolescent-$MaintP_{max}$		-0.389	32.9	
D1001056-Baseline		0.0396	18.9	
D1070004-Baseline		-0.0628	13.3	
D1001056-E_{20}		-0.745	17.0	
D1070004-E_{20}		1.09	12.6	
$IIV_{Baseline}$	CV	0.109	1.47	5.80
IIV_{Pmax}†	logit(SD)	0.960	3.29	35.6
$IIV_{Baseline,Pmax}$	Corr.	-0.0158	94.6	
IIV_{E20}	logit(SD)	1.23	3.38	32.2
$IIV_{Baseline,E20}$	Corr.	-0.164	10.3	
$IIV_{Pmax,E20}$	Corr.	0.189	10.3	
IIV_{TD}	CV	1.36	2.16	32.7
$IIV_{Baseline,TD}$	Corr.	0.0663	20.7	
$IIV_{Pmax,TD}$	Corr.	0.458	3.99	
$IIV_{E20,TD}$	Corr.	-0.0298	66.3	
$IIV_{MaintPmax}$†	logit(SD)	1.06	5.22	28.7
$Err_{Additive}$	SD	4.13	2.55	5.86
$Err_{Proportional}$	CV	0.0423	8.95	5.86

* PANSS typical baseline was 96.6 and typical TD was 2.88 weeks. † P_{max} and $MaintP_{max}$ were estimated on a logit scale with lower bound -0.157 and upper bound 1 and (1-P_{max}), respectively. For P_{max} the typical relative reduction, was 0.375 with sd=0.233 and for $MaintP_{max}$ -0.0578 with sd=0.144. Parameters are explained in Section 4.3. RSE is relative standard error. For correlations RSEs are provided for the square-root of the covariance estimate. All parameter estimates and RSEs have been rounded to three significant digits. SHR is shrinkage. SHR for the residual error is shared across the proportional and additive part. IIV is interindividual variability, CV is coefficient of variation, Corr. is correlation. SD is standard deviation. RSEs for IIV and Err are reported on the approximate SD scale.

A visual predictive check (VPC) of PANSS total score for study D1050302 simulated using the individual predictions of acute phase parameters in the subjects who entered the maintenance phase is shown in **Figure 3**.

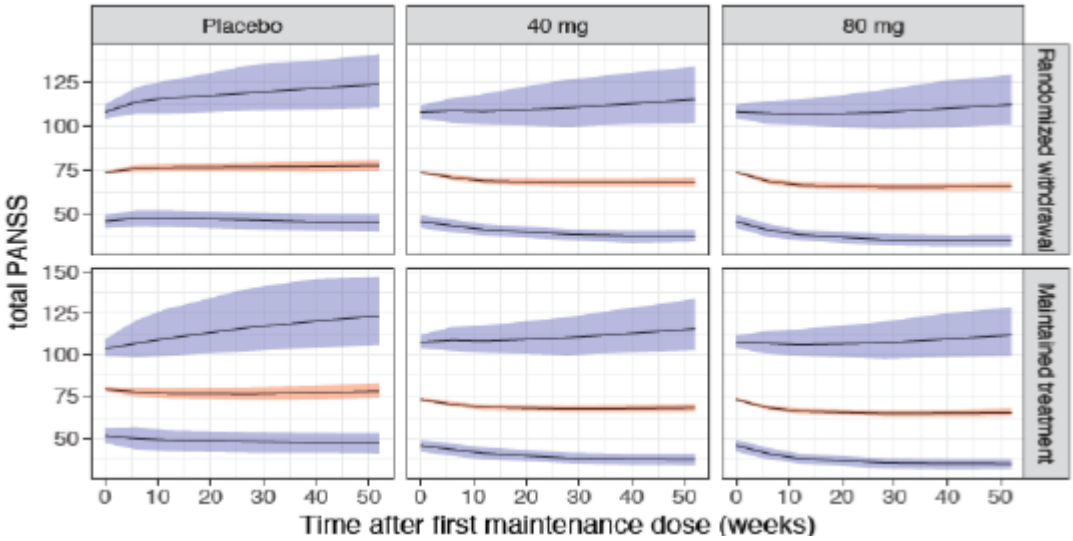
Figure 3 VPC of PANSS for Study D1050302, simulated using the Individual Predictions of Short-Term Treatment Parameters in the Subjects who Entered the Long-Term Treatment Study



Note: PANSS scores are displayed versus time after first long term treatment dose. The solid and dashed red lines represent the mean, 2.5th and 97.5th percentiles of the observations; the shaded purple and blue areas represent the 95% confidence interval of the mean, 2.5th and 97.5th percentiles predicted by the model. Note: PLA = placebo (PBO).

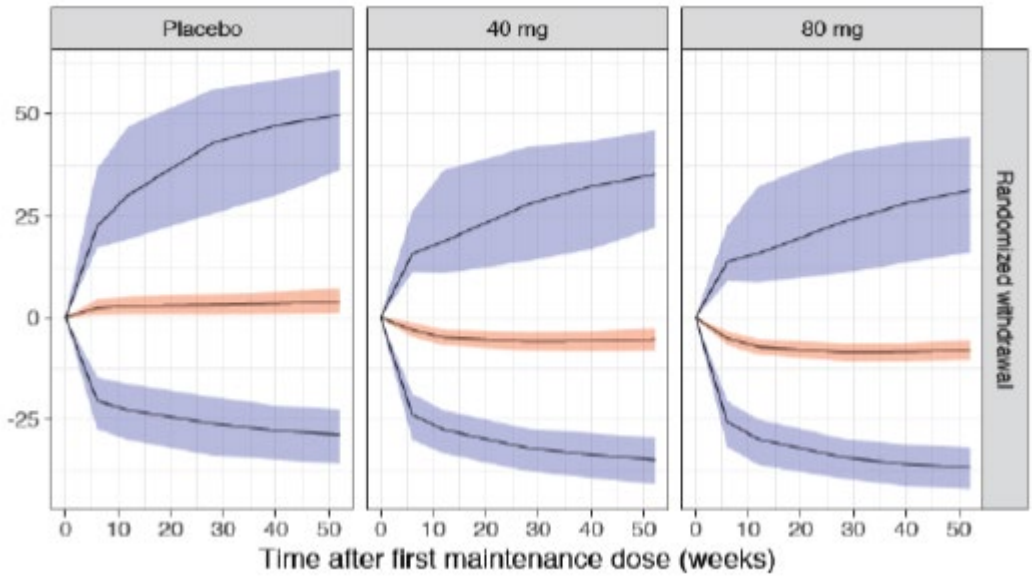
Extrapolation to long-term treatment in Study D1050302 in adolescent subjects with schizophrenia was performed based on the final PANSS total score and dropout models, using LOCF. Simulated PANSS total score using LOCF and the change from long-term treatment Baseline in PANSS total score are presented in Figure 2 and Figure 3, respectively for adolescent subjects (ages 15 to 17 years-old) with schizophrenia. In these 15-17 year-old adolescent subjects, the placebo-adjusted change (95% confidence interval) in PANSS total score from long-term treatment Baseline at Week 28 was estimated to be -9.1 (-13, -5.9) and -12.0 (-15, -8.6) for the 40 mg and 80 mg groups, respectively, in the simulated randomized withdrawal type of study.

Figure 4 Simulated PANSS Total Score (using LOCF) versus Time after First Long-Term Treatment Dose for 15-17 Year Old Patients in the D1050302 Population



Note: Black lines are the model expectation of the mean, 2.5th and 97.5th percentiles of the simulated data. The shaded areas are the corresponding 95% confidence intervals.

Figure 5 Simulated Change from Long-Term Treatment Baseline in PANSS Total Score (using LOCF) versus Time after First Long Term Treatment Dose for 15-17 Year Old Subjects in the D1050302 Population for the Randomized Withdrawal Scenario



Note: Black lines are the model expectation of the mean, 2.5th and 97.5th percentiles of the simulated data. The shaded areas are the corresponding 95% confidence intervals.

In adolescent subjects (ages 13 to 14 years-old) with schizophrenia, the placebo-adjusted change (95% confidence interval) from long-term treatment Baseline at Week 28 in PANSS total score was estimated to be -8.4 (-14.0, -3.0) and -11.0 (-17.0, -5.4) for the 40 mg and 80 mg groups, respectively, in the simulated randomized withdrawal type of study.

Short-term exposure-response

The exposure-response relationship for the short-term data of 40 and 80 mg dosing is close to flat. While it is unclear how well this correlate to long-term exposure-response, this provides some support that there may not be a need for a higher dose in adolescents.

Long-term exposure-response

The exposure-response relationship after long-term lurasidone treatment in adolescent subjects has been extrapolated from a model incorporating short-term and long-term data from adults and adolescents. Some differences in adult and Adolescent were found in the modelling analysis. Adolescent subjects were found to have a later spike time in PANSS total score and a larger placebo effect in the maintenance phase than adult subjects.

The applicant concludes that the models selected were demonstrated to be appropriate and the simulated results are predictive of the actual results from Study D1050302 and that these data support long-term treatment with lurasidone at doses of 40 mg/day and 80 mg/day in adolescent subjects with schizophrenia. The condition number is high (over 1000, suggesting that the model may be overparameterized) and while it is agreed that the VPCs show that the model appear adequate, there are however several limitations. Adolescent as a covariate is considered insensitive, in comparison to e.g. age. The adolescent covariate may be a study effect rather than actual adolescent effect. Using last observation carried forward instead of simulating the whole treatment may also be problematic. The long-term effects are mainly driven by the adult data with any differences in adults/adolescents based on short-term adolescent data. In addition, there are also questions regarding the popPK model that was used to derive the Css,av for the PKPD analysis.

Since higher doses than 80 mg have not been properly investigated in adolescents, the modelling is not considered robust to support that 80 mg provides maximal effect. The modelling can be considered supportive to the efficacy data, that 40 and 80 mg provide better effect on PANSS than placebo.
The model parameters were also updated using the long-term data (table not shown) however for studies with flexible dosing, it is problematic to estimate dose-response or exposure-response, since dose is adjusted based on response.

Overall, the exposure-response modelling conducted may be useful to select doses to study in adolescents however the adolescent studies have been conducted and efficacy data has been collected, therefore the modelling is considered only to be supportive. The limitations regarding the open-label study cannot be mitigated by the modelling. There is a lack in the justification of not going higher in dose than 80 mg in adolescents. Adolescent age was found to be a covariate, but this may be a study effect rather than actual adolescent effect.

2.3.5. Discussion on clinical pharmacology

Pharmacokinetics

The Pharmacokinetics of Lurasidone and its metabolites have previously been established in adults. There is a statement in the SmPC regarding similar PK in adults and paediatric patients however this statement could not be supported by the initially submitted popPK analysis. No differences in PK between adults and adolescents are expected, save for impact of body weight. As there is no observed adult lurasidone exposure following the dosing schemes as described in the paediatric PK study (D1050300), the exposure in adults were simulated. This approach is supported.

The applicant has provided relevant information regarding the final popPk model as well as a discussion supporting the statement that exposure is similar between adults and adolescents based on the simulations from the popPK model.

The metabolites have not been modelled, however as the applicant showed that exposure in adults and adolescent are similar for Lurasidone, then the similar Lurasidone exposure are expected to provide similar metabolite exposures.

The highest dose studied in paediatric population are lower than the highest approved dose in adults. Thus, safety due to too high exposure compared to adults are not expected to be a concern.

Pharmacodynamics

No new data on primary and secondary pharmacology has been submitted by the applicant in this procedure. The same mode of action is expected in the paediatric population as in the adult population buy lurasidone. The exposure-response relationship after long-term lurasidone treatment in adolescent subjects has been extrapolated from a model incorporating short-term and long-term data from adults and adolescents.

Exposure response modelling

Short term exposure-response

The exposure-response relationship for the short-term data of 40 and 80 mg dosing is close to flat. While it is unclear how well this correlate to long-term exposure-response, this provides some support that that there may not be a need for a higher dose in adolescents.

The exposure-response relationship after long-term lurasidone treatment in adolescent subjects has been extrapolated from a model incorporating short-term and long-term data from adults and adolescents. Some differences in adult and Adolescent were found in the modelling analysis. Adolescent subjects were found to have a later spike time in PANSS total score and a larger placebo effect in the maintenance phase than adult subjects.

The applicant claimed that the models selected were demonstrated to be appropriate and the simulated results are predictive of the actual results from Study D1050302 and that these data support long-term treatment with lurasidone at doses of 40 mg/day and 80 mg/day in adolescent subjects with schizophrenia. The condition number is high (over 1000, suggesting that the model may be overparameterized) and while it is agreed that the VPCs show that the model appear adequate. There are however several limitations. Using adolescent as a covariate rather than age or some other biomarker is not considered very sensitive. The adolescent covariate may be a study effect covariate rather than actual adolescent effect. Using last observation carried forward rather than simulating the whole treatment may also be problematic. The long-term effects are mainly driven by the adult data with any differences in adults/adolescents based on short-term adolescent data. In addition, there were also several questions regarding the popPK model that was used to derive the Css,av for the PKPD analysis.
Since higher doses than 80 mg have not been properly investigated in adolescents, the modelling is not considered robust to support that 80 mg provides maximal effect. The modelling can be considered supportive to the efficacy data, that 40 and 80 mg provide better effect on PANSS than placebo.

Overall, the adolescent studies have been conducted and efficacy data has been collected and the PKPD modelling is considered only to be supportive at this stage. Shortcomings of the open label study cannot be mitigated by the model. The information in section 5.1 regarding the exposure-response modelling supporting the 37(40) and 74(80) mg dose was not supported and was removed from the initially proposed labelling, as it can be interpreted as supporting that 80 mg as the highest dose in adolescent has been justified using the modelling, which is not supported.

2.3.6. Conclusions on clinical pharmacology

The Pharmacokinetics of Lurasidone and its metabolites have previously been established in adults. No differences in PK between adults and adolescents are expected, save for impact of body weight. The claim that the lurasidone and metabolite exposure is similar adults and adolescents/paediatric patients is supported.

The same mode of action is expected in the paediatric population as in the adult population by lurasidone.

The exposure-response model may be useful to select doses to study in adolescents however the study has been conducted and efficacy data has been collected, the modelling is considered only to be supportive to the clinical data.

2.4. Clinical efficacy

2.4.1. Dose response study

No dose-response studies in the paediatric population was provided by the applicant. A dose-response study would have been valuable to establish minimum effective dose and the dose for optimal efficacy in the paediatric population. In study D1050300, it was demonstrated that the pharmacokinetic profile appears to be consistent with the profile observed in adult subjects. Further justifications on the absence of a proper dose-response study in the paediatric population was requested and satisfactorily provided.

2.4.2. Main studies

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

Short-term, Placebo-Controlled Study (D1050301)

The short-term efficacy of lurasidone in the treatment of schizophrenia in adolescent subjects with acute schizophrenia has been demonstrated in a single, randomized, parallel, double-blind, placebo-controlled, fixed-dose,6-week multicentre study.).

Methods

The study included a screening period, a baseline assessment, a 6-week double-blind treatment period, and a follow-up visit. During the21-day screening period, eligible subjects were tapered off all psychotropic medications. During
the double-blind treatment phase, subjects were treated with lurasidone or placebo for six weeks.

Study participants

Eligible subjects were males or non-pregnant, non-lactating females, aged 13 to 17 years, who met Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) axis I criteria for a primary diagnosis of schizophrenia and had an acute exacerbation of psychotic symptoms (no longer than two months in duration) and marked deterioration of function from baseline (by history), or had been hospitalized for the treatment of an acute psychotic exacerbation, for two consecutive weeks or less, immediately before screening. The diagnosis of schizophrenia was confirmed by an adequately trained clinician at the time of screening according to the Schedule for Affective Disorders and Schizophrenia for School-age Children. Eligible subjects also had a Positive and Negative Syndrome Scale (PANSS) total score $\geq$ 70 to < 120 at Screening and Baseline, and a Clinical Global Impression-Severity Scale (CGI-S) score $\geq$ 4 at Screening and Baseline.

A total of 327 subjects were randomized and 326 were included in the ITT population used for efficacy evaluations. Of the subjects in the ITT population, 108 subjects were randomized to lurasidone 40 mg/day, 106 subjects were randomized to lurasidone 80 mg/day, and 112 subjects were randomized to placebo. A total of 285 subjects in the ITT population (87% of the randomized subjects) completed the study: 96 (89%) subjects in the lurasidone 40 mg/day group; 96 (91%) subjects in the lurasidone 80 mg/day group; and 93 (82%) subjects in the placebo group.

The diagnosis and selection of eligible subjects is acceptable. The selection of participants that *had an acute exacerbation of psychotic symptoms (no longer than two months in duration) and marked deterioration of function from baseline (by history), or had been hospitalized for the treatment of an acute psychotic exacerbation, for two consecutive weeks or less, immediately before screening*,

represents patients that are more in an acute disease phase that may show a larger response to pharmacological treatment than patients that are in a more chronic phase of the disease.

The participant also had a global Impression-Severity Scale (CGI-S) score ≥ 4 at screening and baseline, which render them to be at least moderately ill. Thus, no mildly ill patients were included in the study.

The MAH provided adequate justifications that the results in the study population is applicable to the proposed target population (schizophrenia irrespective of severity) considering that the study population consisted of subjects with a rather severe and acute form of the disease as defined by the PANSS total score, and Clinical Global Impression-Severity Scale (CGI-S) score at Screening and baseline .

Treatments

The study drug was lurasidone 40 mg/day tablets with matching placebo.
Subjects were randomly assigned to lurasidone 40 mg/day, lurasidone 80 mg/day, or placebo in a 1:1:1 ratio. Study drug was administered orally once daily, in the evening, with a meal of at least 350 calories or within 30 minutes after eating.

Objectives

Primary objective
The primary objective of this study was to evaluate the efficacy of lurasidone (40 mg/day and 80 mg/day) compared with placebo in adolescent subjects with acute schizophrenia (diagnosed by Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision [DSM-IV-TR] criteria) as measured by the change from Baseline in the Positive and Negative Syndrome Scale (PANSS) total score at Week 6.

Secondary Objective
The key secondary objective of this study was to evaluate the efficacy of lurasidone (40 mg/day and 80 mg/day) compared with placebo as measured by the change from Baseline in the Clinical Global Impression – Severity (CGI-S) at Week 6.

Other Secondary Objectives
The secondary objectives of this study were:
•To evaluate the efficacy of lurasidone compared with placebo as measured by the change from Baseline in PANSS positive, negative, general psychopathology, and excitability subscale scores at Week 6;
•To evaluate the efficacy of lurasidone compared with placebo in changes in quality of life as measured by the change from Baseline in the Paediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q) at Week 6;
•To evaluate the efficacy of lurasidone compared with placebo in changes in global functioning as measured by the change from Baseline in the Clinician-rated Children's Global Assessment Scale (CGAS) at Week 6;
•To evaluate the safety and tolerability of lurasidone at 40 mg/day and 80 mg/day.

The Primary and secondary objectives are appropriate and in accordance with guidelines (EMA/CHMP/40072/2010 Rev 1).

Outcomes/endpoints

Primary Endpoint
The primary efficacy endpoint was the change from Baseline in the Positive and Negative Syndrome Scale (PANSS) Total Score at Week 6.
Key Secondary Endpoint
The key secondary endpoint was the change from Baseline in Clinical Global Impression Severity (CGI-S) scale at Week 6.
Other Secondary Endpoints

•Change from Baseline in PANSS positive, negative, general psychopathology, and excitability subscale scores;
•Change from Baseline in Paediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q);
•Change from Baseline in Clinician-rated Children's Global Assessment Scale (CGAS);
•Proportion of responders, where response is based on ≥ 20% improvement from Baseline in PANSS total score at Week 6;
•Proportion of remitters, defined as subjects who have score not exceeding 3 (mild severity) for items P1, P2, P3, N1, N4, N6, G5, and G9 of the PANSS at Week 6.

Safety Endpoints
Safety measurements included AE reporting, laboratory tests, vital signs, physical examination, height (as measured by stadiometer), electrocardiogram (ECG), body weight, body mass index (BMI) and waist circumference. Other safety assessments include the Cogstate Computerized Cognitive Test Battery, Barnes Akathisia Rating Scale (BARS), the Abnormal Involuntary Movement Scale (AIMS), the Simpson-Angus Scale (SAS), the Columbia Suicide Severity Rating Scale (C-SSRS), Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU), Tanner staging, menstrual cyclicity (female subjects), and hormonal parameters.

According to (EMA/CHMP/40072/2010 Rev. 1) special attention should be given to possible effects on sexual maturation, cognition, endocrine function as well as other aspects of development. The safety endpoints included in the study is acceptable.

Sample size

Dunnett's procedure was used to adjust for the multiple comparisons of two lurasidone doses versus placebo for the sample size calculation. Assuming lurasidone differs from placebo by 6.0 points (SD = 18, effect size = 0.333) and 8.5 points (SD = 18, effect size = 0.472) in the change from Baseline in PANSS total score at Week 6 for lurasidone 40 mg/day and 80 mg/day doses respectively, a sample size of 87 subjects per group would provide at least 85% power to reject at least 1 of the null hypotheses of no difference between placebo and lurasidone doses. An upward adjustment of approximately 15% was assumed in order to compensate for subjects who were randomized but did not provide any PANSS post-Baseline efficacy measures. Thus, a total sample size of approximately 309 subjects (103 subjects per group) was planned to be randomized with a ratio of 1:1:1 for placebo, lurasidone 40 mg/day, and 80 mg/day, respectively. The sample size calculation was based on the results from a Monte Carlo computer simulation.
A total of 327 subjects were randomized and 326 were included in the ITT population used for efficacy evaluations. Of the subjects in the ITT population, 108 subjects were randomized to lurasidone 40 mg/day, 106 subjects were randomized to lurasidone 80 mg/day, and 112 subjects were randomized to placebo. A total of 285 subjects in the ITT population (87% of the randomized subjects) completed the study: 96 (89%) subjects in the lurasidone 40 mg/day group; 96 (91%) subjects in the lurasidone 80 mg/day group; and 93 (82%) subjects in the placebo group.

Randomisation

Subjects who met eligibility criteria were randomly assigned to receive either lurasidone 40 mg/day, lurasidone 80 mg/day, or matching placebo in a double-blind fashion (1:1:1).
To avoid potential imbalanced treatment allocation within a specific age group, the randomization was balanced (in Protocol Amendment 1) using permuted blocks with 2 stratification criteria applied: (1) age group (13-15 years old at screening visit and 16-17 years old at screening visit) and (2) countries. Randomization and stratification process, managed by Interactive Voice/Web Response System (IXRS), were performed at Baseline (Visit 2).
At Baseline (Visit 2), the treatment code, which is linked to the randomization schedule, was assigned by the IXRS designated by the Sponsor. A unique subject number was assigned by the IXRS when a subject entered screening period. Each subject was given one subject number comprised of 9 digits. Each subject number specified the study (3 digits), site (3 digits), and subject (3 digits) (e.g., 301001001 denoted: Study 301, Site 001, and Subject 001). If a subject did not meet study entry criteria, his or her subject number could not have been reassigned to another subject. The unique subject number allocated a subject to a particular treatment group and identified the subject for data collection purposes.

Subjects may have been screened up to a maximum of three times, if judged appropriate by the Investigator. Each time the subject was rescreened they received a new subject number, which cannot be reassigned to another subject.

Blinding (masking)

The treatment arms were double-blind. Study subjects, Investigators and study staff, and the Sponsor remained blinded to the randomization scheme until the blind was formally broken for all subjects. This occurred when all subjects completed the study and the study database was locked. In the case of a medical emergency, where knowledge of study treatment by the Investigator or an authorized delegate was essential for immediate medical management, a 24-hour code-break service was available via the IXRS. The breaking of the blind was to result in the withdrawal of the subject and the subject was to return for a final study assessment.
The treatment assignments for all subjects were provided to the Bioanalytical CRO to facilitate serum PK sample handling and analysis. Only samples collected from subjects treated with lurasidone were analysed for lurasidone concentrations.

Statistical methods

The treatment effects of "lurasidone 80 mg/day vs placebo" and "lurasidone 40 mg/day vs placebo" on the primary endpoint "change from Baseline in the Positive and Negative Syndrome Scale (PANSS) Total Score at Week 6" and the key secondary endpoint "change from Baseline in Clinical Global Impression Severity (CGI-S) scale at Week 6" were evaluated in the primary intention-to-treat analysis set. Supportive analysis was performed in the per-protocol analysis set.

The statistical analysis model to test the treatment effects used a Mixed Model for Repeated Measures (MMRM) including fixed-effects terms for treatment, visit (as a categorical variable), pooled country, age group, PANSS total score at Baseline, and treatment-by-visit interaction and an unstructured covariance matrix. The treatment differences (each lurasidone group minus placebo) were estimated as Least-Squares means (LS means) with their 2-sided 95% CIs, and the associated p-values.

Multiple tests comparing treatment effects (80mg/d vs placebo, 40mg/d vs placebo) on multiple endpoints (primary, key secondary) were performed to assess statistical significance. The truncated Hochberg-based gatekeeping procedure described in Procedure 3B by Dmitrienko et. al. was applied to control the study-wise Type 1 error rate at 5% (two-sided) for the hypotheses in Families 1 and 2. The hypotheses associated with the primary and key secondary variables for efficacy claim are grouped into 2 hierarchical families:

- Family 1 (F1): lurasidone 40 mg versus placebo (H1) and lurasidone 80 mg versus placebo (H2) based on change from baseline in the PANSS total score at Week 6 (Endpoint 1)
- Family 2 (F2): lurasidone 40 mg versus placebo (H3) and lurasidone 80 mg versus placebo (H4) based on change from baseline in CGI-S at Week 6 (Endpoint 2)

The (simplified) procedure is as follows: Let $p(1) < p(2)$ denote the ordered p-values in Family 1 and let H(1) and H(2) denote the associated null hypotheses. Let $p(3) < p(4)$ denote the ordered p-values in Family 2 and let H(3) and H(4) denote the associated null hypotheses. In Step 1, the null hypotheses in Family 1 are tested using the truncated Hochberg procedure at the full α level. In Step 2, logically corresponding null hypotheses in Family 2 are tested transferring the alpha based on significant tests in Step 1. In Step 3, if only one null hypothesis is rejected in Family 1 and only one null hypothesis is rejected in Family 2, the remaining null hypothesis in Family 1 is re-tested at the full α level. If this null hypothesis is rejected, the associated null hypothesis in Family 2 is tested at the full α level.

Missing data was adjusted for using maximum-likelihood-based Mixed-Model for Repeated Measures under the Missing-At-Random (MAR) assumption. Additional sensitivity analysis was performed using a pattern mixture model using a placebo-based multiple imputation under a conservative Missing-Not-At-Random (MNAR) assumption. In addition, a random effects pattern mixture model and an analysis of covariance based on a last-observation-carried forward imputation were performed.

Secondary endpoints included Positive, Negative, General Psychopathology, and Excitability Subscale Scores (PANSS), Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q), Clinician-Rated Children's Global Assessment Scale (CGAS), Responder (20% reduction) Rate, and Remitter Rate.

Subgroups included gender (male or female), race group (white, black, asian, and other), age group (13-15, 16-17 years old), ethnicity (hispanic, non-hispanic), country : US, non-US, baseline BMI (kg/m2): <25th percentile, 25th to 85th percentile, >85th percentile).

An interim analysis was performed for the final determination of sample size per blinded sample size re-estimation (BSSR) at 90% enrolment based on blinded estimation of variance.

The *primary analysis set* for the efficacy analysis was the Intent-to-Treat (ITT) population. The ITT population included all randomized subjects who receive at least one dose of study drug and had at least one post-Baseline assessment in any efficacy variable. The Per Protocol (PP) analysis set included all ITT subjects who had no major protocol deviations that may have an impact on the efficacy analysis. Subjects in the PP population were summarized with the treatment group to which they were randomized. The safety population included all randomized subjects who receive at least one dose of study drug and were used for all safety data analyses. Subjects were analyzed based on the predominant treatment received, in the event that a subject received a treatment other than the one to which he/she was randomized.

A summary of the efficacy analyses in Study D1050301 is shown in Table 8.

Table 8

Table 1: Efficacy Assessments in Placebo-Controlled Study D1050301

Efficacy Endpoints	Method, Study Population, and Handling of Missing Data
Primary	
PANSS total score change from Baseline to Week 6	MMRM, ITT, Observed ANCOVA, ITT, LOCF MMRM, PP, Observed PMM, ITT
Key Secondary	
CGI-S score change from Baseline to Week 6	MMRM, ITT, Observed ANCOVA, ITT, LOCF MMRM, PP, Observed PMM, ITT
Other Secondary	
PANSS subscale scores (positive, negative, general psychopathology, and excitability) change from Baseline to Week 6	MMRM, ITT, Observed ANCOVA, ITT, LOCF
PQ-LES-Q % maximum possible score change from Baseline to Week 6	ANCOVA, ITT, LOCF
CGAS score change from Baseline to Week 6	ANCOVA, ITT, LOCF
Proportion of responders (≥ 20% improvement in PANSS total score from Baseline to Week 6)	Logistic regression, ITT, LOCF
Proportion of remitters (score not exceeding 3 [mild severity] for items P1, P2, P3, N1, N4, N6, G5, and G9 of the PANSS at Week 6)	Logistic regression, ITT, LOCF

Abbreviations: ANCOVA = analysis of covariance; CGAS = Clinician-rated Children's Global Assessment Scale; CGI-S = Clinical Global Impression – Severity Scale; ITT = Intent-to-Treat; LOCF = last observation carried forward; MMRM = mixed model repeated measures; PANSS = Positive and Negative Syndrome Scale; PMM = Pattern Mixture Model; PP = Per Protocol; PQ-LES-Q = Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire.
Sources: Protocol D1050301, Statistical Analysis Plan D1050301

In *summary* the statistical methodology for the main study is generally considered acceptable.

Sample size estimation, randomisation, and blinding procedure are adequate.

The treatment effects on the *primary endpoint* (PANSS) was analysed using a Mixed Model for Repeated Measures (MMRM) in the Intention-To-Treat (ITT) population. The *key secondary endpoint* (CGI-S) was analysed correspondingly. This is supported.

The definition of *primary analysis set* based on the ITT population with at least one dose and one post-baseline value in any efficacy measure deviates from a strict definition including all randomized patients. However, since the deviation of the ITT sample (N=326) from the all-randomized sample (N=327) is minimal, this issue will not be pursued further.

Regarding *missing data*, the primary analysis model is unbiased under the Missing-At-Random (MAR) assumption. Additional sensitivity analyses, eg a pattern mixture model (PMM) with placebo-based imputation under a Missing-Not-At-Random (MNAR) assumption, and others were applied. The PMM with placebo-based imputation is considered a conservative approach. The sensitivity analyses supported the results of the primary analysis. Therefore, the handling of missing data seems adequate.

The *Multiple Testing Procedure (MTP)* used a truncated Hochberg-based gatekeeping procedure with two test families controlling the global type 1 error at a two-sided alpha level of 5%. There was no adjustment for multiplicity for other secondary efficacy analyses or safety analyses. This is acceptable.

An *interim analysis* was performed for the final determination of sample size per blinded sample size re-estimation (BSSR) at 90% enrolment based on blinded estimation of variance. No other interim analysis was conducted. This is acceptable.

Subgroups were pre-specified and analysed accordingly in general. However, subgroups regarding age (13-14 years vs 15-17 years) used for presentation of results do not correspond to age groups (13-15 years, 16-17 years) used for stratification, which impairs interpretation of treatment effects in subgroups, for example, because of unreported specific baseline data (see question in "Results" section below). No adjustment for multiplicity was performed. This is acceptable.

The *Statistical Analysis Plan* (SAP, Version 2.0) was finalized on 2016-02-04. The exact date of the database lock and unblinding was not mentioned in the Clinical Study Report (CSP). The company states that the SAP was finalized prior to database lock for unblinding and that there were no changes in the planned analysis according to final protocol and SAP. The applicant was requested to provide the date of database lock which was resolved.

Results

Recruitment and Numbers analysed

Of 380 subjects screened, 327 (86.1%) were randomized to receive study treatment. In total, 53 (13.9%) subjects were screen failures, including: 40 (10.5%) subjects who failed to meet inclusion criteria; 10 (2.6%) subjects who withdrew their consent; 2 (0.5%) subjects who were withdrawn by the Investigator prior to initiation of study treatment; and 1 (0.3%) subject who was lost to follow-up Seventeen (5.2%) subjects discontinued the study due to an AE, with the highest proportion of subjects in the placebo group (8.0%) and the lowest proportion in the lurasidone 80 mg/day group (2.8%). Seven (2.1%) subjects withdrew due to lack of efficacy, with the highest proportion of subjects in the placebo group (3.5%) and 1.4% for the two lurasidone groups combined. One (0.3%) subject, receiving placebo, discontinued because of a protocol violation. A total of 14 (4.3%) subjects, 4 (3.5%) in the placebo group and 10 (4.7%) in the combined lurasidone group withdrew their consent to participate in the study.

Two hundred eighty-five (87.2%) subjects in the ITT population completed the 6-week double-blind treatment phase of the study, 96 (89%) subjects in the lurasidone 40 mg/day group; 96 (91%) subjects in the lurasidone 80 mg/day group; and 93 (82%) subjects in the placebo group.

Table 9

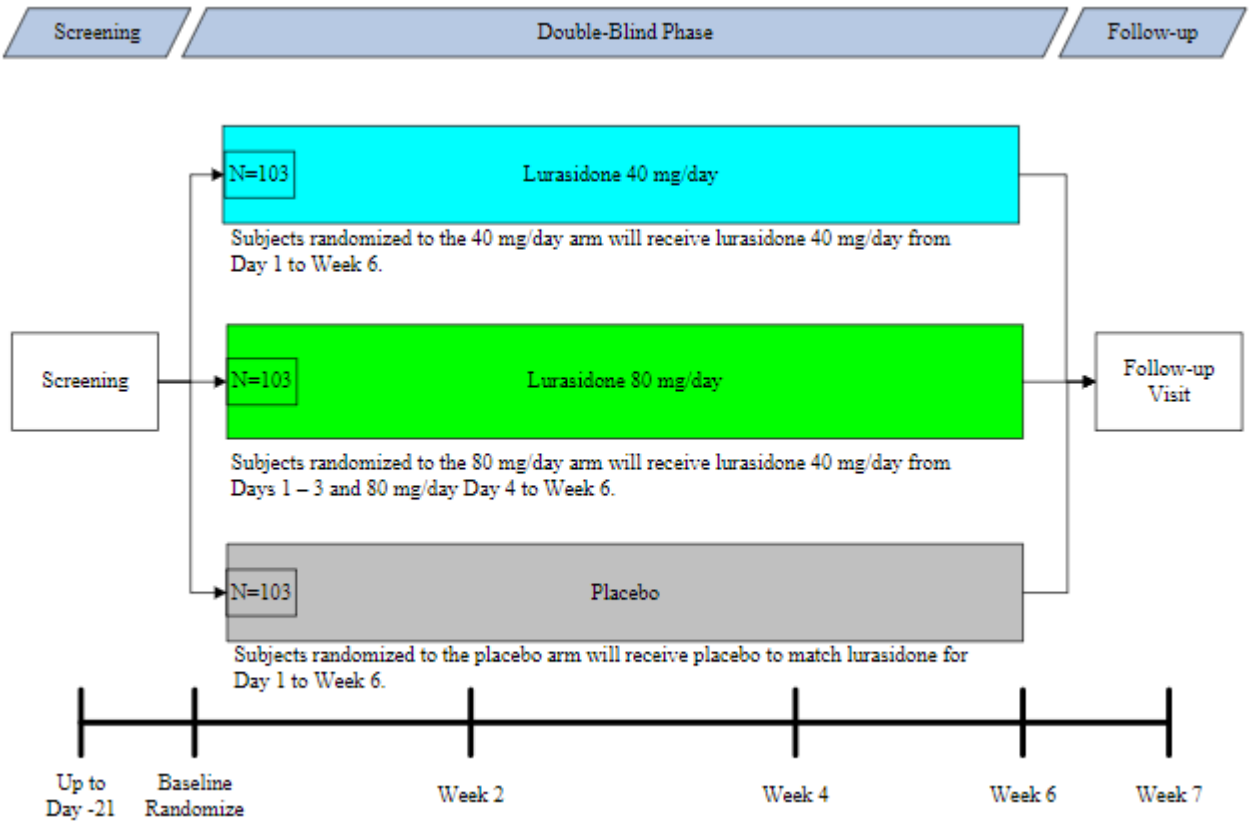
		Lurasidone		
Disposition	**Placebo (N=113) n (%)**	**40 mg/day (N=108) n (%)**	**80 mg/day (N=106) n (%)**	**All (N=214) n (%)**
Number of Subjects Completed	93 (82.3)	96 (88.9)	96 (90.6)	192 (89.7)
Number of Subjects Discontinued	20 (17.7)	12 (11.1)	10 (9.4)	22 (10.3)
Lack of Efficacy	4 (3.5)	1 (0.9)	2 (1.9)	3 (1.4)
Adverse Event	9 (8.0)	5 (4.6)	3 (2.8)	8 (3.7)
Lost to Follow-Up	1 (0.9)	0	0	0
Protocol Violation	1 (0.9)	0	0	0

Disposition	Placebo (N=113) n (%)	Lurasidone		
		40 mg/day (N=108) n (%)	80 mg/day (N=106) n (%)	All (N=214) n (%)
Withdrawal of Consent	4 (3.5)	5 (4.6)	5 (4.7)	10 (4.7)
Other	1 (0.9)	1 (0.9)	0	1 (0.5)

Compliance
All subjects and caregivers were to be reminded at each study visit of the importance of strict compliance with taking study drug as directed, with food. Compliance with study drug was to be monitored closely at each visit. Subjects were instructed to bring all unused study drug with them to each visit. Subjects missing more than 25% (ie, 2 or more doses per week) or taking more than 125% (ie, 9 doses per week) of scheduled doses between visits was to be immediately reported to and discussed with the Medical Monitor.

Conduct of the study

Figure 6 Study set up



Of the 327 randomized subjects, 49 (15.0%) had protocol deviations, with the most common deviations being not having ≥ 14 days of continuous exposure to study drug (5.5%), violation of inclusion/exclusion criteria (5.2%), and noncompliance with administration of study drug (4.9%).

Baseline data

Demographic information is provided in Table 14.1.2.1 (ITT population), Table 14.1.2.2 (PP population), Table 14.1.2.3 (Safety population), Table 14.1.2.4 (by age group; ITT population), Table 14.1.2.5 (US vs. Rest of World; ITT population), and Table 14.1.2.6 (by region; US vs. non-US).

Approximately 2/3 of the study population were male (63.8%) and approximately 1/3 were female (36.2%). The mean age was 15.4 ± 1.35 years. Approximately 2/3 were White (67.5%) and 86.5% were non-Hispanic/Latino. Approximately 2/3 were from countries outside the United States (66.3%), with more than half (53.7%) from Europe (Table 19).

The mean PANSS total score at Baseline was 94.0 ± 11.12 for the lurasidone 80 mg/day group, 94.5 ± 10.97 for the lurasidone 40 mg/day group, and 92.8 ± 11.08 for the placebo group.

Table 10

Parameter	Statistic	Placebo (N = 112)	Lurasidone 40 mg (N = 108)	Lurasidone 80 mg (N = 106)
Gender				
Male	n (%)	71 (63)	67 (62)	70 (66)
Female	n (%)	41 (37)	41 (38)	36 (34)
Age (years)	Mean (SD)	15.3 (1.4)	15.5 (1.3)	15.3 (1.4)
	Median	16.0	16.0	15.0
	Min, Max	13, 17	13, 17	13, 17
13-15 years	n (%)	55 (49)	50 (46)	55 (52)
16-17 years	n (%)	57 (51)	58 (54)	51 (48)
Race				
White	n (%)	74 (66)	72 (67)	74 (70)
Black or African American	n (%)	22 (20)	19 (18)	19 (18)
Asian	n (%)	5 (5)	6 (6)	4 (4)
Other	n (%)	11 (10)	11 (10)	9 (9)
Ethnicity				
Hispanic or Latino	n (%)	13 (12)	12 (11)	19 (18)
Not Hispanic or Latino	n (%)	99 (88)	96 (89)	87 (82)
Country				
US	n (%)	37 (33)	36 (33)	37 (35)
Non-US	n (%)	75 (67)	72 (67)	69 (65)
Geographic Region[a]				
North America	n (%)	37 (33)	36 (33)	37 (35)
South America	n (%)	9 (8)	9 (8)	8 (8)
Europe	n (%)	61 (55)	57 (53)	57 (54)
Asia	n (%)	5 (5)	6 (6)	4 (4)

Abbreviations: ITT–Intent-to-Treat, Max–maximum, Min–minimum, SD–standard deviation, US–United States
[a] North American countries include the United States and Puerto Rico. South American countries include Mexico and Colombia. European countries include Ukraine, Russia, Bulgaria, Romania, Poland, Spain, France, and Hungary. Asian countries include the Philippines, South Korea, and Malaysia.
Source: Study D1050301 Table 14.1.2.1.

Age group was defined as: "13 to 15 years", and "16 to 17 years" at the screening visit, also efficacy and safety data is provided by age group from 13 to 15 years of age. However, it would have been appropriate to stratify data for the age group 13-14, since this age group is of interest from an efficacy point of view. The applicant has also presented efficacy data in the forest plot stratified in the age groups 13-14 and 15-17 rather than 13-15 and 16-17. As it was difficult to assess efficacy for the age group 13-14, the applicant presented baseline efficacy and safety data for the age groups "13-14 years" and "15-17 years", with numbers and demographics.

Outcomes and estimation

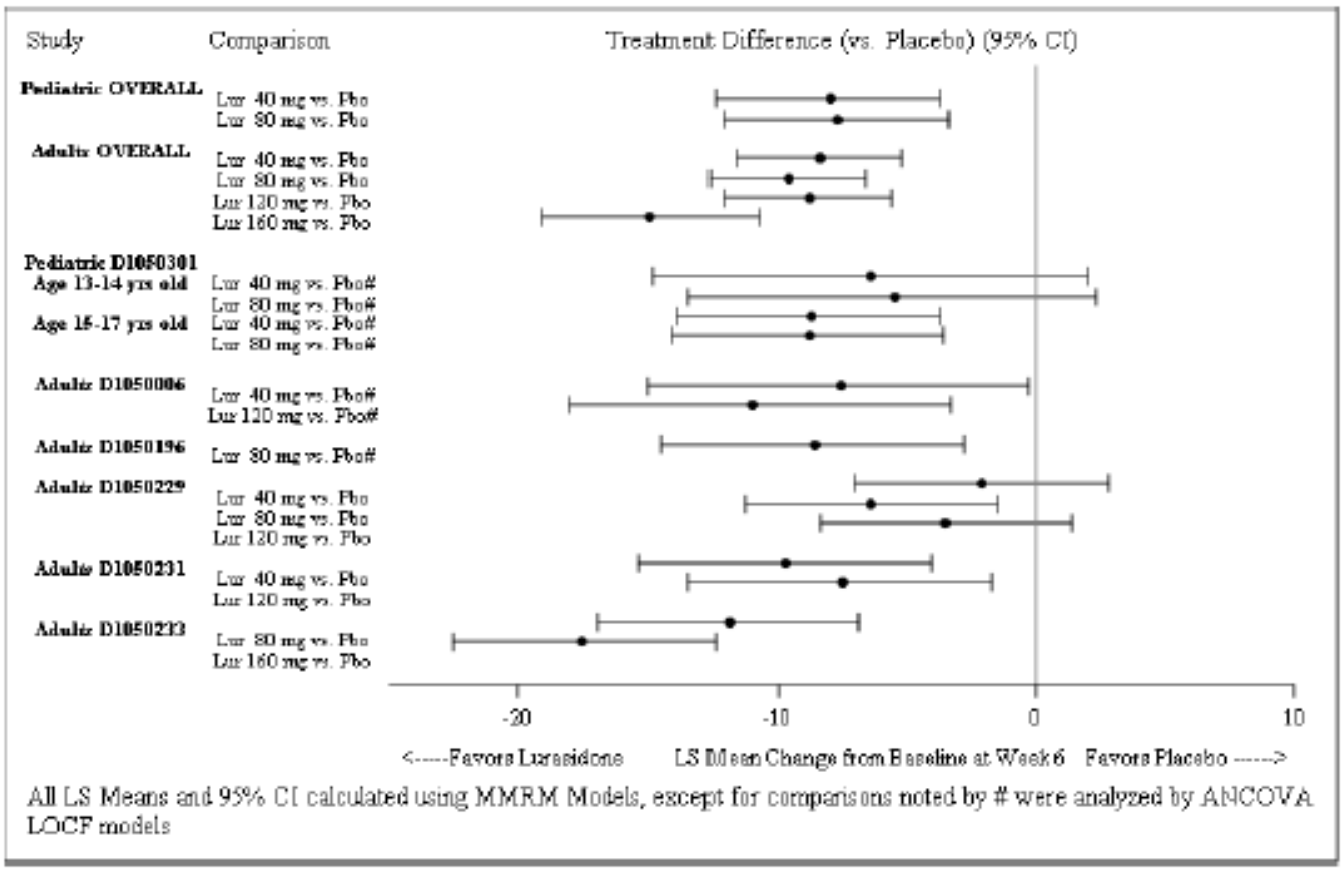
Based on MMRM analysis for the primary efficacy endpoint (PANSS total score), the LS mean change (± SE) from Baseline to Week 6 was -18.3 ± 1.60 for the lurasidone 80 mg/day group, -18.6 ± 1.59 for the lurasidone 40 mg/day group, and -10.5 ± 1.59 for the placebo group. The placebo-adjusted LS mean changes (± SE) from Baseline to Week 6 in PANSS total score for both the lurasidone 80 mg/day (-7.7 ± 2.22) and 40 mg/day (-8.0 ± 2.21) groups were significantly different from placebo (80 mg/day: adjusted p = 0.0008; 40 mg/day: adjusted p = 0.0006).

In the supportive analysis of the primary efficacy endpoint using the ANCOVA model at Week 6 with LOCF, there were significant differences from placebo for both the lurasidone 80 mg/day (-7.8 ± 2.19, p = 0.0004) and 40 mg/day (-8.2 ± 2.18, p = 0.0002) treatment groups.

The LS mean change (±SE) from Baseline to Week 6 in the CGI-S score, based on the MMRM model, was -0.92 ± 0.093, -0.97 ± 0.093, and -0.50 ± 0.094 for the lurasidone 80 mg/day, 40 mg/day, and placebo groups, respectively. The placebo-adjusted LS mean changes were -0.42 ± 0.130 for the lurasidone 80 mg/day group and -0.47 ± 0.130 for the 40 mg/day group. The improvement in the CGI-S scores at Week 6 were significantly different from placebo for both the lurasidone 80 mg/day (-0.42 ± 0.130, adjusted p = 0.0015) and lurasidone 40 mg/day (-0.47 ± 0.130, adjusted p = 0.0008) treatment groups.

In the supportive analysis of the key secondary efficacy endpoint using the ANCOVA model at Week 6 with LOCF, there was a statistically significant treatment difference from placebo for both the 80 mg/day (−0.42, p = 0.0009) and 40 mg/day (−0.45, p = 0.0003) groups, respectively). These results demonstrate that lurasidone, at doses of 40 mg/day and 80 mg/day, showed statistically significant and clinically meaningful efficacy in treating symptoms of schizophrenia in adolescent subjects.

Table 11



The mean PANSS total score at Baseline was 94.0 ± 11.12 for the lurasidone 80 mg/day group, 94.5 ± 10.97 for the lurasidone 40 mg/day group, and 92.8 ± 11.08 for the placebo group.

Based on MMRM analysis for the primary efficacy endpoint (PANSS total score), the LS mean change (± SE) from Baseline to Week 6 was -18.3 ± 1.60 for the lurasidone 80 mg/day group, -18.6 ± 1.59 for the lurasidone 40 mg/day group, and -10.5 ± 1.59 for the placebo group.

The placebo-adjusted LS mean changes (± SE) from Baseline to Week 6 in PANSS total score for both the lurasidone 80 mg/day (-7.7 ± 2.22) and 40 mg/day (-8.0 ± 2.21) groups were significantly different from placebo (80 mg/day: adjusted p = 0.0008; 40 mg/day: adjusted p = 0.0006).

However, there are noticeable differences in the endpoint in group "Age 13-14 years old" with subgroups "40 mg vs Pbo" and 80mg vs Pbo" in comparison to the respective "Age 15-17 years old" subgroups. Although the confidence intervals in these subgroups are not nominally statistically significant different from a null effect at the 5% level and there is non-ignorable evidence supporting lower efficacy in "Age 13-14 years old", the pooled results in "Pediatric OVERALL" with subgroups "40 mg vs Pbo" and 80mg vs Pbo" seem of similar efficacy and nominally statistically significant.

Therefore, the applicant was requested to discuss and support with additional data analysis the following issues during the assessment:

- The clinical relevance of the difference in effect between the "Age 13-14 years old" group and the "Age 15-17 years old" (to justify the pooling of the groups)
- The clinical relevance of the difference in effect between the "Age 13-14 years old" group and a null effect (to justify the application of the drug in this group).

Furthermore, the applicant provided further elements to discuss if there is a biological rationale to expect a different treatment effect in this age group or if data in children older than 14 years can be extrapolated to children 13-14 old.

The company presented a scientific discussion with further elements on treatment-subgroup and literature review that taken together supports a view that there is continuity between childhood, adolescent, and adult schizophrenia; and that they may be treated with similar agents, although the difficulties to diagnose younger patients was acknowledged. In children, lurasidone should be prescribed by an expert in paediatric psychiatry. This was adequately reflected in the labelling.

In addition, baseline data for the age group 13-14 years in study D1050301 were presented.

The applicant was asked to also present the same age stratification for the CGI-S (as a secondary endpoint) and this was satisfactorily resolved.

Table 12

Table 12: PANSS Responder Analysis at Week 6 (Observed, LOCF) for ITT Population in Study D1050301

Responder Criteria at Week 6	Placebo (N = 112)	Lurasidone	
		40 mg/day (N = 108)	80 mg/day (N = 106)
Week 6 (Observed)			
n[a]	93	96	97
≥ 20% Reduction, n (%) [b]	46 (49.5)	65 (67.7)	69 (71.1)
NNT (95% CI)		6 (3, 23)	5 (2, 13)
Effect Size (vs. Placebo) [c]		0.42	0.51
Odds Ratio (vs. Placebo) [d]		2.281 (1.246, 4.176)	2.616 (1.419, 4.823)
p-value [d]		0.0075**	0.0021**
Week 6 (LOCF)			
n[a]	112	108	106
≥ 20% Reduction, n (%) [b]	47 (42.0)	69 (63.9)	69 (65.1)
NNT (95% CI)		5 (2, 12)	5 (2, 10)
Effect Size (vs. Placebo) [c]		0.49	0.52
Odds Ratio (vs. Placebo) [d]		2.581 (1.486, 4.484)	2.636 (1.512, 4.594)
p-value [d]		0.0008**	0.0006**

Abbreviations: CI=confidence interval, ITT=Intent-to-Treat, LOCF=Last Observation Carried Forward, NNT=number needed to treat, PANSS=Positive and Negative Syndrome Scale, US=United States.

** $p \leq 0.01$ vs placebo.

[a] Includes only those subjects who had both Baseline and post-Baseline PANSS total score at that post-Baseline visit.

[b] Percentage is calculated with the number of subjects in each treatment group as denominator.

[c] Effect size (vs placebo) is calculated as log(odds ratio)*sqrt(3)/pi, where odds ratio is based on 2 by 2 contingency table.

[d] Odds ratio (vs placebo), CIs, and the associated p-values are based on the logistic regression model with treatment, age strata, pooled country (US vs. non-US), and Baseline PANSS total scores.

Source: Study D1050301 Table 14.2.1.8.1

The PANSS Responder Analysis at Week 6 demonstrate statistically significant treatment effects of lurasidone 40 and 80 mg/day. Responders were also separately presented for the age group 13-14 years old.

Long-term, Open-Label Study (D1050302)

Methods

The study was an open-label (OL), 104-week, multicentre, extension study designed to evaluate the long-term safety, tolerability, and effectiveness of flexibly dosed lurasidone (20, 40, 60, or 80 mg/day) in paediatric subjects who completed a 6-week treatment period in one of three preceding studies of various indications: Study D1050301 (schizophrenia), Study D1050325 (irritability associated with autistic disorder), or Study D1050326 (bipolar depression). Subjects who met entry criteria were transitioned to this extension study directly after their last assessment in the preceding study.

The study included an OL baseline assessment (for which some evaluations were based on data from the last visit in the preceding study), a 104-week treatment period, and a follow-up visit (that occurred one week after the last dose of lurasidone). Safety and effectiveness assessments were conducted at scheduled visits during the study.

As this application is being submitted to support an indication for adolescent subjects with schizophrenia, only results for subjects with schizophrenia who enrolled from Study D1050301 are discussed.

According to guideline (EMA/CHMP/40072/2010 Rev 1), long term safety data (2 years) should be generated in a paediatric population. Thus, the duration of D1050302 is considered to be appropriate.

However, it is questioned if the results from the open label study D1050302 are robust enough demonstrate a maintenance of effect due to the lack of a comparator. It should be noted that maintenance of effect in the adult studies with lurasidone was established with a randomized withdrawal study. Importantly, according to the EMA schizophrenia guideline, extrapolation from adult data is possible to subjects aged > 15 years (see EMA schizophrenia guideline: EMA/CHMP/40072/2010 Rev. 1). Therefore, the MAH was requested to further substantiate maintenance of efficacy in adolescents and evaluate whether extrapolation from the adult data is possible, in particular for the subgroup 13- < 15 years in light of the EMA guideline. The CHMP reviewed the evidence provided and the issue was considered resolved.

Study participants

The study enrolled a total of 271 subjects who completed the 6-week treatment period in Study D1050301 and, as judged by the investigator, for whom an outpatient setting was appropriate. Of these, 186 subjects (68.6%) completed through 52 weeks and 156 (57.6%) subjects completed 104 weeks of flexible dosing with lurasidone 20 to 80 mg/day.

One analysis population was utilized for the extension study, ie, the Safety Population, which consisted of all subjects who received at least 1 dose of study drug.

Treatments

Flexibly dosed lurasidone (20, 40, 60, or 80 mg/day).

Objectives

Primary: The primary objective of this study was to evaluate the long-term safety, tolerability, and effectiveness of lurasidone (20, 40, 60, or 80 mg/day, flexibly dosed) in paediatric subjects who had completed a prior lurasidone study.

Secondary: The secondary objectives were:

- Proportions of subjects with adverse events (AEs), discontinuations due to AEs, and serious AEs (SAEs)
- Change in Positive and Negative Syndrome Scale (PANSS) total, positive, negative, general psychopathology, and excitability subscale scores
- Change in the Clinical Global Impression – Severity (CGI-S)
- Change in the Clinician-rated Children's Global Assessment Scale (CGAS)
- Change in the Paediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)

Outcomes/endpoints

As in Study D1050301, PANSS total score was the primary effectiveness measure, while the PANSS positive, negative, general psychopathology and excitability subscale scores were secondary effectiveness measures. The CGI-S, the Paediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q), and the Children's Global Assessment Scale (CGAS) were also evaluated as other measures of effectiveness.

Sample size

This current report presents the results of safety and effectiveness analyses using only the subset of subjects (N = 271) who continued from Study D1050301. One analysis population was utilized for the extension study, ie, the Safety Population, which consisted of all subjects who received at least 1 dose of study drug.

Statistical methods

No inferential statistics on effectiveness were performed.
Subjects who continued from Study D1050301 are summarized by analysis subgroup as follows:

- PBO-LUR: previously randomized to placebo
- LUR40-LUR: previously randomized to lurasidone 40 mg/day
- LUR80-LUR: previously randomized to lurasidone 80 mg/day
- All LUR-LUR: previously randomized to lurasidone (40 or 80 mg/day)
- 301-LUR: all subjects with schizophrenia who continued from Study D1050301

Descriptive summary statistics (N, mean, standard deviation, median, range, and a 95% confidence interval) are presented by analysis subgroup at DB baseline, OL baseline, each of post-OL visit, Week 52 LOCF, and Endpoint in the open-label study. All analyses for the scheduled assessments are on observed cases (OC). For all effectiveness evaluations, changes from DB baseline and OL baseline is presented using summary statistics.

In addition, at each visit in the extension study, PANSS responders relative to Baseline (either DB or OL) were defined as those who had a 20% or more reduction (ie, improvement) from Baseline. Frequencies and percentages of PANSS responders relative to both DB Baseline and OL Baseline over time are reported by analysis subgroup, respectively.
Effectiveness results are presented for the 301-LUR population.

The statistical methods are acceptable in principle. However, to mitigate potential biases in the data due to missingness, advanced imputation of the primary endpoint was requested. In addition, to support the conclusions, inferential statistical methods, i.e. statistical tests, were performed.

Results

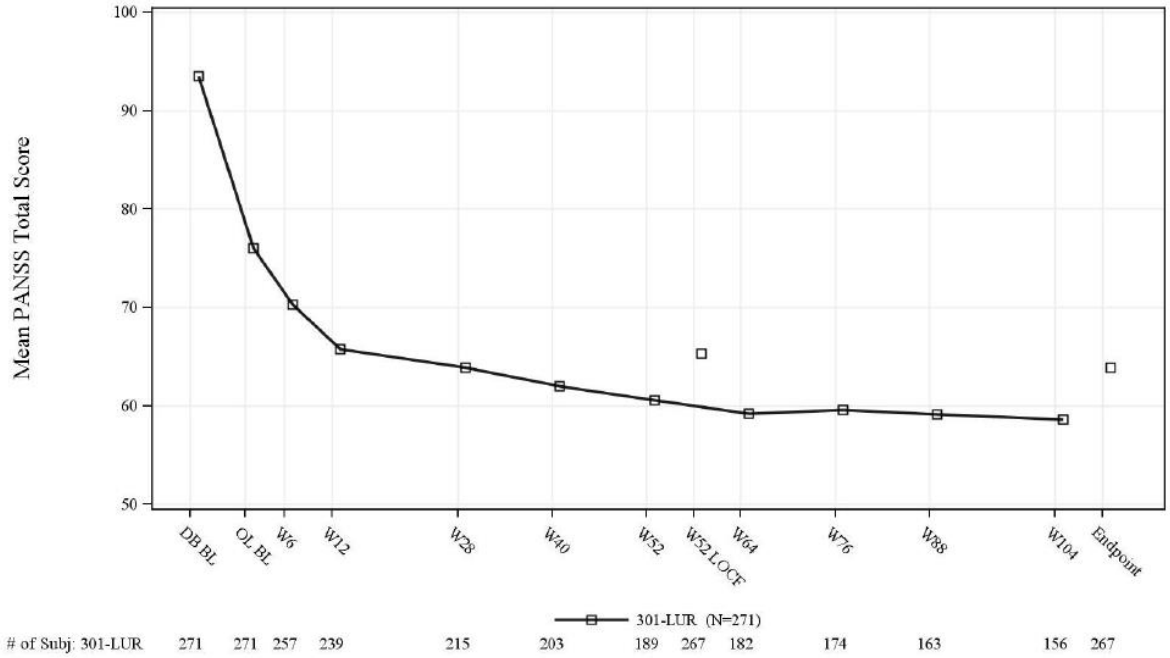
Numbers analysed

271 included in the study and 156 completed study (57,6%)

Outcomes and estimation

The duration of effect after treatment with lurasidone was demonstrated in this extension study by continued improvement of schizophrenia outcome measures. Decreases in mean PANSS total score were observed over time in the 301-LUR population

Figure 7 Mean Observed Values over Time in PANSS Total Score for Subjects Continued from Study D1050301 – Overall 301-LUR Group (Safety Population)



Abbreviations: BL = Baseline; DB = double-blind; LOCF = last observation carried forward; OL = open-label; PANSS = Positive and Negative Syndrome Scale; W = week; 301-LUR = all subjects continued from Study D1050301.
Note: Higher values of PANSS total score represent greater severity of illness. The number of subjects at each visit represents the number of subjects with a non-missing assessment. Week 52 LOCF was defined as the assessment at Week 52 visit or the last post-OL Baseline assessment before the Week 52 visit if the value at the Week 52 visit was missing. Endpoint was defined as the last post-OL Baseline assessment during the OL treatment period.

At OL Baseline, the mean (± SD) PANSS total score was 76.0 ± 17.72 for the 301-LUR group. The mean (± SD) change in PANSS total score from DB Baseline in the overall 301-LUR group was -29.2 ± 14.73 at Week 28 and increased to -32.4 ± 14.61 at Week 52 and -34.3 ± 16.32 at Week 104. Mean change from DB Baseline to Endpoint was -29.5 ± 18.48. Mean change relative to OL Baseline in the overall 301-LUR group was -11.9 ± 13.74 at Week 28, -15.6 ± 14.97 at Week 52, -18.4 ± 16.73 at Week 104, and -12.2 ± 19.54 at Endpoint.

There was an increase in the overall proportion of responders with long-term treatment. At OL baseline, 63.1% of subjects were responders relative to DB Baseline. At Week 52, 92.1% of subjects were considered responders relative to DB Baseline and 68.8% relative to OL Baseline. At Week 104, 91.0% and 76.9% of subjects were considered responders relative to DB Baseline and OL Baseline, respectively. At Endpoint, the proportions of responders were 82.8% relative to DB Baseline and 58.1% relative to OL Baseline.

A trend toward decreases in mean (± SD) CGI-S scores from DB Baseline was observed over time. At OL Baseline the mean (± SD) CGI-S score for the 301-LUR group was 4.0 ± 0.97. The overall 301-LUR group demonstrated a reduction of -1.87 ± 1.084 at Week 52 and -2.04 ± 1.121 at Week 104. Mean change from DB Baseline to Endpoint was -1.67 ± 1.194.

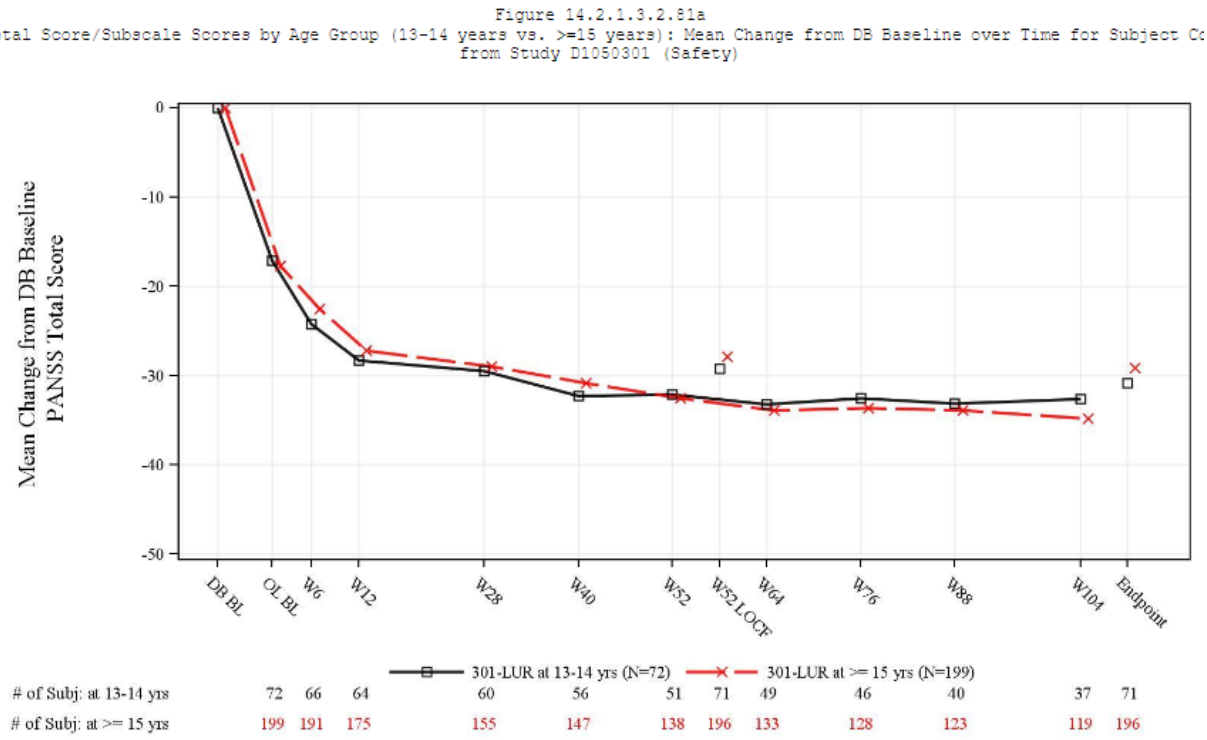
An increasing trend in mean (± SD) PQ-LES-Q scores from DB Baseline was observed over time. At OL Baseline, the mean (± SD) PQ-LES-Q score for the 301-LUR group was 57.14 ± 14.850. The overall 301-LUR group demonstrated a mean increase of 15.67 ± 17.419 at Week 52 and 17.09 ± 19.950 at Week 104. Mean change from DB Baseline to Endpoint was 12.47 ± 20.596.

Similarly, an increasing trend in mean (± SD) CGAS scores from DB Baseline was observed over

time. At OL Baseline, the mean (± SD) CGAS score for the 301-LUR group was 55.0 ± 11.96. The overall 301-LUR group demonstrated an increase of 24.37 ± 12.600 at Week 52 and 27.62 ± 14.168 at Week 104. Mean change from DB Baseline to Endpoint was 22.15 ± 15.783.

PANSS total score by age group

Figure 8



The observed effect in the 13-14 years age group appeared to be more modest compared to ≥ 15 year in study D1050301 was further discussed by the applicant**.** In study D1050302 maintenance of effect was observed in both age groups.

The efficacy analysis is based on the primary endpoint "Mean Observed Values over Time in PANSS Total Score" for subjects continued from study D1050301 in the safety analysis set using observed values. The sample size decreased from 271 (100%) at baseline to 156 (58%) at week 104 due to missingness. It seems that LOCF imputation was only used for the "W52 LOCF" and the "Endpoint". "W52 LOCF" and "Endpoint" show considerable deviation from the overall trajectory of the PANSS Total Score and indicate that the presented trajectory is biased. Therefore, the company was asked to perform analysis using LOCF imputation for all time points for the PANSS Total Score to reduce the impact of missingness on the (visual) presentation of the trajectory. LOCF imputation, however, is only acceptable under specific restrictive assumptions (cf EMA Guideline EMA/CPMP/EWP/1776/99 Rev. 1), which do not seem plausible here. For example, the increase of responders over time may indicate systematic drop-out of non-responders. Although the high degree of missingness (up to 42%), lack of information about the underlying missing data process, and the lack of a comparison group, will make it difficult to fully resolve this issue, the company satisfactorily provided results based on advanced imputation data under the Missing-At-Random (MAR) assumption, for example, using multiple imputation, to mitigate expected biases at all visits. Finally, all estimates were reported or visualized with measures of uncertainty, ie 95% confidence intervals (as appropriate).

Summary of main study(ies)

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

Table 13 Summary of Efficacy for trial

Title: Short-term, placebo-controlled study D1050301				
Study identifier	D1050301			
Design	Short-term, double-blind, placebo-controlled			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	6-weeks 3-weeks not applicable		
Hypothesis	Superiority			
Treatments groups	Placebo	112 randomized		
	Lurasidone 40 mg/day	108 randomized		
	Lurasidone 80 mg/day	106 randomized		
Endpoints and definitions	Primary endpoint	PANSS total score change from Baseline to Week 6		
	Key Secondary	CGI-S score change from Baseline to Week 6		
	Other secondary	PANSS subscale scores (positive, negative, general psychopathology, and excitability) change from Baseline to Week 6 PQ-LES-Q % maximum possible score changes from Baseline to Week 6 CGAS score change from Baseline to Week 6 Proportion of responders (≥ 20% improvement in PANSS total score from Baseline to Week 6) Proportion of remitters (score not exceeding 3 [mild severity]for items P1, P2, P3, N1, N4, N6, G5, and G9 of the PANSS at Week 6)		
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	326 was included in the Intent to treat population			
Descriptive statistics and estimate variability	Treatment group	Placebo	Lurasidone 40 mg/day	Lurasidone 80 mg/day
	Number of subjects	112	108	106

	PANSS total score change from baseline (Mixed model repeated measures, MMRM)	-10.5	-18.6	-18.3
	variability statistic ± SE	± 1.59	± 1.59	± 1.60
	CGI total, change from baseline (MMRM)	-0,50	-0.97	-0.92
	variability statistic	± 0.094	± 0.093	± 0.093

Effect estimates per comparison	Primary endpoint PANSS total score change	Comparison groups	40 mg lurasidone/placebo
		test statistic	point estimate
		P-value	0.0006
	Co-Primary PANSS total score change	Comparison groups	80 mg lurasidone/placebo
		test statistic	point estimate
		P-value	0.0008
	Key Secondary, CGI-S score change	Comparison groups	40 mg lurasidone/placebo
		test statistic	point estimate
		P-value	0.0008
	Key Secondary, CGI-S score change	Comparison groups	80 mg lurasidone/placebo
		test statistic	point estimate
		P-value	0.0015

Title: Long-term, Open-Label Study (D1050302)			
Study identifier	D1050302		
Design	Long-term, Open-Label Study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		104 weeks not applicable not applicable
Hypothesis	Maintenance of Safety and Efficacy		
Treatments groups	lurasidone		(20, 40, 60, or 80 mg/day, flexibly dosed treatment for 104 weeks, 271 included
Endpoints and definitions	Primary endpoint		Change PANSS total score at endpoint

	Secondary		Change in CGI-S at endpoint PANSS subscale scores (positive, negative, general psychopathology, and excitability) change from Baseline to Week 6 Change in the PQ-LES-Q percentage maximum possible score Change in the CGAS total score

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	271 included in the study and 156 completed study (57,6%)		
Descriptive statistics and estimate variability	Treatment group	Overall 301-LUR	
	Number of subjects	156	
	Mean change relative OL-baseline, PANSS total score change.	-18.4	
	variability statistic ±SD	±16.73	
	Secondary	Overall 301-LUR	
	Mean change relative OL-baseline, CGI-S total score change.	-2.04	
	variability statistic ±SD	±1.121	
Notes			

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study D1050301
Study D1050301 was a randomized, parallel, double-blind, placebo-controlled, fixed-dose, 6-week multicentre study. The overall study design, objectives, endpoint and conduct of the study is acceptable and according to the paediatric investigation plan.

The diagnosis and selection of eligible subjects is acceptable. The selection of participants that *had an acute exacerbation of psychotic symptoms (no longer than two months in duration) and marked deterioration of function from baseline (by history), or had been hospitalized for the treatment of an acute psychotic exacerbation, for two consecutive weeks or less, immediately before screening*,

represents patients that are more in an acute disease phase that may show a larger response to pharmacological treatment than patients that are in a more chronic phase of the disease.

The Primary and secondary objectives are appropriate and in accordance with guidelines.

Study D1050302
The study was an open-label (OL), 104-week, multicentre, extension study designed to evaluate the long-term safety, tolerability, and effectiveness of flexibly dosed lurasidone (20, 40, 60, or 80 mg/day) in paediatric subjects who completed a 6-week treatment period in one of three preceding studies of various indications: Study D1050301 (schizophrenia), Study D1050325 (irritability associated with autistic disorder), or Study D1050326 (bipolar depression). Only results for subjects with schizophrenia who enrolled from Study D1050301 are discussed and relevant in this procedure.

The, objectives, endpoint and conduct of the study is according to the paediatric investigation plan. However, see discussion below regarding the statistical analysis.

Efficacy data and additional analyses

Study D1050301
In study D1050301, 6-weeks treatment with lurasidone (40 mg and 80mg) led to decrease in the positive and negative symptoms of schizophrenia as well as general psychopathology for both dose groups. The effect is largely comparable to what is observed in the adult population.

In the subgroup analyses the results of the primary endpoint (change in PANSS total score) was somewhat less pronounced in children aged 13-14 years compared to older study subjects. The company provided further justifications to support that there is a biological rationale to expect a different treatment effect in this age group or if data in children older than 14 years can be extrapolated to children 13-14 old. In addition, baseline data and the same age stratification for the CGI-S (as a secondary endpoint), for the age group 13-14 years in study D1050301 were presented.

The MAH justified that the results in the study population is applicable to the proposed target population (schizophrenia irrespective of severity) considering that the study population consisted of subjects with a rather severe and acute form of the disease as defined by the PANSS total score, and Clinical Global Impression-Severity Scale (CGI-S) score at Screening and baseline.

No dose-response studies in the paediatric population was provided by the applicant. A dose-response study would have been valuable to establish minimum effective dose and the dose for optimal efficacy in the paediatric population. In study D1050300 it was demonstrated that the pharmacokinetic profile appears to be consistent with the profile observed in adult subjects. However, the lack of a proper dose-response study in the paediatric population needs to be further justified. Please provide a data and/or a discussion to ensure that correct start dose and posology is recommend to adolescent subjects. According to the proposed SmPC, the effective dose range in children is 37 to 74 mg once daily. However, there is a lack in the justification for not going higher in dose than 80 mg in adolescents. This should be further discussed. Furthermore, a lower dose has not been examined in the controlled lurasidone study D1050301, while a 20 mg dose was included in the flexible dose regimen in the open-label extension study D1050302. However, only about 3% of subjects in D1050302 were dosed with 20 mg. Therefore, justification/ discussion were additionally provided on the lower limit of the proposed dose range with regard to clinical efficacy and safety aspects.

Study D1050302
A flexible dose of (20, 40, 60, 80 mg/day) lurasidone maintained a clinical improvement of symptoms of schizophrenia in adolescent subjects as measured in total PANSS score in subjects with schizophrenia continued from study D1050301. Also, other disease outcomes of symptoms of schizophrenia and functionality indicated maintenance of effect. However, since the efficacy was more modest in the 13-14 years age group compared to >15 year group in study D1050301, efficacy data for primary and secondary endpoint was discussed satisfactorily by age group by the applicant also for study D1050302.

However, it was questioned if the results from the open label study D1050302 are robust enough demonstrate a maintenance of effect due to the lack of a comparator. It should be noted that maintenance of effect in the adult studies with lurasidone was established with a randomized withdrawal study. Importantly, according to the EMA schizophrenia guideline, extrapolation from adult data is possible to subjects aged > 15 years (see EMA schizophrenia guideline: EMA/CHMP/40072/2010 Rev. 1). Therefore, the MAH substantiated maintenance of efficacy in adolescents and evaluated whether extrapolation from the adult data was possible, in particular for the subgroup 13- < 15 years in light of the EMA guideline. The CHMP reviewed the evidence provided and the issue was considered as resolved.

The efficacy analysis is based on the primary endpoint "Mean Observed Values over Time in PANSS Total Score" for subjects continued from study D1050301 in the safety analysis set based on observed values. The sample size decreased from 271 (100%) at baseline to 156 (58%) at week 104. The results are expected to be unbiased under the Missing-Completely-At-Random (MCAR) assumption, which, however, does not seem plausible here, since, for example, the increase of responders over time rather indicates systematic drop-out of non-responders. In principle, the same problems apply to the interpretation of other efficacy and also safety endpoints. It was acknowledged that the high degree of missingness (up to 42%), lack of information about the underlying missing data process, and the lack of a comparison group, will make it difficult to fully resolve this issue. The company provided also further results (descriptive and inferential) based on advanced imputation data, to try and mitigate expected biases.

- Overall the studies D105301 and D1050302 provided short-term (40 and 80 mg) and long-term efficacy flexible dose of (20, 40, 60, 80 mg) data for lurasidone in adolescents 13-17 years. Primary endpoints were statistically significant superior to placebo and the efficacy data can be considered to be clinically meaningful for the treatment of adolescents with acute schizophrenia. Issues on how inclusion criteria in study D105301 reflects the indication applied for, justification of a significant and clinically meaningful effect in all age groups 13-14 years versus 15-17 years in both the short-and long-time frame as wel as justification for the definition of clinically significant response. were resolved satisfactorily.

2.4.4. Conclusions on the clinical efficacy

Based on the review of all information provided, the CHMP concluded that lurasidone has efficacy in treating schizophrenia in the study population investigated, adolescents 13-17 years.

2.5. Clinical safety

Introduction

Lurasidone is an atypical neuroleptic and some of the most important risk with lurasidone treatment includes. are listed below.

Suicidality
The occurrence of suicidal behaviour is inherent in psychotic illnesses and in some cases has been reported early after initiation or switch of antipsychotic therapy.
Extrapyramidal symptoms (EPS)
Medicinal products with dopamine receptor antagonistic properties have been associated with extrapyramidal adverse reactions including rigidity, tremors, mask-like face, dystonias, drooling of saliva, drooped posture and abnormal gait.
Tardive dyskinesia
Medicinal products with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia characterised by rhythmical involuntary movements, predominantly of the tongue and/or face.

Hyperprolactinaemia
Lurasidone elevates prolactin levels due to antagonism of dopamine D2 receptors. Patients should be counseled on signs and symptoms of elevated prolactin, such as gynecomastia, galactorrhea, amenorrhea and erectile dysfunction.
Weight gain
Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.
Neuroleptic malignant syndrome (NMS)
Neuroleptic Malignant Syndrome, characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated serum creatine phosphokinase levels, has been reported to occur with lurasidone.
Cerebrovascular accident
An approximately 3-fold increased risk of cerebrovascular adverse reactions has been seen in randomised placebo-controlled clinical trials in the dementia population with some atypical antipsychotics, including risperidone, aripiprazole and olanzapine.
Venous thromboembolism
Cases of venous thromboembolism (VTE) have been reported with antipsychotic medicinal products.
Cardiovascular disorders/QT prolongation
Caution should be exercised when lurasidone is prescribed in patients with known cardiovascular disease or family history of QT prolongation, hypokalaemia, and in concomitant use with other medicinal products thought to prolong the QT interval.
Hyperglycaemia
Rare cases of glucose related adverse reactions, e.g. increase in blood glucose, have been reported in clinical trials with lurasidone.
Orthostatic hypotension/syncope
Lurasidone may cause orthostatic hypotension, perhaps due to its α1-adrenergic receptor antagonism.

Patient exposure

A total of 271 adolescent subjects with schizophrenia were exposed to lurasidone at doses of 20 to 80 mg/day for up to 24 months across Studies D1050301 and D1050302.

Table 14

Type of Study	Protocol No. (Phase)	Study Population	Age Range (Years)	Study Duration	Treatment Groups (N)	Number of Subjects Exposed to Lurasidone
Short-term, double-blind, placebo-controlled	D1050301 (3)	Subjects with acute schizophrenia	13 – 17	6 weeks	Placebo (112) Lurasidone 40 mg (110) Lurasidone 80 mg (104)	214
Long-term, open-label extension	D1050302 (3)	Subjects who have completed the 6-week treatment period in study D1050301	13 – 18	104 weeks	Lurasidone 20 to 80 mg flexibly dosed (180)	271

A total of 214 unique subjects received at least one dose of lurasidone in the short-term double-blind study D1050301. A total of 90 unique subjects randomized to placebo in study D1050301 who continued into the long-term open-label study D1050302 received at least one dose lurasidone in the open-label study. Therefore, a total of 304 unique subject have received at least one dose of lurasidone across one completed double-blind study and one open-label extension

study in adolescent subjects with schizophrenia.

Of the 271 subjects who entered Study D1050302 from Study D1050301, 186 (68.6%) subjects completed 12 months of treatment, and 156 (57.6%) subjects completed the full 104 weeks of treatment.

From the study report for D1050301, 50+55 subjects in the lurasidone 40 and 80mg/day group were 13-15 years old and 60+49 subjects were 16-17 years old, respectively. In study D1050302 that continued from D105301, 121 subjects were 13-15 years old. The Applicant presented the number of patients included in these two studies who were in the age range of 13 to 14 years to further clarify how many patients in each treatment group were 13-14 years old.

Adverse events

In the double-blind, placebo-controlled Study D1050301 (adolescent subjects with schizophrenia)
A higher percentage of subjects treated with lurasidone completed the study (89.7% than placebo (82.3%). The most common reason for discontinuation from the study was due to AE; however, the proportion of subjects who discontinued due to an AE was lower while on lurasidone (3.7% in the "all lurasidone" group versus 8.0% in the placebo group).

Table 15

System Organ Class / Preferred Term[a]	Number (%) of Subjects			
	Placebo	Lurasidone 40 mg/day	Lurasidone 80 mg/day	All Lurasidone
	N = 112	N = 110	N = 104	N = 214
Number of Subjects with at Least One TEAE	64 (57.1)	70 (63.6)	67 (64.4)	137 (64.0)
Gastrointestinal Disorders	13 (11.6)	28 (25.5)	29 (27.9)	57 (26.6)
Nausea	3 (2.7)	14 (12.7)	15 (14.4)	29 (13.6)
Vomiting	2 (1.8)	9 (8.2)	7 (6.7)	16 (7.5)
Nervous System Disorders	25 (22.3)	34 (30.9)	36 (34.6)	70 (32.7)
Somnolence	6 (5.4)	10 (9.1)	12 (11.5)	22 (10.3)
Akathisia	2 (1.8)	10 (9.1)	9 (8.7)	19 (8.9)
Headache	14 (12.5)	7 (6.4)	11 (10.6)	18 (8.4)
Sedation	2 (1.8)	6 (5.5)	2 (1.9)	8 (3.7)
Psychiatric Disorders	31 (27.7)	29 (26.4)	19 (18.3)	48 (22.4)
Anxiety	9 (8.0)	11 (10.0)	3 (2.9)	14 (6.5)
Insomnia	10 (8.9)	6 (5.5)	7 (6.7)	13 (6.1)
Agitation	5 (4.5)	5 (4.5)	6 (5.8)	11 (5.1)
Schizophrenia	9 (8.0)	3 (2.7)	2 (1.9)	5 (2.3)

Abbreviations: TEAE=treatment-emergent adverse event
[a] Adverse events are coded using Medical Dictionary for Regulatory Activities Version 16.0.
Note: Percentage is calculated by using the number of subjects in each treatment group as denominator. Incidence is based on the number of subjects experiencing at least one TEAE, not the number of events.
System organ classes are ordered alphabetically; within a system organ class, preferred terms are ordered by descending frequency in the All Lurasidone group.

Of the 214 lurasidone-treated subjects, 137 (64.0%) reported one or more TEAEs. Of the 112 placebo-treated subjects 64 (57.1%) reported one or more TEAEs. The proportion of subjects with one or more TEAEs was similar between the two lurasidone dose groups.

The number of subjects reporting one or more study drug-related TEAEs (definite, possibly, or probably related) included 94 subjects (43.9%) in the "all lurasidone" group and 33 subjects (29.5%) in the placebo group. Amongst lurasidone-treated subjects, comparable percentages experienced treatment-related TEAEs, with 43.6% in the 40 mg group and 44.2% in the 80 mg group.

The most frequently-reported TEAEs in the "all lurasidone" group included Nervous System Disorders (32.7%), Gastrointestinal Disorders (26.6%) and Psychiatric Disorders (22.4%). For subjects receiving placebo, the most common TEAEs were in the SOC categories of Psychiatric Disorders (27.7%) and Nervous System Disorders (22.3%).

Among the TEAEs reported in at least 2% of subjects in any treatment group and the incidence for lurasidone was higher than placebo, nausea, somnolence, akathisia, vomiting, dizziness, and diarrhea occurred with notably greater frequency among subjects receiving lurasidone than those receiving placebo.

When preferred terms were combined for dystonia, parkinsonism, or somnolence: - Somnolence was the most common TEAE in subjects receiving lurasidone (occurring in 14.5% of subjects in the "all lurasidone" group, as compared to 7.1% for the placebo group. There was no trend in the frequency of somnolence with dose.
- The reported incidence of parkinsonism in the lurasidone-treated subjects was 3.6% in the 40 mg group; no subject experienced parkinsonism in the 80 mg group. -Dystonia was not among the most common TEAEs reported in lurasidone-treated subjects (ie, in ≥ 2% of subjects and with greater incidence for lurasidone compared to placebo).

The incidence of extrapyramidal symptom (EPS)-related TEAEs was higher in the lurasidone 80 mg (10.6%) and 40 mg (13.6%) treatment groups than in the placebo group (2.7%), with akathisia being the most common EPS-related TEAE and reported with an appreciably higher frequency in the combined lurasidone group (8.9%) than in the placebo group (1.8%).

The incidence of metabolic TEAEs was similar in the combined lurasidone treatment groups (2.3%) and the placebo group (2.7%). Weight gain was reported in three (2.9%) subjects receiving lurasidone 80 mg, one (0.9%) subject receiving lurasidone 40 mg, and three (2.7%) subjects receiving placebo.

The majority of TEAEs were mild-to-moderate in severity, with six subjects each in the lurasidone 40 mg (5.5%) and placebo (5.4%) groups having had severe TEAEs. No subjects receiving the 80 mg dose of lurasidone experienced severe TEAEs.

The safety profile based on the provided data did not differ significantly from what is so far known for the adults. The most common TEAEs included akathisia, somnolence, nausea, vomiting, insomnia, anxiety and schizophrenia. The SAEs and treatment discontinuations were mainly in the category of psychiatric disorders. When compared to the frequencies in the placebo controlled short-term studies in adults, the frequency of nausea and somnolence were slightly more common among children compared to adults. As expected, EPS, with the most frequent akathisia, was reported. Serious TEAEs were more common among subjects in the placebo group. There were no deaths reported.

<u>In open-label extension Study D1050302 (subjects from Study D1050301):</u>

Of the 271 subjects who entered Study D1050302 from Study D1050301, 186 (68.6%) subjects completed 12 months of treatment, and 156 (57.6%) subjects completed the full 104 weeks of treatment.

-There were 28 (10.3%) subjects overall who discontinued study drug due to a TEAE.

-The most common TEAEs resulting in study drug discontinuation were schizophrenia (9 subjects, 3.3%), suicidal ideation (5 subjects, 1.8%), and psychotic disorder (3 subjects, 1.1%).

The most commonly reported TEAE (preferred term level) was headache (24.0%). The only other TEAEs that were reported at a frequency ≥ 10% overall were schizophrenia (12.5%), anxiety (12.5%), nausea (12.5%), and somnolence (12.2%). Note: Somnolence includes the combined preferred terms of hypersomnia, sedation, somnolence, and hypersomnolence.

Severe TEAEs occurred in 20 (7.4%) subjects overall. Severe TEAEs experienced by more than 1 subject included schizophrenia in 6 (2.2%) subjects; insomnia, psychotic disorder, and suicidal ideation in 3 (1.1%) subjects each; and depression in 2 (0.7%) subjects. The majority of TEAEs across analysis groups were mild to moderate in severity.

The most common treatment-related TEAEs overall were headache (13.7%) and nausea (11.4%). Other related TEAEs that were reported at a frequency ≥ 5% in the 301-LUR group were somnolence (8.1%), akathisia (7.7%), and weight increased (6.3%). Severe TEAEs that were considered by the Investigator to be related to study drug were reported for 6 (2.2%) subjects.

A total of 23 subjects experienced 1 or more TEAEs leading to a dose reduction of study drug, most commonly nausea (5 subjects), akathisia (4 subjects), and somnolence (3 subjects). All other TEAEs leading to dose reduction were reported in only 1 or 2 subjects each.

The incidence of EPS-related TEAEs was 16.2%. The most common EPS-related TEAEs (combined terms) were akathisia (22 subjects, 8.1%) and Parkinsonism (15 subjects, 5.5%).

The incidence of metabolic-related TEAEs was 14.0%. The most common metabolic-related TEAEs were weight increased (21 subjects, 7.7%) and weight decreased (13 subjects, 4.8%). All other metabolic-related TEAEs were reported by no more than 1 or 2 subjects each.

Suicidal ideation was reported by 9 (3.3%) subjects and intentional overdose by 2 (0.7%) subjects overall. Episodes of suicidal behaviour, suicide attempt, and self-injurious behaviour were reported by 1 subject each.

The incidence of TEAEs related to hypersensitivity was 4.4%. TEAE preferred terms related to hypersensitivity that were reported by more than 1 subject overall included urticaria (3 subjects), and pruritus, rash, and conjunctivitis (2 subjects each).

In study D105302, the most commonly reported TEAE (preferred term level) was headache (24.0%). The only other TEAEs that were reported at a frequency ≥ 10% overall were schizophrenia (12.5%), anxiety (12.5%), nausea (12.5%), and somnolence (12.2%).

Suicidal ideation was reported by 9 (3.3%) subjects and intentional overdose by 2 (0.7%) subjects. Serious TEAEs were reported by 28 (10.3%) subjects overall. Most of the serious TEAS were related to the psychiatric conditions which also was the most common reason for discontinuation of the study. The safety profile based on provided data does not significantly differ from what is known for adults.

Serious adverse event/deaths/other significant events

Study D1050301
No deaths were reported during this study. Serious TEAEs were more common among subjects receiving placebo (8.0%) than among subjects receiving lurasidone (2.8%).

Study D1050302
There were no deaths reported during this extension study. Serious TEAEs were reported by 28 (10.3%) subjects overall. Serious TEAEs reported by more than 1 subject included schizophrenia (11 subjects, 4.1%), suicidal ideation (8 subjects, 3.0%), psychotic disorder (5 subjects, 1.8%), and intentional overdose (2 subjects, 0.7%).

Laboratory findings

Liver Function Tests
In double-blind, placebo-controlled Study D1050301:

- At Week 6, the mean ± SD change in alkaline phosphatase was -4.5 ± 27.19 IU/L in lurasidone-treated subjects and + 3.8 ± 26.54 IU/L in the placebo group.

- TEAEs of ALT and AST increased were reported in two subjects treated with lurasidone 40 mg, one of whom ultimately withdrew from study due to an AE of blood creatinine phosphokinase increased.

In open-label extension Study D1050302:

- Median change in alkaline phosphatase from OL Baseline to Endpoint was -14.0 U/L. There were no other notable changes from Baseline in liver function parameters.

- Potentially Markedly Abnormal Post-Baseline Laboratory Values (PMAPLV) of high ALT, AST, and bilirubin occurred in 16 subjects (5.9%), six subjects (2.2%), and four subjects (1.5%).

- When analysed by age group, PMAPLV occurred with a similar incidence in both the 13- to 15-years-old and ≥ 16-years-old age groups.

- TEAEs of ALT and AST increased each occurred in three subjects (1.1%), while TEAEs of blood alkaline phosphate decreased and blood alkaline phosphate increased were observed for two subjects (0.7%) and one subject (0.4%), respectively.

- No subject had a liver function-related SAE or discontinued from the study due to a liver function-related AE.

There were no serious SAEs changes observed in liver function parameters with lurasidone over time in any of the Phase 3 studies that led to discontinuation from the studies. ALT increased is listed as uncommon ADR under SmPC 4.8.

Renal function tests
In double-blind, placebo-controlled Study D1050301:

- The proportion of subjects with normal to high shifts in BUN was 3.1% in lurasidone treated subjects and 1.0% in the placebo group.

- A TEAE of blood bicarbonate decreased was reported one lurasidone-treated subject. TEAEs of hypernatraemia, azotaemia, and hyperkalaemia were reported in another lurasidone-treated subject. No subject withdrew from study due to a renal function related TEAE.

In open-label extension study D1050302:

- There were no notable mean changes in renal function tests from OL Baseline to Endpoint.

- PMAPLVs in creatinine, calcium, and chloride occurred in fewer than three subjects each. PMAPLVs of low bicarbonate occurred in 61 subjects (22.6%). PMAPLVs of high sodium occurred in 23 subjects (8.5%). PMAPLVs of high potassium occurred in 20 subjects (7.4%).

- When analysed by age group, PMAPLVs occurred with a similar incidence in both the 13- to 15-years-old and ≥ 16-years-old age groups.

- No subject had a TEAE related to renal function tests or discontinued study due to a change in renal function parameters.

- No subjects had serious TEAEs related to renal function parameters that led to discontinuation in any of the Phase 3 studies.

Metabolic Parameters

In double-blind, placebo-controlled Study D1050301:

- There were no statistically significant or clinically meaningful differences seen between lurasidone and placebo in the change from Baseline to Endpoint in fasting or overall glucose, HDL, LDL, triglycerides, insulin, or HOMA-IR.

- Shifts in fasting triglycerides from normal at Baseline to high at Endpoint occurred in eight (9.0%) subjects in the lurasidone 40 mg group, two (2.2%) subjects in the lurasidone 80 mg group, and five (5.3%) of the subjects in the placebo group.

- Shifts in fasting cholesterol from normal at Baseline to high at Endpoint occurred in 16 (18.0%) subjects in the lurasidone 40 mg group, 12 (13.0%) subjects in the lurasidone 80 mg group, and 11 (11.6%) subjects in the placebo group.

- Change from Baseline in fasting cholesterol was +0.039 ± 0.7675 mmol/L in the lurasidone 80 mg group and -0.035 ± 0.6883 mmol/L in the "all lurasidone" group, statistically different from placebo (-0.249 ± 0.6419) (p = 0.0240 and p = 0.0476, respectively).

- A TEAE of hyperinsulinaemia was reported in one subject treated with lurasidone.

In open-label extension study D1050302:

- Median change in overall triglycerides from OL Baseline to Endpoint was +5.0 mg/dL. Relative to DB Baseline, the change was greater at +8.0 mg/dL. Similarly, median change in fasting triglycerides was +3.0 mg/dL relative to OL Baseline and +4.0 mg/dL relative to DB Baseline.

- Median change in overall HDL Cholesterol from OL Baseline to Endpoint was -1.0 mg/dL. Relative to DB Baseline, the change was greater at -3.0 mg/dL. Similarly, median change in fasting HDL cholesterol was -1.0 mg/dL relative to OL Baseline and -3.0 mg/dL relative to DB Baseline.

Unless otherwise noted, shifts occurred with similar incidence relative to DB Baseline.

- Shifts from normal to high fasting triglycerides occurred in 25 subjects (10.9%). These changes were more frequent relative to DB baseline, with 31 subjects (12.4%) experiencing shifts from normal to high fasting triglycerides.

- Shifts from normal to high fasting cholesterol were seen in 20 subjects (8.7%). These changes were more frequent relative to DB baseline, with 26 subjects (10.4%) experiencing shifts from normal to high fasting cholesterol.

- Shifts from normal to low fasting HDL cholesterol occurred in 66 subjects (29.1%) and shifts from high to low fasting overall cholesterol in an additional five subjects (2.2%). Shifts from normal to high fasting LDL cholesterol occurred in eight subjects (3.5%).

- Shifts from normal to high fasting glucose occurred in 16 subjects (7.0%). Shifts from normal to high overall glucose occurred in 20 subjects (8.0%). Shifts from normal to high fasting insulin occurred in 19 subjects (8.5%). Shifts from normal to high overall insulin occurred in 29 subjects (12.0%).

- There were no notable shifts in glycosylated hemoglobin (HbA1C).

- PMAPLVs of high fasting triglycerides occurred in 61 subjects (22.9%).

- PMAPLVs of high fasting cholesterol occurred in 22 subjects (8.3%).

- PMAPLVs of low fasting HDL cholesterol occurred in 119 subjects (44.7%). PMAPLVs of high fasting LDL cholesterol occurred in 23 subjects (8.6%).

- PMAPLVs of high fasting glucose (≥ 126 mg/dL) occurred in 13 subjects (4.9%); one PMAPLV of high overall glucose (> 200 mg/dL) occurred in two subjects (0.7%).

- When analysed by age group, PMAPLVs occurred with a similar incidence in both the 13- to 15-years-old and ≥ 16-years-old age groups.

- TEAEs related to metabolic laboratory parameters were as follows: blood insulin increased, blood triglycerides increased, and HDL decreased each in two subjects (0.7%), and blood cholesterol increased, blood glucose increased, LDL increased, hyperglycemia, hyperinsulinemia, and hyperlipidemia in one subject (0.4%) each. One subject had a metabolism-related SAE (Type I Diabetes Mellitus), the subject was discontinued from the study due to the event.

There were several laboratory tests that were classified as Potentially Markedly Abnormal Post-Baseline Laboratory Values (PMAPLV). Many of these findings have been listed in under *Investigations* in the tabulated summary of adverse events in the SmPC for adolescents by the applicant, whereas non are listed for the adult population. It's questionable if this is appropriate, since there was no placebo group in the study the data could be interpreted as if these findings are exclusive for the adolescent population. The applicant also states in the clinical overview that: In addition, no consistent adverse effects on measures of body weight or laboratory parameters including prolactin, lipids, and measures of glycaemic control have been observed. The safety profile of lurasidone in adolescent subjects with schizophrenia is consistent with that seen in the adult population.

The applicant was asked to further clarify if there are significant differences in the adult and adolescent population when it comes laboratory parameters and another adverse reaction, and if not, to reconsider if a separate tabulated summary of adverse reactions is required for adolescents. Taken together, the data provided demonstrated that adolescents 13-14 years old are not at greater metabolic risk with lurasidone treatment compared to adolescents ≥ 15 years old.

Neither the clinical overview nor clinical safety summary document provided information on how the ADRs in the additional table have been defined. Discrepancies have been detected in some frequency categories. The Applicant was asked to present the detailed approach and a justification for the definition of ADRs and assignment to frequency categories in section 4.8, which was satisfactorily done.

Muscle function

In double-blind, placebo-controlled Study D1050301:

- PMAPLVs of high creatinine kinase occurred in five subjects (2.5%) in the "all lurasidone" group and seven subjects (6.8%) in the placebo group. There were no meaningful differences between age groups in the frequency of these PMAPLVs.

- One TEAE of creatinine phosphokinase increased was reported in subject treated with lurasidone.

In open-label Study D1050302:

- There was negligible median change at Endpoint relative to OL or DB Baselines for CK.

- Shifts from normal to high CK occurred in 28 subjects (11.2%) relative to OL Baseline.

- PMALVs of high CK occurred in 24 subjects (8.9%).

- When analysed by age group, PMALVs occurred with a similar incidence in both age groups (13-15 years old vs ≥ 16 years old, 13-14 years old vs ≥ 15 years old).

- There were no TEAEs related to muscle function parameters.

Hormone Assessments

In double-blind, placebo-controlled Study D1050301:

- In the overall population at Endpoint, median change from Baseline in prolactin showed statistically significant differences between lurasidone 80 mg/day (+1.20 ng/mL) and placebo (+0.10 ng/mL) (p = 0.0173) and between "all lurasidone" (+1.10 ng/mL) and placebo (p = 0.0378).

- In females at Endpoint, median changes in prolactin were also significantly different between lurasidone 80 mg/day (+4.40 ng/mL) and placebo (+0.70 ng/mL) (p = 0.0318) and between "all lurasidone" (+2.60 ng/mL) and placebo (p = 0.0490).

- There were no statistically significant differences between lurasidone and placebo for median changes in prolactin in males.

- Shifts in prolactin from normal to high were seen in 8.0% of females and 8.7% of males in the "all lurasidone" group, compared to 10.3% of females and 9.4% of males in the placebo group. Incidence of shifts in prolactin in the overall population was not notably different between placebo and lurasidone.

- PMAPLVs of high overall prolactin (≥ ULN) occurred in 19.4% of the "all lurasidone" group and 9.7% of the placebo group. These PMAPLVs were more common in the 16 to 17-year-old age group, affecting 22.9% of lurasidone-treated subjects and 9.3% in the placebo group in this age group; in the 13 to 15-year-old age group, PMAPLVs of high prolactin were seen in 15.6% of lurasidone-treated subjects and 10.2% of the placebo group.

- No subject discontinued study due to a change in hormone parameters or experienced a hormone-related TEAE.

In open-label Study D1050302:

- Relative to OL Baseline, median change in prolactin at Endpoint was -0.40 ng/mL in the overall population, -0.10 ng/mL in female subjects, and -0.60 ng/mL in male subjects. Relative to DB Baseline, the median changes were +0.50, +1.00, and 0.30 ng/mL in the overall population, for female subjects, and for male subjects, respectively.

- In female subjects, shifts from normal to high prolactin occurred in nine subjects (9.4%) relative to OL Baseline and seven subjects (7.2%) relative to DB Baseline. In male subjects, shifts from normal to high prolactin occurred in eight subjects (5.1%), shifts from normal to low prolactin occurred in seven subjects (4.5%) and shifts from high to low prolactin occurred in one subject (0.6%) relative to OL Baseline.

- PMAPLVs of high prolactin occurred in 55 subjects (18.2%).

- PMAPLVs of high prolactin were reported for 59 (39.3%) subjects in the ≥ 16-years-old group at any extension visit, a higher incidence than for subjects in the 13- to 15-years-old group, 30 (25.0%) subjects. For the age group of subjects 13- to 14-years-old and ≥ 15-years-old, prolactin ≥ 1 × ULN at any extension visit was reported for 19 (26.8%) subjects and 70 (35.2%) subjects, respectively.

- TEAEs related to hormone parameters were as follows: blood prolactin increased in four subjects (1.5%) and anti-thyroid antibody positive, blood luteinizing hormone increased, blood thyroid stimulating hormone increased, hyperprolacinemia, blood testosterone decreased in 2 subjects, and thyroxine free decreased in one subject (0.4%) each. No subject had a hormone-related SAE or discontinued from the study due to a hormone-related AE.

There was a significant increase in prolactin levels between all lurasidone groups and placebo. According to guideline, undesirable changes with regard to prolactin levels should be actively studied in the paediatric population. Menstrual cyclicity and Tanner staging were assessed but no discussion regarding other consequences of increased prolactin was discussed by the applicant.

There is already a warning regarding Hyperprolactinaemia under 4.4; *Lurasidone elevates prolactin levels due to antagonism of dopamine D2 receptors. Patients should be counseled on signs and symptoms of elevated prolactin, such as gynecomastia, galactorrhea, amenorrhea and erectile dysfunction. Patient should be advised to seek medical attention if they experience any signs and symptoms.*

Hyperprolactinemia is listed under 4.8 both for both adults and adolescents as uncommon, considering the frequent reports of PMAPLVs of high prolactin 59 (39.3%) subjects in the ≥ 16-years-old group at any extension visit, a higher incidence than for subjects in the 13- to 15-years-old group, 30 (25.0%) subjects. The listed frequency in 4.8 (Uncommon) is questioned, please justify. In line with these findings, the applicant was asked to discuss if adolescents are more sensitive to hyperprolactinemia than adults.
Overall, it was concluded that lurasidone had a modest effect on prolactin elevation, which occurred to a larger extent in female subjects and in older adolescents ages ≥ 15 years, which is consistent with previously observations with lurasidone and with other atypical antipsychotics.

C-Reactive Protein

There were no clinically meaningful changes in C-reactive protein with lurasidone in the double-blind, placebo-controlled study. A TEAE of C-reactive protein increased was reported in one subject treated with lurasidone in Study D1050301.

In the open-label Study D1050302, the median change in C-reactive protein at Endpoint was +0.130 mg/L. Shifts from normal to high at Endpoint in C-reactive protein occurred in 35 (13.8%) subjects relative to DB Baseline and 33 (13.4%) subjects relative to OL Baseline. Six subjects (2.2%) experienced treatment-emergent AEs of C-reactive protein increased. No subject experienced an SAE related to C-reactive protein, and no subject discontinued due to changes in C-reactive protein.

Haematology

There were no clinically meaningful changes in hematology parameters with lurasidone in any of the Phase 3 studies.

In double-blind, placebo-controlled Study D1050301:

- Shifts from normal to high absolute lymphocytes occurred in 5.2% in the "all
- lurasidone" group and 3.0% in the placebo group. In the "all lurasidone" group, shifts from normal to high percent lymphocytes were seen in six subjects (3.1%), whereas no subject in the placebo group had a shift from normal to high.

- PMAPLVs of low and high haemoglobin occurred in 1.0% and 1.5%, respectively, of the "all lurasidone" No subject treated with placebo had a PMAPLV related to haemoglobin.

- PMAPLVs of high erythrocyte counts occurred in 3.5% of the "all lurasidone" group; none were seen in the placebo group.

In open-label Study D1050302:

There were no notable changes in mean values from Baseline to Endpoint for haematology parameters.

- PMAPLVs of low haemoglobin were reported in five subjects (1.9%). PMAPLVs of high haemoglobin were reported in five subjects (1.9%).

- PMAPLVs of high haematocrit were reported in 31 subjects (11.5%).
- PMAPLVs of low leukocytes were reported in seven subjects (2.6%).
- PMAPLVs of high erythrocytes were reported in 12 subjects (4.4%).
- PMAPLVs of high platelets were reported in one subject (0.4%).
- PMAPLVs of high percent eosinophils were seen in 13 subjects (4.8%).
- When analysed by age group, the majority of PMAPLVs associated with haematology parameters occurred with a similar incidence in both the 13- to 15-years-old and ≥ 16-years-old age group, with the exception of elevated (≥ 50%) haematocrit, which occurred in nine (7.5%) subjects in the 13- to 15-years-old group and 22 (14.7%) subjects in the ≥ 16-years-old group. For the age group of subjects 13- to 14-years-old and ≥ 15-years-old, potentially markedly abnormal elevated haematocrit was reported for seven (9.9%) subjects and 37 (18.6%) subjects, respectively.
- TEAEs related to haematology were as follows: neutropenia in two subjects (0.7%) and anaemia, iron deficiency anaemia, haemoglobin decreased, and eosinophilia in one subject (0.4%) each. No subject had a haematology-related SAE; however, one (0.4%) subject was withdrawn from the study due to a nonserious TEAE of neutropenia.

Urinalysis

There were no clinically meaningful changes in urinalysis parameters with lurasidone in any of the Phase 3 studies. In Study D1050301, PMAPLVs of high urine erythrocytes were reported in 15.6% of lurasidone-treated subjects, and 5.6% of subjects in the placebo group.

In Study D105302, there were no meaningful median changes in urine pH or specific gravity.

Vital Signs, Physical Findings, and Other Observations Related to Safety

- Overall, there were no clinically meaningful effects of lurasidone, including no dose related effects, on the vital sign parameters of BP, pulse, and body temperature.
- The results for QTcF (rather than QTcB) are considered more sensitive in the pediatric and adolescent population. Treatment with lurasidone was not associated with clinically relevant changes in any ECG parameter.
- With respect to QTc prolongation, no subject in any treatment group had QTcF > 460 msec or a ≥ 60 msec increase from Baseline in the 6-week double-blind study in subjects with acute schizophrenia (D1050301). Two subjects in the placebo group and three subjects in each of the lurasidone groups had an increase QTcF ≥ 30 msec.
- In the open-label study (D1050302), 1 subject had increases in QTcF ≥ 60 msec relative to DB Baseline; however, this increase was less than 60 msec when compared to open-label Baseline.
- Changes in movement disorder signs or symptoms, as measured by change in SAS, BARS, and AIMS scores, were generally absent to mild in subjects treated with lurasidone. Relatively small changes from Baseline were observed in the SAS mean score, BARS total score, and AIMS total score over the short-term double-blind and long-term open-label studies, which were not considered clinically relevant.
- Rates of suicidal ideation or behaviour, as measured by the C-SSRS, were comparable between the lurasidone and placebo groups in the 6-week double-blind study in subjects with acute schizophrenia (D1050301). The majority of subjects who continued from Study D1050301 had no suicidal ideation at any extension visit (92.2%).

Growth Parameters

To analyse the effects of lurasidone on growth parameters, changes from Baseline in mean body weight, height, BMI, and waist circumference were measured. In the 6-week double-blind study, lurasidone and placebo treatment groups were compared by applying a mixed model for repeated measures (MMRM) with fixed effects terms for treatment, visit (as a categorical variable), pooled countries, age group, the corresponding Baseline, and treatment-by-visit interaction for body weight and BMI data. In addition, an analysis of covariance (ANCOVA) model including factors of treatment, pooled countries, age group, and corresponding Baseline score as covariate was applied for height, waist circumference, body weight, and BMI, as well as Z-scores for weight, height, and BMI.

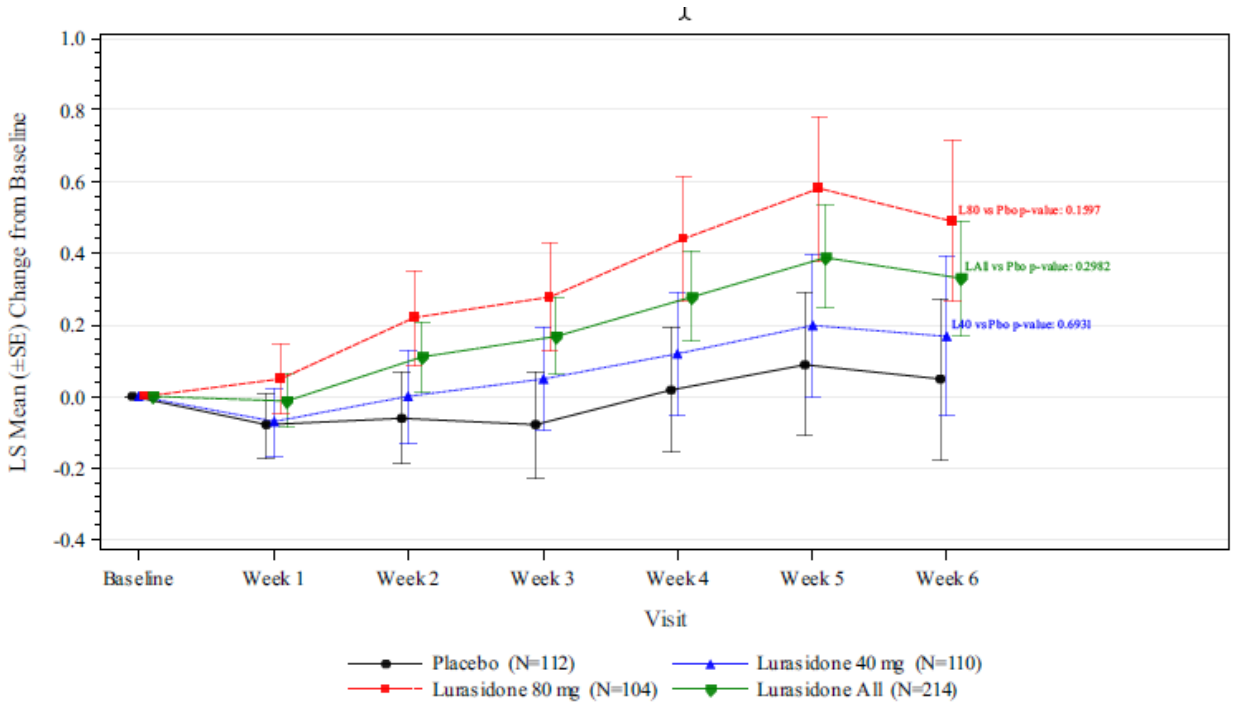
In the open-label extension study (D1050302), age-and-gender specific Z-scores and percentiles Z-scores were analysed in order to standardize the comparisons of growth index across the genders and different ages of subjects in these studies. Age and gender specific Z-scores and percentiles of height and BMI were obtained by using the World Health Organization (WHO) 2007 growth charts (D1050301).

In the open-label extension study (D1050302), age-and-gender specific Z-scores and percentiles presented for summaries of height and BMI were derived using the WHO 2007 growth reference; age and-gender specific Z-scores and percentile spresented for summaries of height and BMI were derived using the WHO 2007 growth reference; age-and-gender specific Z-scores and percentiles presented for summaries of weight were derived using the CDC 2000 growth reference since no corresponding WHO growth reference is available.

In the open-label extension study, to better interpret changes in observed growth parameters in the absence of a placebo-controlled group, the expected values of height, weight, and BMI at each open-label visit was calculated for each subject based on the corresponding percentile of a growth parameter at the double-blind baseline. Expected change from DB baseline at each OL visit was then calculated as the difference between the expected value at the visit and the value at DB baseline. Summary statistics of the expected value and expected change from DB Baseline were also generated.

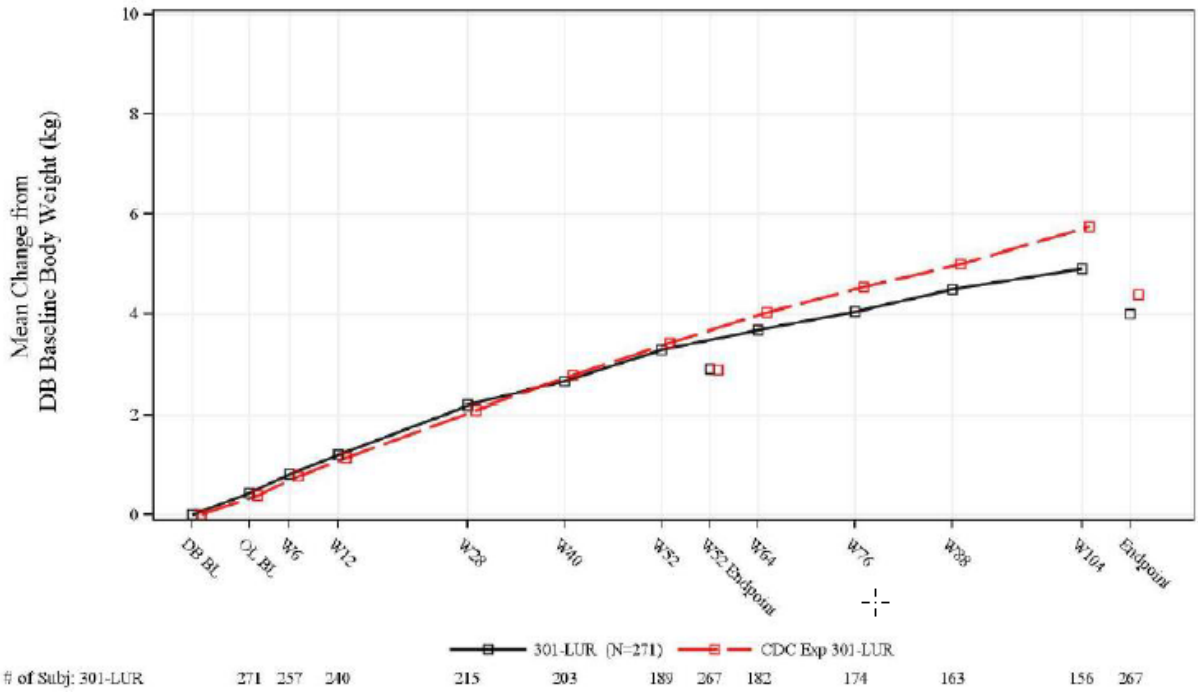
Overall, after six weeks of treatment in subjects with acute schizophrenia (D1050301), there was a minimal increase in body weight in subjects treated with lurasidone, as demonstrated by the small mean changes from Baseline in body weight and BMI Z-score of 0.49 ± 0.225 kg and 0.011 ± 0.2055, respectively, for the 80 mg group, and 0.17 ± 0.223 kg and -0.011 ± 0.2534, respectively, for the 40 mg group. The corresponding mean changes from Baseline for the placebo group were 0.05 ± 0.225 kg and -0.018 ± 0.2562, respectively. These changes are illustrated below. The changes observed were not statistically significantly different for either lurasidone treatment group as compared to placebo based on MMRM or ANCOVA.

Figure 9 Body Weight (kg): LS Mean (± SE) Change from Baseline over Time – Mixed Model for Repeated Measure (D1050301 Safety Population)



In the long-term open-label extension study, increases in weight were observed relative to expected weights predicted based on the CDC growth charts for the overall population. Mean (± SD) Baseline body weight was 64.18 ± 12.309 kg at DB Baseline and 64.62 ± 12.454 kg at OL Baseline. The mean percentile of Baseline body weight was 63.65 ± 27.793 at DB Baseline and 63.57 ± 27.571 at OL Baseline. The mean change from DB Baseline in weight was 3.27 ± 6.324 kg at Week 52 and 4.97 ± 7.778 kg at Week 104, compared with an expected weight gain of 3.41 ± 1.837 kg and 5.74 ± 3.173 kg, respectively, based on the age-and-gender specific CDC growth chart.

Figure 10 Mean Change from DB Baseline over Time in Body Weight (kg) for Subjects Continued from Study D1050301 (Safety Population)



Abbreviations: BL = Baseline; CDC = Centers for Disease Control and Prevention; DB = double-blind; Exp = expected; OL = open-label; W = week; 301-LUR = all subjects continued from Study D1050301.
Note: The number of subjects at each visit represents the number of subjects with a non-missing weight value. Week 52 Endpoint was defined as the assessment at Week 52 visit or the last post-OL Baseline assessment before the Week 52 visit. Endpoint was defined as the last post-OL Baseline assessment during the OL treatment period.

There was an increase in weight in the lurasidone treated subjects compared to placebo after six weeks in the short-term study D1050301.
The applicant states that, in the long-term open-label extension study, increases in weight were observed relative to expected weights predicted based on the CDC growth charts for the overall population. However, in the figure above the 301-LUR group appears to have a smaller mean change of body weight compared to the CDC Exp 301-Lur prediction.

SmPC 4.4 states that weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended, this was endorsed.

Menstrual Cyclicity and Tanner Staging

To monitor menstrual cyclicity, information on any changes in frequency and quality of menstrual cycles were collected from female subjects who had begun menses. These subjects were given a calendar at Baseline to mark the beginning and end of each menses during the study. Lurasidone treatment had no apparent effect on menstrual cyclicity, as the reported frequency of menstrual cycles did not show a significant change in lurasidone-treated females between open-label Baseline and Endpoint in the long-term open-label extension study. Few menstrual related AEs were reported during long-term treatment with lurasidone: amenorrhea in 4 (1.5%) subjects; dysmenorrhea, galactorrhea, and menstruation irregular in 3 (1.1%) subjects each; and hypomenorrhea, metrorrhagia, and oligomenorrhea in 1 (0.4%) subject each.

Physical development and sexual maturity were assessed by analysis of the frequency distribution of Tanner stage over time. Key observations from the open-label extension study D1050302,

focusing on the 13-15 years and ≥ 16 years age groups, are summarized below:

- No shifts in Tanner stage from DB Baseline to Endpoint were observed in the majority of male subjects, including 55.9% of males showing no shift in pubic hair development and 58.4% with no shift in genitalia development. There was an upward shift in Tanner stage by 1 category for pubic hair development in 36.6% of male subjects, with 5.6% (9 subjects) having an upward shift by 2 categories, and 1.2% (2 subjects) by 3 categories.

- No shifts in Tanner stage from DB Baseline were observed in most female subjects at Endpoint, including 57.7% of subjects showing no shift in pubic hair development, and 55.7% with no shift in breast development. For those subjects with upward shifts in Tanner stage category, no subject had an upward shift of more than 2 categories. There was an upward shift in Tanner stage by 1 category for pubic hair development in 34.0% of female subjects, with 8.2% (8 subjects) having an upward shift by 2 categories. For breast development, 38.1% of female subjects had an upward shift by 1 category and 6.2% (6 subjects) had an upward shift by 2 categories.

Few subjects overall had an increase in Tanner stage of more than one category at Endpoint. No subject reportedly experienced a downward shift in Tanner stage from OL Baseline.

The applicant states that physical development and sexual maturity was assessed by analysis of the frequency distribution of Tanner stage over time from DB baseline to Endpoint in the extension study D1050302. However, there is no analysis of discrepancies with regard to expected changes of tanner staging over time provided by the applicant. An analysis and discussion was provided with regard to what is expected over a 104-week period for females and males in terms of shift in Tanner staging in the age groups studied and what was actually observed in the study.

Clinical Assessments: Cognitive Performance and Psychiatric Effects

Both studies D1050301 and D1050302 measured the effects of lurasidone on cognitive performance with the Cogstate Computerized Cognitive Test Battery, and the Udvalg for Kliniske Undesogelser (UKU) Side Effect Rating Scale captured changes in psychotropic side effects.
In study D1050301, there was no worsening in cognitive function in subjects treated with lurasidone compared to placebo, as measured by the Cogstate Computerized Cognitive Test Battery, and there were no statistically significant differences between lurasidone and placebo for the Cognitive Composite Standardized Score 2 or the Cognitive Composite Standardized Score. The results of the UKU side effect rating scales (psychic, neurological, autonomic, and other) as well as the UKU total score indicate changes from baseline to endpoint were generally similar between the placebo and lurasidone treated groups.

In study D1050302, the mean (± SD) overall Baseline Cognitive Composite Standardized Score was -1.10 ± 1.417 at DB Baseline and -1.07 ± 1.346 at OL Baseline. Slight mean increases were observed from DB Baseline to Week 52 (0.18 ± 1.453), Week 104 (0.06 ± 1.774), and Endpoint (0.06 ± 1.552); generally, no worsening was observed during the overall OL treatment period. Mean (± SD) overall UKU total score was 5.42 ± 4.928 at DB Baseline and 4.11 ± 4.079 at OL Baseline. A gradual improvement over time was observed, with mean decreases from DB Baseline at Week 52 of -2.89 ± 4.666 (median -2.00) and at Week 104 of -4.09 ± 4.387 (median -3.00).

Cognitive dysfunction is a core feature of schizophrenia. There was an initial increase in Cognitive Composite Standardized Score, but no significant improvement was observed at endpoint.

Overdose, Drug abuse, Withdrawal and Rebound

No clinical studies of abuse potential with lurasidone were conducted in the paediatric population. In the studies supporting this submission, there were no reports of AEs suggesting drug abuse.

No clinical studies of abuse potential with lurasidone were conducted in the paediatric population. In the studies supporting this submission, there were no reports of AEs suggesting drug abuse. Consistent with the approved labelling, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed carefully for signs of lurasidone misuse or abuse (e.g., development of tolerance, drug-seeking behaviour, increases in dose).

Based on the data available in the lurasidone paediatric clinical program, 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 paediatric studies.

Based on the nonclinical observation of dose-dependent motor hyperactivity in the post-treatment period, hyperactivity-related adverse events with an onset after the last dose of study medication was analysed for subjects who either early terminated Study D1050301 or did not enter the D1050302 long-term extension study. None of the 55 subjects who met these criteria experienced any post-treatment hyperactivity-related AEs.

Discontinuation due to adverse events

Study D1050301
The most common reason for discontinuation from the study was due to AE; however, the proportion of subjects who discontinued due to an AE was lower while on lurasidone (3.7% in the "all lurasidone" group versus 8.0% in the placebo group).

Study D1050302
There were 28 (10.3%) subjects overall who discontinued study drug due to a TEAE. The most common TEAEs resulting in study drug discontinuation were schizophrenia (9 subjects, 3.3%), suicidal ideation (5 subjects, 1.8%), and psychotic disorder (3 subjects, 1.1%).

Post marketing experience

The most commonly reported adverse drug reactions (ADRs) were categorized in the Psychiatric Disorders SOC, followed by the Nervous System Disorders SOC, General Disorders and Administration Site Conditions SOC, and Gastrointestinal Disorders SOC.

The most commonly reported ADRs were drug ineffective, nausea, akathisia, off-label use, somnolence, weight increased, insomnia, suicidal ideation, anxiety, feeling abnormal, and bipolar disorder, and the most commonly reported serious ADRs were suicidal ideation, seizure, death, neuroleptic malignant syndrome, psychotic disorder, suicide attempt, aggression, completed suicide, mania, and swollen tongue.

The review of the available safety data from launch to 27 October 2018 did not identify any potential signals of unanticipated or emerging risk with exposure to lurasidone. The safety profile does not differ from that observed in the clinical development program.

2.5.1. Discussion on clinical safety

Assessment of paediatric data on clinical safety

The safety profile of lurasidone in adolescent subjects with schizophrenia is largely consistent with that seen in the adult population.

Study D1050301
The number of subjects reporting one or more study drug-related TEAEs (definite, possibly, or probably related) were more common in the groups treated with lurasidone and included 94 subjects (43.9%) in the "all lurasidone" group and 33 subjects (29.5%) in the placebo group.

The most common TEAEs included akathisia, somnolence, nausea, vomiting, insomnia, anxiety and schizophrenia. The SAEs and treatment discontinuations were mainly in the category of psychiatric disorders. When compared to the frequencies in the placebo controlled short-term studies in adults, the frequency of nausea and somnolence were slightly more common among children compared to adults. As expected, EPS, with the most frequent akathisia, was reported. Serious TEAEs were more common among subjects in the placebo group. There were no deaths reported.

When compared by age-groups 13-15 and 16-17 years old, there appears not to be any notable differences when it comes to number of adverse events, adverse events related to study drug and serious adverse events.

From the study report for D1050301, 50+55 subjects in the lurasidone 40 and 80mg/day group were 13-15 years old and 60+49 subjects were 16-17 years old, respectively. In study D1050302 that continued from D105301, 121 subjects were 13-15 years old. However, it is unclear. The Applicant clarified how many in each treatment group were 13-14 years old.

In study D105301 changes from baseline in prolactin levels were significant different in the lurasidone treatment groups compared to placebo. Prolactin levels improved slightly in the long-term study D1050302 but remained elevated. Relative to DB Baseline, the median changes were +0.50, +1.00, and 0.30 ng/mL in the overall population, for female subjects, and for male subjects, respectively. 80 mg/day (+1.20 ng/mL) and placebo (+0.10 ng/mL) (p = 0.0173) and between "all lurasidone" (+1.10 ng/mL) and placebo (p = 0.0378). Hyperprolactinemia is listed under 4.8 both for both adults and adolescents as uncommon, considering the frequent reports of PMAPLVs of high prolactin 59 (39.3%) subjects in the ≥ 16-years-old group at any extension visit, a higher incidence than for subjects in the 13- to 15-years-old group, 30 (25.0%) subjects. Prolactin increases in the two age strata of interest, i.e. 13 to 14 years and 15 to 17 years in study D1050301 were evaluated and discussed. Discussion also included any differences compared to adults especially with a focus on long-term consequences.

The listed frequency in 4.8 (Uncommon) was questioned and clarified, in line with these findings, the applicant discussed also in an appropriate manner the sensititivity to hyperprolactinemia in adolescents and in adults.

Study D105302
The most commonly reported TEAE (preferred term level) was headache (24.0%). The only other TEAEs that were reported at a frequency ≥ 10% overall were schizophrenia (12.5%), anxiety (12.5%), nausea (12.5%), and somnolence (12.2%).

Suicidal ideation was reported by 9 (3.3%) subjects and intentional overdose by 2 (0.7%) subjects o. Serious TEAEs were reported by 28 (10.3%) subjects overall. The majority of the serious TEAES were related to the underlying psychiatric conditions which also was the most common reason for discontinuation of the study. The safety profile based on provided data does not significantly differ from what is known for adults. No deaths were reported in any of the studies.

The number of adverse events related to study drug was similar between the age groups, the number of reported serious adverse events was somewhat higher in the 13-14 year age group compared to the 15-17 age group, 7 (15.9%) compared to 12 (8.8%).

There were several laboratory tests that were classified as, Potentially Markedly Abnormal Post-Baseline Laboratory Values (PMAPLV). Many of these findings have been listed under *Investigations* the tabulated summary of adverse events in the SmPC for adolescents by the applicant, whereas non are listed for the adult population. It's questionable if this is appropriate, since there was no placebo group in the study, and it could be interpreted that these findings are exclusive for the adolescent population.

The applicant clarified if there are significant differences in the adult and adolescent population when it comes laboratory parameters and another adverse reaction.

Neither the clinical overview nor clinical safety summary document provided information on how the ADRs in the additional table have been defined. Discrepancies have been detected in some frequency categories. The Applicant presented the detailed approach and a justification for the definition of ADRs and assignment to frequency categories in section 4.8.

In the paediatric population special attention should be given to possible adverse effects on sexual maturation, cognition, endocrine function and other aspects of development.

Cognitive dysfunction is a core feature of schizophrenia. There was an initial increase in Cognitive Composite Standardized Score, but no significant improvement was observed at endpoint.

There was an increase in weight in the lurasidone treated subjects compared to placebo after six weeks in the short-term study D1050301. The applicant states that, in the long-term open-label extension study, increases in weight were observed relative to expected weights predicted based on the CDC growth charts for the overall population. SmPC 4.4 states that weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

According to the applicant, physical development and sexual maturity was assessed by analysis of the frequency distribution of Tanner stage over time from DB baseline to Endpoint in the extension study D1050302. However, there was no analysis of discrepancies with regard to expected changes of Tanner staging over time provided by the applicant. An analysis and discussion with regard to what is expected over a 104-week period for females and males in terms of shift in Tanner staging in the age groups studied, as compared to the observed in the study was provided.

2.5.2. Conclusions on clinical safety

The MAH has provided long-term data safety, tolerability of lurasidone a time for periods up to two years. Lurasidone appears tolerable with a safety profile largely in line with what is known for the adult population in the dose range investigated.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan (RMP):

The PRAC considered that the RMP version 8.1 is acceptable.

The CHMP endorsed RMP version 8.1 with the following content:

Safety concerns

Table 16 Summary of safety concerns

Important identified risks	Extrapyramidal symptoms Drug interactions with strong cytochrome P-450 3A4 inhibitors or inducers Neuroleptic malignant syndrome

Important potential risks	Metabolic profile (hyperglycaemia, weight increased, dyslipidaemia) Rhabdomyolysis Suicidality (suicidal ideation, suicidal behaviour, suicide attempt, self-harm and completed suicide) Agranulocytosis Seizure 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 Latuda (160 mg/day lurasidone hydrochloride) Third trimester exposure during pregnancy and risk to neonates
Missing information	Elderly patients Patients with cardiac impairment Pregnant or lactating women Long-term safety

Pharmacovigilance plan

Table 17 On-going and planned additional pharmacovigilance activities in the PV Plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 – Required additional pharmacovigilance activities				
Lurasidone PASS Program *PLANNED*	<u>Primary objective</u> Compare the incidence of important identified risks and important potential risks in patients treated with lurasidone to patients treated with other second generation OAAs	Extrapyramidal symptoms, drug interactions, neuroleptic malignant syndrome, metabolic profile, rhabdomyolysis, suicidality, agranulocytosis, seizures, use with severe or moderate renal and/or hepatic impairment, third trimester exposure during pregnancy	Protocol approval	February 2020
			EU PAS register	February 2020
			Start of data collection	March 2020
			End of data collection	September 2020
			Final report submission	December 2020

Risk minimisation measures

Table 18 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Extrapyramidal symptoms	Routine risk minimization measures: • SmPC sections 4.4 and 4.8. • PL sections 2 and 4. • recommendation regarding treatment discontinuation in case of tardive dyskinesia is included in section 4.4 of the SmPC. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Lurasidone PASS program
Drug interactions with strong cytochrome P-450 4A inhibitors or inducers	Routine risk minimization measures: • SmPC sections 4.2, 4.3 and 4.5. • PL section 2. • recommendations regarding dose adjustments are reported in section 4.2 of the SmPC. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Lurasidone PASS program
Neuroleptic malignant syndrome	Routine risk minimization measures: • SmPC sections 4.4 and 4.8. • PL sections 2 and 4. • recommendation to seek medical attention immediately is included in section 4 of the PL. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Lurasidone PASS program
Metabolic profile	Routine risk minimization measures: • SmPC sections 4.4 and 4.8. • PL sections 2 and 4. Additional risk minimization measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Safety concern	Risk minimization measures	Pharmacovigilance activities
	None	None Additional pharmacovigilance activities: Lurasidone PASS program
Rhabdomyolysis	Routine risk minimization measures: • SmPC section 4.8. • PL section 4. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Lurasidone PASS program
Suicidality	Routine risk minimization measures: • SmPC sections 4.4 and 4.8. • PL section 4. • recommendation to a close supervision in high risk patients is included in section 4.4 of the SmPC. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Lurasidone PASS program
Agranulocytosis	Routine risk minimization measures: • SmPC section 4.8 reports *leukopenia* and *neutropenia*. • PL section 4. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Lurasidone PASS program
Seizure	Routine risk minimization measures: • SmPC sections 4.4 and 4.8. • PL section 4. • recommendation for a cautious use is included in section 4.4 of the SmPC.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Additional risk minimization measures: None	None Additional pharmacovigilance activities: Lurasidone PASS program
Use in patients with moderate or severe renal impairment	Routine risk minimization measures: • SmPC sections 4.2 and 4.4. • PL section 2. • recommended posology is included in section 4.2 of the SmPC. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Lurasidone PASS program
Use in patients with moderate or severe hepatic impairment	Routine risk minimization measures: • SmPC sections 4.2 and 4.4. • PL section 2. • recommended posology is included in section 4.2 of the SmPC. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Lurasidone PASS program
Off-label use	Routine risk minimization measures: • SmPC sections 4.1, 4.2, 4.4 and 4.9. • PL sections 1 and 3 (overdose). • in case of overdose, recommendations are reported in section 4.9 of the SmPC. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Third trimester exposure during pregnancy and risk to neonates	Routine risk minimization measures: • SmPC section 4.6. • PL section 2. • recommendation for neonates is included in section 4.6 of the SmPC. • recommendation for babies is included in	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	section 2 of the PL. Additional risk minimization measures: None	Additional pharmacovigilance activities: Lurasidone PASS program
Elderly	Routine risk minimization measures: • SmPC sections 4.2 and 4.4. • recommendation regarding posology is included in section 4.2 of the SmPC. Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Patients with cardiac impairment	Routine risk minimization measures: • SmPC section 4.4. • PL section 2. • recommendation for a cautious use is included in section 4.4 of the SmPC. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Pregnant or lactating women	Routine risk minimization measures: • SmPC section 4.6. • PL section 2. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Long-term safety	Routine risk minimization measures: • SmPC section 5.1. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Safety concern	Risk minimization measures	Pharmacovigilance activities
		Additional pharmacovigilance activities: None

2.7. Update of the Product information

As a result of this variation for a new indication, section(s) 4.1, 4.2, 4.7, 4.8 and 5.1, 5.2, 5.3 of the SmPC are being updated particularly: The Package Leaflet (PL) is updated accordingly.

- 4.1, the indication is updated to include adolescents aged 13 and over.

Latuda is indicated for the treatment of schizophrenia in adults and adolescent aged 13 years and over.

- 4.2, a dose recommendation in the paediatric population is included.

The recommended starting dose is 37 mg of lurasidone once daily. No initial dose titration is required. It is effective in a dose range of 37 to 74 mg once daily. Dose increase should be based on physician judgement and observed clinical response. The maximum daily dose should not exceed 74 mg.

- 4.8, a new tabulated summary of adverse events for adolescents (Table 2) is included.
- 5.1, clinical data for the paediatric population for studies D1050302 is included.

The Package Leaflet (PL) is updated accordingly.

Changes are also made to the PI to bring it in line with the Excipients guideline which were reviewed and accepted by the CHMP.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative of Spain.

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH 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

3.1. Therapeutic Context

3.1.1. Disease or condition

The applicant has applied for the following indication:

Latuda is indicated for the treatment of schizophrenia in adults and adolescent aged 13 years and over.

The current indication is:

Latuda is indicated for the treatment of schizophrenia in adults aged 18 years and over.

Schizophrenia is a chronic and debilitating illness that has an estimated lifetime adult prevalence of 0.5 to 1%. Schizophrenia is rare in pre-pubertal children. Thus, within the paediatric age group, a diagnosis of schizophrenia is most commonly made in adolescents, and the symptoms in this age group are generally similar to those in adults.

3.1.2. Available therapies and unmet medical need

There are several available antipsychotic drugs for the treatment of schizophrenia including quetiapine, clozapine, haloperidol, risperidone, ziprasidone, lurasidone, aripiprazole and olanzapine. However, data in the paediatric population is often missing and use in adolescents under 18 years of age is therefore not recommended for several of the approved drugs.

So far, no antipsychotic has received approval for the treatment of schizophrenia in children aged 13-14 years old. Paliperidone and Aripiprazole are indicated in adolescents from 15 years and above. Thus, there are limited treatment alternatives for schizophrenia adolescents under the age of 15.

3.1.3. Main clinical studies

Study D1050300

Open-label, multicentre, single and multiple fixed ascending dose study to evaluate pharmacokinetics, safety, and tolerability of lurasidone in the paediatric population.

Study D1050301

Randomised, parallel, double-blind, placebo-controlled, fixed-dose regimen, multicentre, study to evaluate the efficacy and safety of lurasidone in adolescent patients with schizophrenia.

Study D1050302

A 104-week, flexible-dose, open-label multicentre extension study to evaluate the long-term safety and effectiveness of lurasidone in adolescent patients with schizophrenia.

3.2. Favourable effects

The applicant has presented efficacy and safety data from two clinical studies as presented above (D1050301 and D1050302) and pharmacokinetics data from one additional study (D1050300).

In study D1050301

For the primary endpoint the change in PANSS total score from Baseline to endpoint (Week 6) using MMRM analysis, the LS mean changes were -18.6 for the lurasidone 40mg/day group, -18.3 for the lurasidone 80mg/day group, and -10.5 for the placebo group. The treatment differences for the lurasidone groups versus the placebo group were statistically significant for both lurasidone 40mg/day (-8.0, p=0.0003) and lurasidone 80mg/day (-7.7, p=0.0006).

Also, the key secondary efficacy endpoint change in CGI-S scores at Week 6 were significantly different from placebo for both the lurasidone 74 mg/day (-0.42 ± 0.130, adjusted p = 0.0015) and lurasidone 37 mg/day (-0.47 ± 0.130, adjusted p = 0.0008) treatment groups.

Other secondary endpoints like change from baseline to week 6 on the PQ-LES-Q and CGAS scales were statistically significantly different from placebo for both doses.

Thus, the 6-weeks treatment with lurasidone (40 mg and 80mg) demonstrated a statistically significant decrease in the positive and negative symptoms of schizophrenia as well as general psychopathology for both doses.

Extension study D1050302

Maintenance of efficacy was shown in study D1050302. The mean (± SD) change in PANSS total score from baseline of Study D1050301 group was -29.2 ± 14.73 at Week 28 and increased to -32.4 ± 14.61

at Week 52 and -34.3 ± 16.32 at Week 104. Mean change from baseline of Study D1050301 to Endpoint was -29.5 ± 18.48. _Mean (± SD) change in PANSS total score relative to the open label baseline was -11.9 ± 13.74 at Week 28, -15.6 ± 14.97 at Week 52, -18.4 ± 16.73 at Week 104, and -12.2 ± 19.54 at Endpoint.

Also, other disease outcomes of symptoms of schizophrenia and functionality indicated maintenance of effect.

Overall the studies D1050301 and D1050302 provided short-term (40 and 80 mg) and long-term efficacy flexible dose of (20, 40, 60, 80 mg) data for lurasidone in adolescents 13-17 years. Primary endpoints were statistically significant and superior to placebo and maintenance of effect was demonstrated. The effect observed in adolescents appears to be of similar magnitude to what is observed for adults.

3.3. Uncertainties and limitations about favourable effects

No dose-response studies in the paediatric population was provided by the applicant. A dose-response study would have been valuable to establish minimum effective dose and the dose for optimal efficacy in the paediatric population, although justifications was provided on the absence of a proper dose-response study in the paediatric population.

The selection of participants in study D1050301 that *had an acute exacerbation of psychotic symptoms (no longer than two months in duration) and marked deterioration of function from baseline (by history), or had been hospitalized for the treatment of an acute psychotic exacerbation, for two consecutive weeks or less, immediately before screening*, represents patients that are more in an acute disease phase that may show a larger response to pharmacological treatment than patients that are in a more chronic phase of the disease. Also, eligible subjects had a Positive and Negative Syndrome Scale (PANSS) total score ≥ 70 to < 120 at Screening and Baseline, and a Clinical Global Impression-Severity Scale (CGI-S) score ≥ 4 at Screening and baseline. This means that not the whole covered study population is included in the application. To address the question of whether efficacy could be generalized to patients with a broader range of schizophrenia symptom severity, a post-hoc analysis was conducted to examine the effect of baseline severity on response to lurasidone treatment.

Results of these analyses show that patients in each of the baseline severity categories continued to maintain PANSS total score reductions and to further improve over time; no difference in terms of magnitude of PANSS improvement was observed between subjects with different disease severity.

Furthermore, the consistency of significant improvement across all efficacy measures and symptom domains in study D1050301, and their clinical relevance as shown by secondary endpoints, demonstrated the generalisability of lurasidone efficacy results.

In the subgroup analyses the results of the primary endpoint (change in PANSS total score) was somewhat less pronounced in children aged 13-14 years compared to older study subjects in study D1050301. The applicant further explained satisfactorily that despite the differences in magnitude of improvement, the results showed that overall, there was a net improvement in both age cohorts in both lurasidone dose groups compared to placebo.

It is questioned if the results from the open label study D1050302 are robust enough to demonstrate a maintenance of effect due to the lack of a comparator. It should be noted that maintenance of effect in the adult studies with lurasidone was established with a randomized withdrawal study. Importantly, according to the EMA schizophrenia guideline, extrapolation from adult data is possible to subjects aged > 15 years (see EMA schizophrenia guideline: EMA/CHMP/40072/2010 Rev. 1). Therefore, the MAH provided additional clarifications to further substantiate maintenance of efficacy in adolescents and

evaluate whether extrapolation from the adult data is possible, in particular for the subgroup 13- < 15 years in light of the EMA guideline.

Despite some differences in age group, study design, symptom severity at the start of the maintenance period, and criteria for relapse, the estimated risk of relapse was shown to be quite consistent between lurasidone treatment of adolescents and adults with schizophrenia, and between treatment of adolescents with lurasidone and aripiprazole. As both the lurasidone adult schizophrenia maintenance study and the aripiprazole adolescent schizophrenia study demonstrated superiority vs. placebo in delaying time to relapse, one may infer lurasidone is similarly effective as a long-term treatment for adolescents with schizophrenia. This was deemed satisfactory by the CHMP.

However, there is no clear biological rational to make a distinction between adolescents under and above the age of 15. In addition, a comparable effect was observed also in the younger age strata even if the studies were not designed and powered to detect a statistical significance.

Age stratification in the provided analysis (obviously showing the primary endpoint analysis) represents age groups 13 to 14 years and 15 to 17 years for lurasidone 40 mg/day and 80 mg/day, with the results demonstrating a higher treatment effect in the older age group of adolescents 15 to 17 years as compared to those aged 13 to 14 years. The applicant further presented the same age stratification for the CGI-S (as a secondary endpoint).

3.4. Unfavourable effects

A higher percentage of subjects treated with lurasidone completed the study (89.7%) than placebo (82.3%). The most common reason for discontinuation from the study was due to AE; however, the proportion of subjects who discontinued due to an AE was lower while on lurasidone (3.7% in the "all lurasidone" group versus 8.0% in the placebo group).

The most common TEAEs compared to placebo included, nausea (13.6 %), vomiting (7.5%), somnolence (10.3 %), akathisia (8.9%), sedation (3.7%) and agitation (5.1%).

The number of subjects reporting one or more study drug-related TEAEs (definite,

possibly, or probably related) where more common in the groups treated with lurasidone and included 94 subjects (43.9%) in the "all lurasidone" group and 33 subjects (29.5%) in the placebo group.

There was an increase in weight in the lurasidone treated subjects compared to placebo after six weeks in the short-term study D1050301.

In study D105301 changes from baseline in prolactin levels were significantly different from placebo. Prolactin levels improved slightly in the long-term study D1050302 but remained elevated.

3.5. Uncertainties and limitations about unfavourable effects

There are several discrepancies between adults and adolescents in the SmPC list of adverse events under section 4.8. Further analyses were performed to examine the proportion of subjects in each age group (13-14 and ≥ 15 years old).

Physical development and sexual maturity were assessed by analysis of the frequency distribution of Tanner stage over time from DB baseline to endpoint in the extension study D1050302. Data, including shifts table of Tanner stages, suggested that lurasidone did not impact on the growth and physical or sexual maturation of the adolescent patients.

From the study report for D1050301, 50+55 subjects in the lurasidone 40 and 80mg/day group were 13-15 years old and 60+49 subjects were 16-17 years old, respectively. In study D1050302 that continued from D105301, 121 subjects were 13-15 years old. However, it is unclear how many in each treatment group were 13-14 years old. The Applicant further presented the number of patients included in these two studies who were in the age range of 13 to 14 years.

Neither the clinical overview nor clinical safety summary document provided information on how the ADRs in the additional table have been defined. Discrepancies have been detected in some frequency categories. The MAH presented the detailed approach and a justification for the definition of ADRs and assignment to frequency categories in section 4.8.

3.6. Effects Table

Table 19 Effects Table for lurasidone in the treatment of Schizophrenia in adult and adolescents 13 years and over

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Significant short-term efficacy	Study D1050301	PANSS total score	40 and 80 mg/day lurasidone	Placebo	The treatment was statistically significant versus placebo for both 40 mg/ day (-8.0, P=0.0003) and 80 mg/day (-7.7 P=0.0006)	
maintenance of efficacy	Study D1050302	PANSS Total score	Flexible dose		Maintenance of efficacy was shown. The mean (± SD) change in PANSS total score from baseline of Study D1050301 group was -29.2 ± 14.73 at Week 28 and increased to -32.4 ± 14.61 at Week 52 and -34.3 ± 16.32 at Week 104	
Unfavourable Effects						
TEAEs	Study D1050301	%	40 and 80 mg/day lurasidone	Placebo	Related TEAEs were more common in the groups treated with lurasidone and included 94 subjects (43.9%) in the "all lurasidone" group and 33 subjects (29.5%) in the placebo group. The most common TEAEs compared to placebo included, nausea, vomiting, somnolence, akathisia, sedation and agitation.	
Prolactin levels increased	Study D1050301 and D1050302 D	ng/ml	40 and 80 mg/day lurasidone Flexible dose	Placebo	80 mg/day (+1.20 ng/mL) and placebo (+0.10 ng/mL) (p = 0.0173) and between "all lurasidone" (+1.10 ng/mL) and placebo (p = 0.0378) Relative to DB Baseline, the median changes were +0.50, +1.00, and 0.30 ng/mL in the overall population, for female	

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
					subjects, and for male subjects, respectively.	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In study D1050301, a 6-weeks treatment with lurasidone (40 mg and 80mg) led to decrease in the positive and negative symptoms of schizophrenia as well as general psychopathology for both dose groups in adolescents aged 13 to 17 years of age.

The mean PANSS total score at Baseline was 94.0 ± 11.12 for the lurasidone 80 mg/day group, 94.5 ± 10.97 for the lurasidone 40 mg/day group and 92.8 ± 11.08 for the placebo group. Based on MMRM analysis for the primary efficacy endpoint (PANSS total score), the LS mean change (± SE) from Baseline to Week 6 was -18.3 ± 1.60 for the lurasidone 80 mg/day group, -18.6 ± 1.59 for the lurasidone 40 mg/day group, and -10.5 ± 1.59 for the placebo group. This effect corresponds to 19.5% reduction for the lurasidone 80 mg group and 19.7 % for the lurasidone 40 mg group.

In this study, when the overall efficacy of lurasidone 40mg/day and 80 mg/day in adolescents (13-17 years) is compared to adults treated with the same doses, the magnitude of the effect is similar. However, when the results are broken down in age groups, the younger age group consisting of 13-14 years old subjects, demonstrate a somewhat weaker response on the primary endpoint total PANSS, compared to the older age group of 15-17. However, after further analyses, it is concluded that the effect is more or less of the same magnitude in younger and older teenagers.

In study D105302 A flexible dose of (20, 40, 60, 80 mg/day) lurasidone maintained a clinical improvement of symptoms of schizophrenia in adolescent subjects as measured in total PANSS score in subjects with schizophrenia continued from study D1050301. The mean (± SD) change in PANSS total score from DB Baseline in the overall 301-LUR group was -29.2 ± 14.73 at Week 28 and increased to -32.4 ± 14.61 at Week 52 and -34.3 ± 16.32 at Week 104. This effect is considered robust and clinically significant. Other disease outcomes of symptoms of schizophrenia and functionality indicated maintenance of effect. It is recognized that proportion of patients relapsing was somewhat higher in younger teenagers. However, the group was rather small, and it seems reasonable to extrapolate maintenance of effect from adults to the whole group of teenagers (i.e. not only to those who are 15 years and older).

The most common TEAEs included akathisia, somnolence, nausea, vomiting, insomnia, anxiety and schizophrenia. In study D1050302 headache was also commonly reported. The SAEs and treatment discontinuations were mainly in the category of psychiatric disorders. The safety profile based on the provided data, did not differ significantly from what is so far known for the adults.

There was an increase in body weight compared to placebo in the short-term study D1050301 (the changes were not statistically significant). This is expected but should be taken into consideration in the risk-benefit balance.

Cognitive performance was investigated with the Cogstate Computerized Cognitive Test Battery. In Study D1050301 there was no worsening nor improvement of cognitive function in subjects treated with lurasidone compared to placebo. Also, in the long-term study D1050302 no worsening of cognitive function was observed.

Similar to other antipsychotic drugs that bind dopamine D2 receptors, lurasidone has been shown to elevate prolactin levels. In study D105301 change from baseline in prolactin was significant different from placebo. Prolactin levels improved slightly in the long-term study D1050302 but remained elevated.

Sexual development was studied by investigating menstrual cyclicity and Tanner staging. However, no in-depth analysis of the data with regard to what is expected for the studied age population over a two-year period is included, which makes any interpretation of a possible effect on sexual maturation difficult to do. Growth data from the two year extension study D1050302 and analysis of expected changes compared to age-and-gender specific growth charts were later provided, demonstrating that lurasidone did not influence growth in adolescent patients studied in the clinical program.

3.7.2. Balance of benefits and risks

At present there are limited treatment alternatives for adolescents with schizophrenia available. The applicant has presented short- as well as long-term data providing statistically significant evidence for effect of lurasidone 40mg/day and 80 mg/day in the adolescent population 13-17 years old. The safety profile is generally acceptable and appears to be consistent with what is known for the adult population. The benefit/risk balance is considered as positive in adolescents 13-17 years old.

3.7.3. Additional considerations on the benefit-risk balance

The MAH has submitted a claim for a significant clinical benefit in comparison with existing therapies in accordance with Article 14(11) of Regulation (EC) No 726/2004. It is agreed that that Latuda provides a significant clinical benefit over haloperidol based on improved safety in the age group 13-14 years.

3.8. Conclusions

The overall B/R of Lurasidone is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication for the treatment of schizophrenia in adolescent from 13 years and over; as a consequence, sections 4.1, 4.2, 4.7, 4.8, 5.1, 5.2, 5.3 of the SmPC are updated. The Package Leaflet is

updated accordingly. Version 8.1 of the RMP has also been agreed.

In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest excipient guideline.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0359/2019 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and the Package Leaflet.

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 1).

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication for the treatment of schizophrenia in adolescent from 13 years and over; as a consequence, sections 4.1, 4.2, 4.7, 4.8, 5.1, 5.2, 5.3 of the SmPC are updated. The Package Leaflet is updated accordingly. Version 8.1 of the RMP has also been agreed.

In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest excipient guideline.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Summary

Please refer to Scientific Discussion ‘Latuda-H-C-2713-II-Var.29’.