20 November 2014
EMA/748413/2014
Human Medicines Development and Evaluation

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Latuda

International non-proprietary name: lurasidone

Procedure No. EMEA/H/C/002713/P46 001.1

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Introduction

On 14 May, the MAH submitted a completed paediatric study for Latuda® (lurasidone), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

Latuda® was approved for the treatment of schizophrenia in adults in EU in 21st March 2014.

Currently Latuda® has no paediatric indication. The MAH stated that the submitted paediatric study does not influence the benefit risk for Latuda® and that there is no consequential regulatory action.

This is the first of four agreed studies in the Paediatric Investigation Plan (PIP) (EMEA-001230-PIP01-11-M01) for the treatment of schizophrenia with lurasidone.

The studies in the pediatric clinical program are:

- PK study (D1050300): An open-label, multicenter, single and multiple fixed-dose study to evaluate PK, safety, and tolerability of lurasidone in adolescent subjects (6 to <18 years old) with schizophrenia spectrum disorders, bipolar spectrum disorders and other psychotic disorders. This study is now complete.

- Short-term efficacy and safety study (D1050301): A randomized, double-blind, placebo-controlled, multicenter, 6-week, fixed-dose, clinical study to evaluate the efficacy and safety of lurasidone in adolescent subjects (13 to <18 years old) with schizophrenia. This study is on-going.

- Long-term extension study (D1050302): A 2-year, open-label extension to D1050301, multicenter, flexible-dose clinical study to evaluate the long-term safety and efficacy of lurasidone in adolescent subjects (13 to <18 years old) with schizophrenia. This study is on-going.

- Maintenance study (5474): A 26-week, double-blind, active-controlled, multicenter, flexible-dose clinical study to evaluate the maintenance of the efficacy and safety of lurasidone compared with aripiprazole in adolescent subjects (13 to <18 years old) with schizophrenia. This study is planned to begin enrolling in 2015.

According to the updated PIP (October 2013), it should be completed by April 2018.

Additional clarification was requested 14th July, 2014 (see Section 4) and the MAH responses are assessed in the present report (see Section 5), including a new overall conclusion (see Section 6).

1. Scientific discussion

1.1. Information on the pharmaceutical formulation used in the study

There is no paediatric indication for Latuda and no specific paediatric formulation is available. In the paediatric study the following formulations were administered:

20 mg film-coated tablets (Lot Number 69731E0) and 40 mg film-coated tablets (Lot Number 69731F0) of lurasidone hydrochloride (18.5 mg and 37 mg lurasidone, respectively) supplied by Sunovion Pharmaceuticals Inc.

1.2. Clinical aspects

1.3. 1. Introduction

Lurasidone is a new chemical entity belonging to the chemical class of piperidinyl-benzisoxazole derivatives. It has high affinity for dopamine D2- and serotonergic 5HT2A- and 5-HT7-receptors. It also inhibits α2c-adrenergic receptor and α2a-adrenergic receptors and also exhibits some partial agonistic effect at the 5HT1A receptor.

The MAH submitted a final report for:

- D1050300

1.4. 2. Clinical study

D1050300: A PHASE 1 OPEN-LABEL, MULTICENTER, SINGLE AND MULTIPLE-ASCENDING DOSE STUDY TO EVALUATE PHARMACOKINETICS, SAFETY, AND TOLERABILITY OF LURASIDONE IN SUBJECTS 6 TO 17 YEARS OLD WITH SCHIZOPHRENIA SPECTRUM, BIPOLAR SPECTRUM, AUTISTIC SPECTRUM DISORDER, OR OTHER PSYCHIATRIC DISORDERS

- **Description**

This was a multicenter, open-label study to evaluate the PK, safety and tolerability of single and multiple-dose lurasidone tablet administration in children and adolescent subjects 6 to 17 years of age with schizophrenia spectrum, bipolar spectrum, autistic spectrum disorder, or other psychiatric disorders.

- **Methods**

  - Objectives

Primary Objective
The primary objective was to characterize the PK and assess safety and tolerability of single and multiple oral doses of 20, 40, 80, 120, or 160 mg/day lurasidone in subjects 6 to 17 years old with schizophrenia spectrum, bipolar spectrum, autistic spectrum disorder, or other psychiatric disorders.

Secondary Objective
The secondary objective was to characterize the PK for metabolites of lurasidone (ID-14283, ID-14326, ID-11614, ID-20219, and ID-20220) following single and multiple oral doses of 20, 40, 80, 120, or 160 mg/day lurasidone in subjects 6 to 17 years old with schizophrenia spectrum, bipolar spectrum, autistic spectrum disorder, or other psychiatric disorders.

  - Study design

Sequential escalating doses of lurasidone (20, 40, 80, 120, or 160 mg/day) were administered to 4 age groups (6 to 9, 10 to 12, 13 to 15, and 16 to 17 years) of subjects. All subjects received a single dose of lurasidone followed by a 2-day washout period, then once-daily dosing of lurasidone for 7 days (20 mg through 120 mg cohorts) or 9 days (160 mg cohort).

  - Study population /Sample size

Male or female subjects 6 to 17 years of age, inclusive. Approximately 100 subjects were planned to be enrolled to obtain 80 completed subjects in the 4 age groups. To reach 20 completed subjects per age group (i.e., 4 subjects/age group/dose level x 5 doses), clinical sites were to collectively enrol approximately 25 subjects per age group.

Subjects with the following diagnoses were eligible for participation: primary schizophrenia spectrum diagnosis (schizophrenia, schizoaffective, schizophreniform, or psychotic disorder Not Otherwise Specified [NOS]), bipolar spectrum disorder (bipolar I, II, or bipolar NOS), PDD including autistic spectrum disorder (autistic disorder, Asperger's syndrome, or PDD-NOS), ADHD with aggressive behavior (meeting co-morbid diagnostic criteria for Conduct Disorder/Disruptive Behavior Disorders [CD/DBD-NOS]), or Tourette's syndrome, via clinical interview (using MINI-Kid and diagnostic interview and the DSM-IV-TR as a reference). Autistic disorder was also confirmed by the ADI-R.

Subjects were tapered off their psychotropic medications as outpatients with the last dose of these medications taken no later than Day -3, if, in the investigator's opinion, the subject was not at risk for worsening symptoms. Subjects resumed psychiatric medication treatment, per the investigator's discretion after collection of the last PK sample and Columbia-Suicide Severity Rating Scale (C-SSRS) assessment on Day 11 or Day 13.

Subjects who had used of any inhibitor or inducer of cytochrome P450 3A4 (CYP3A4) taken within 28 days prior to drug administration and until discharge on Day 11 (20 to 120 mg cohorts) or Day 13 (160 mg cohort) were excluded. Exceptions (e.g., for grapefruit juice consumption) could be discussed on a case-by-case basis with the medical monitor.

- Treatments

All subjects received a single dose of lurasidone followed by a 2-day washout period, then once-daily dosing of lurasidone for 7 days (20 mg through 120 mg cohorts) or 9 days (160 mg cohort).

For the 120 mg cohort, the following doses were used: Day 1, 80 mg; Days 4 to 5, 80 mg; and Days 6 to 10, 120 mg. For the 160 mg cohort, the following doses were used: Day 1, 80 mg; Days 4 to 5, 80 mg; Days 6 to 7, 120 mg; and Days 8 to 12, 160 mg

Breakfast (minimum of 350 calories) was given 30 minutes prior to the planned dosing time. Study drug was administered to 6- to 12-year-old subjects with approximately 180 mL of room temperature water and to 13- to 17-year-old subjects with approximately 240 mL. No fluid intake was permitted for 2 hours after dose administration; after which fluids were allowed ad libitum. No food was allowed for at least 4 hours after dosing. Total daily calorie intake was not to exceed 3000 calories.

- Analytical methods

Serum samples were measured for the concentrations of lurasidone and its 3 metabolites (ID-14283, ID 14326, and ID-11614) using a validated LC-MS/MS method (Covance report number 8249-822). Serum samples were also analyzed for the concentrations of the other 2 metabolites (ID 20219 and ID-20220) using a separate validated LC-MS/MS method (Covance report number 7589-156).

The linear range for lurasidone was 0.100 to 100 ng/mL with the lower limit of quantitation (LLOQ) of 0.100 ng/mL. The linear range for each of metabolites ID-14283, ID-14326, and ID-11614 was 0.0500 to 50.0 ng/mL with the LLOQ of 0.0500 ng/mL. The linear range for each of the metabolites ID-20219 and ID-20220 was 0.500 to 500 ng/mL with the LLOQ of 0.500 ng/mL.

In this sample analysis study, for the measurement of lurasidone and its metabolites ID-14283, ID 14326, and ID-11614 concentrations, overall assay precision (relative standard deviation [RSD%] of quality control samples) was in the range of 4.9 to 9.4%, and accuracy (RE%) was in the range of -5.5 to 1.5%; for the measurement of other 2 metabolites ID-20219 and ID-20220 concentrations, overall assay precision (RSD% of quality control samples) was 4.3 to 8.6%, and accuracy (RE%) was -1.1 to 2.4%.

Assessor´s comment:
It is stated that the plasma concentration were determined with validated methods, however bioanalytical reports are missing. The pre-study validation and the within study validation (analysis of

the study samples) reports should be provided and the Guideline on the bioanalytical method validation (EMEA/CHMP/EWP/192217/2009) should be fulfilled.

- Outcomes/endpoints

Pharmacokinetic assessments for serum lurasidone and its metabolite concentrations (ID-4283, ID-14326, ID-11614, ID-20219, and ID-20220) included the following: 48 hour serial blood sampling following Day 1 dose administration and 24 hour serial blood sampling following Day 10 (or Day 12) dose administration. Pharmacokinetic parameters were derived using non-compartmental methods.

Adverse event reporting began at the time of signed informed consent and continued until study completion (follow-up). All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Out of range clinical laboratory, 12-lead ECG, vital sign, or physical examination findings considered clinically significant by the investigator were reported as an AE as outlined below. Spontaneous AE reporting, including extrapyramidal side effects or symptoms (EPS) assessments was reported.

- Statistical Methods

Pharmacokinetics: Descriptive statistics were performed to summarize the data by dose level and by age group in tabular and graphical formats. Lurasidone Cmax, AUClast, and AUC(0–∞) (Day 1); and Cmax and AUC0–24 (Day 10 or Day 12) were considered the primary PK parameters.

Safety: Safety data were listed and summarized descriptively by dose cohort/level and age group in tabular format. Change from baseline was calculated for selected endpoints (clinical laboratory data, vital signs, ECGs, BAS, SAS, AIMS, and CGI-S).

➢ **Results**

- Recruitment/ Number analysed

A total of 105 subjects (6 to 9 years, 20 subjects; 10 to 12 years, 29 subjects; 13 to 15 years, 31 subjects; and 16 to 17 years, 25 subjects) were enrolled into the study and included in the safety population (i.e., received at least 1 dose of study drug), and 102 subjects were included in the PK population.

- Baseline data

A total of 68 male (64.8%) and 37 female (35.2%) subjects were included in the safety population of the study. The ratio of male to female subjects was comparable between the dose cohorts. Mean age was comparable between dose cohorts and was 12.7 years.

Table 1. Current Primary Psychiatric History by Dose Cohort - All Age Groups (6-17 Years) Combined (Safety Population).

Reported Term[a]	Dose Cohort - All Age Groups (6-17 Years) Combined Number of Subjects, n (%)					All Subjects N=105
	20 mg N=20	40 mg N=25	80 mg N=19	120 mg N=25	160 mg N=16	
ADHD with Conduct Disorder/DBD, NOS	16 (80.0)	16 (64.0)	12 (63.2)	21 (84.0)	13 (81.3)	78 (74.3)
Bipolar Spectrum Disorder, Bipolar I	2 (10.0)	6 (24.0)	6 (31.6)	2 (8.0)	1 (6.3)	17 (16.2)
Bipolar Spectrum Disorder, NOS	1 (5.0)	1 (4.0)	0	0	0	2 (1.9)
PDD/ASD, Autistic Disorder	1 (5.0)	0	0	0	0	1 (1.0)
Schizophrenia Spectrum Diagnosis Schizoaffective	0	1 (4.0)	0	0	0	1 (1.0)
Schizophrenia Spectrum Diagnosis Schizophrenia	0	0	1 (5.3)	1 (4.0)	2 (12.5)	4 (3.8)
Tourette's Syndrome	0	1 (4.0)	0	1 (4.0)	0	2 (1.9)

Abbreviations: ADHD = attention-deficit hyperactivity disorder; ADI-R = Autism Diagnostic Interview, Revised; ASD = autistic spectrum disorder; DBD = Disruptive Behavior Disorder; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, 4th edition Text Revision; MINI-Kid = Mini-International Neuropsychiatric Interview-Kid; N = number of subjects enrolled; n = number of subjects in category; NOS = Not Otherwise Specified; PDD = pervasive developmental disorder.
Notes: Subjects are counted only once per reported term.
Note: Psychiatric disorders are coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 15.0.
[a] Diagnosis was via clinical interview using MINI-Kid and diagnostic interview, and the DSM-IV-TR as a reference. Autistic disorder was confirmed by the ADI-R.

- Efficacy results

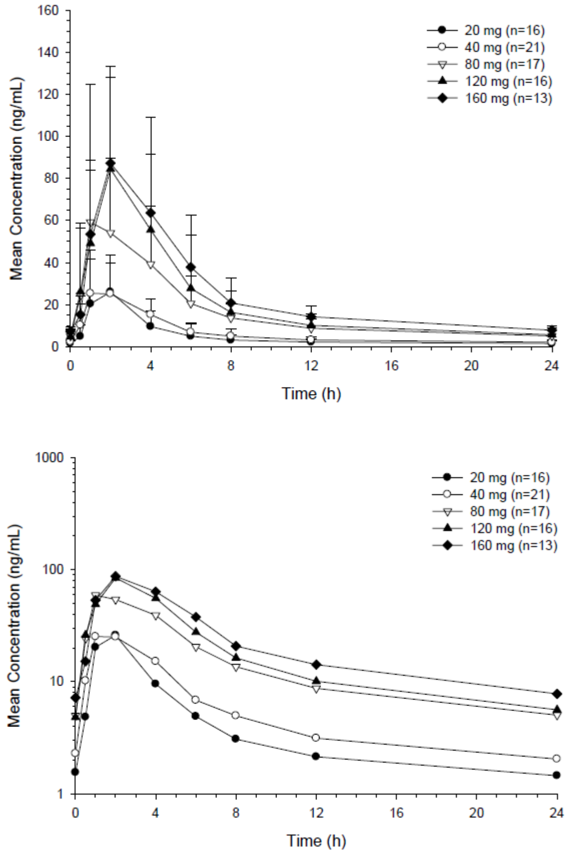
This was an open-label PK study and thus no efficacy results were obtained. Pharmacokinetics and tolerability were evaluated. There were 102 subjects in the PK analysis set. At day 1, seven subjects were excluded and at last day of dosing 19 were excluded from PK parameters. Most common reasons for exclusion were vomiting or early termination from the study.

Assessor´s comment:
The reasons for exclusion are acceptable in all cases except for subject 300013355. For this subject "An abnormal PK profile on day 10" was given as reason for exclusion. This is not acceptable and the MAH needs to discuss the PK of this subject. No profile is submitted for this subject and it is important to understand if it was unusually high or low exposure and if so the possible underlying reasons.

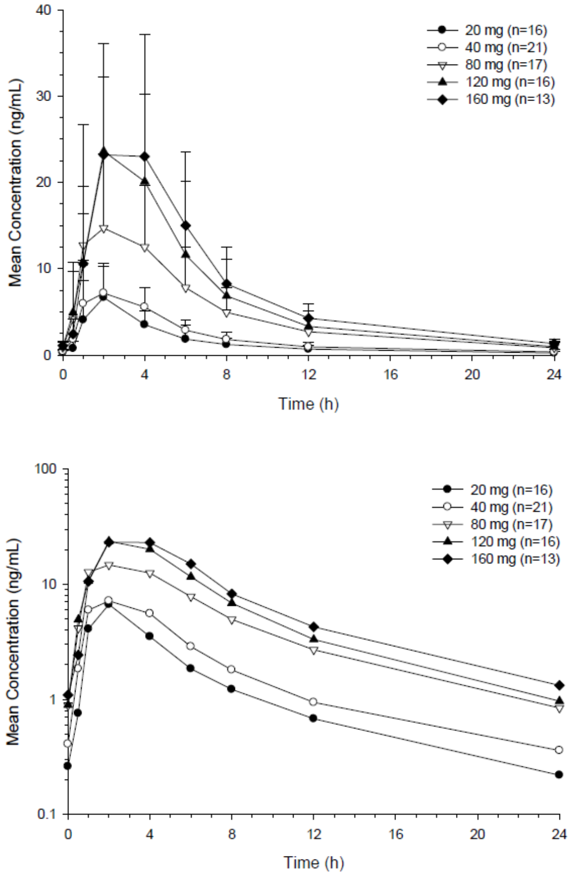
It is noted that a majority of study population had a diagnosis of ADHD with conduct disorder. However, in the adult population there was no difference in exposure between healthy volunteers compared to schizophrenic patients.

In this study PK parameters were determined for lurasidone and its metabolites, ID-14283 (minor active), ID-14326 (minor active), ID-11614 (inactive), ID-20219 (major inactive), and ID-20220 (major inactive). Plasma profiles of lurasidone and one of its active metabolites (ID-14283) are presented in Figure 1 below. In Appendix 1 the exposure of lurasidone at last day of dosing in each dose and age group is given.

Figure 1. Mean (SD) Lurasidone (left) ID-14283 (right) Serum Concentration-time Profiles on Day 10 (or Day 12 for the 160 mg cohort) on Linear and Semi-logarithmic Scales



Lurasidone



ID-14283

Table 2. Summary of Lurasidone Key Pharmacokinetics Parameters for All Age Groups on Day 10 (or Day 12 for 160 mg)

Dose	Statistic	AUC_{0-24} (ng·h/mL)	C_{max} (ng/mL)	t_{max} (h)	CL/F (L/h)	$RAUC_{0-24}$	RC_{max}
20 mg	n	16	16	16	16	16	16
	Mean	115	30.0	2.25	256	1.66	1.40
	SD	72.2	18.0	1.34	172	0.575	0.789
	Min	28.4	5.90	1.00	78.8	0.867	0.378
	Median	96.3	26.2	2.00	208	1.55	1.25
	Max	254	71.7	6.00	705	3.02	3.56
40 mg	n	21	21	21	21	20	20
	Mean	154	36.2	1.64	323	1.30	1.16
	SD	67.4	17.5	0.94	173	0.275	0.554
	Min	47.1	8.58	0.50	141	0.732	0.351
	Median	135	38.9	1.00	297	1.35	1.08
	Max	284	71.7	4.00	849	1.92	2.85
80 mg	n	17	17	17	17	15	15
	Mean	387	80.0	2.24	262	1.37	1.17
	SD	194	59.6	1.56	144	0.354	0.632
	Min	117	15.2	1.00	86.1	0.713	0.497
	Median	348	71.0	2.00	230	1.38	1.04
	Max	929	265	6.00	684	2.16	2.58
120 mg	n	16	16	16	16	ND	ND
	Mean	494	94.2	2.31	315	ND	ND
	SD	271	46.6	1.08	182	ND	ND
	Min	143	31.1	1.00	98.1	ND	ND
	Median	416	86.7	2.00	289	ND	ND
	Max	1220	205	4.00	842	ND	ND
160 mg	n	13	13	13	13	ND	ND
	Mean	590	99.7	2.31	313	ND	ND
	SD	227	44.3	1.03	126	ND	ND
	Min	307	41.3	1.00	161	ND	ND
	Median	546	91.1	2.00	293	ND	ND
	Max	994	182	4.00	522	ND	ND

Abbreviations: SD = standard deviation; Min = minimum; Max = maximum; ND = not determined.

Following the single lurasidone dose on Day 1, mean PK exposure (AUC0-∞, AUClast, and Cmax) for all age groups combined increased with dose from 20 to 80 mg. Median tmax was independent of dose and was observed at 2 hours post-dose. Mean t½ was similar and ranged from 16.2 to 21.3 hours across all 3 dose groups. Mean CL/F and Vz/F values of lurasidone were similar across all dose groups and ranged from 317 to 346 L/h and 6940 to 8700 L for CL/F and Vz/F, respectively.

Following multiple lurasidone doses on last day of dosing, mean PK exposure (AUC0-24 and Cmax) for all age groups combined increased with dose from 20 to 160 mg. Median tmax appeared independent of dose and was observed between 1 and 2 hours across the 5 dose groups. Mean CL/F values of lurasidone were similar across all dose groups and ranged from 256 to 323 L/h. Some accumulation was observed following 10 days of dosing. Mean RAUC0-24 and RCmax appeared to be independent of dose over the dose range of 20 to 80 mg and ranged from 1.30 to 1.66 and from 1.16 to 1.40, respectively (Table 2).

As indicated in Table 3 by the point estimates and 95% CIs of the slope estimates, AUC0-24 of lurasidone on Day 10 or 12 increased approximately dose proportionally over the dose range of 20 to 160 mg while Cmax of lurasidone increased less than dose proportionally.

Table 3. Assessment of Dose Proportionality for Lurasidone Serum Pharmacokinetic Parameters Following Multiple Doses on Day 10 (or Day 12)

Parameter[a] (Units)	n	Slope			Coefficient of Determination
		Estimate	SE	95% CI	
AUC_{0-24} (ng·h/mL)	83	0.90	0.08	(0.74, 1.06)	0.6213
C_{max} (ng/mL)	83	0.70	0.09	(0.52, 0.87)	0.4267

Abbreviations: SE = standard error; CI = confidence interval.
[a] Combined for Day 10 from the 20 to 120 mg cohorts and Day 12 from the 160 mg cohort.

The effects of age, weight, and BSA on lurasidone PK parameters were evaluated graphically. Individual lurasidone dose-normalized Cmax, AUClast, and AUC0-∞ on Day 1, and dose-normalized Cmax and AUC0-24 on Day 10 or 12 appeared to decrease with the increase of age (from 6 to 17 years), weight (from 19.4 to 86 kg), or BSA (from 0.79 to 2.09 m2). Consistently, individual lurasidone CL/F on Day 1 and Day 10 or 12 appeared to increase with the increase of age (from 6 to 17 years), weight (from 19.4 to 86 kg), or BSA (from 0.79 to 2.09 m2). Figures 2 and 3 shows AUC(0-24) and Cmax vs. age on last day of dosing, respectively. In Figures 4 and 5 the CL/F vs. age and body weight are given. No further statistical analysis was planned or performed for the relationship between age, weight, or BSA and lurasidone PK parameters due to the exploratory nature of this study.

Figure 2. Individual Dose-normalized AUC0-24 for Lurasidone on Day 10 (or Day 12 for the 160 mg cohort) versus Age with a Regression Line

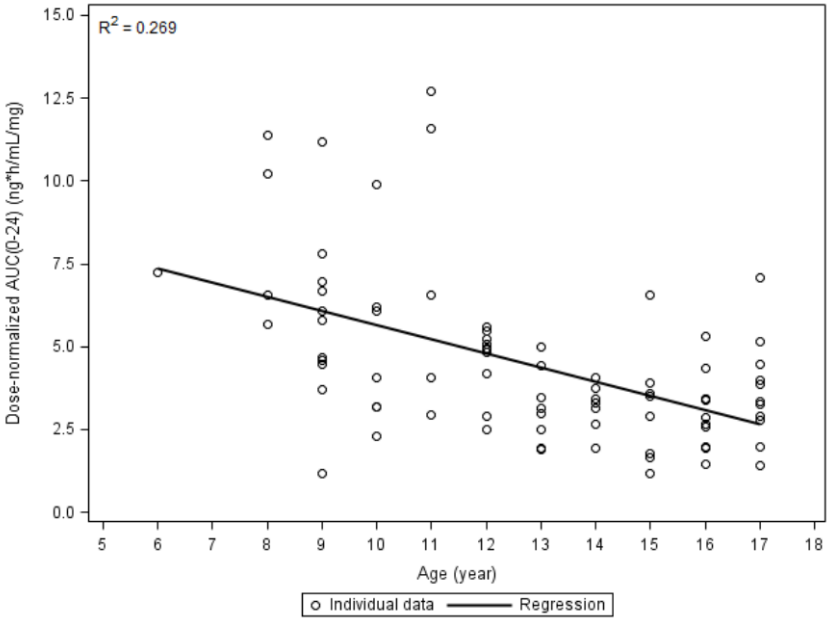


Figure 3. Individual Dose-normalized Cmax for Lurasidone on Day 10 (or Day 12 for the 160 mg cohort) versus Age with a Regression Line

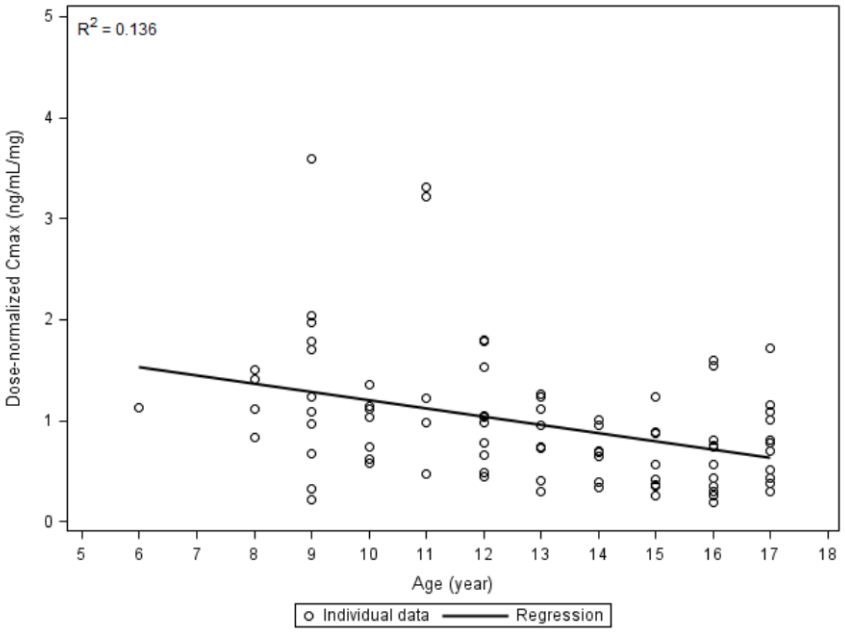


Figure 4. Individual CL/F for Lurasidone on Day 10 (or Day 12 for the 160 mg cohort) versus Age with a Regression Line

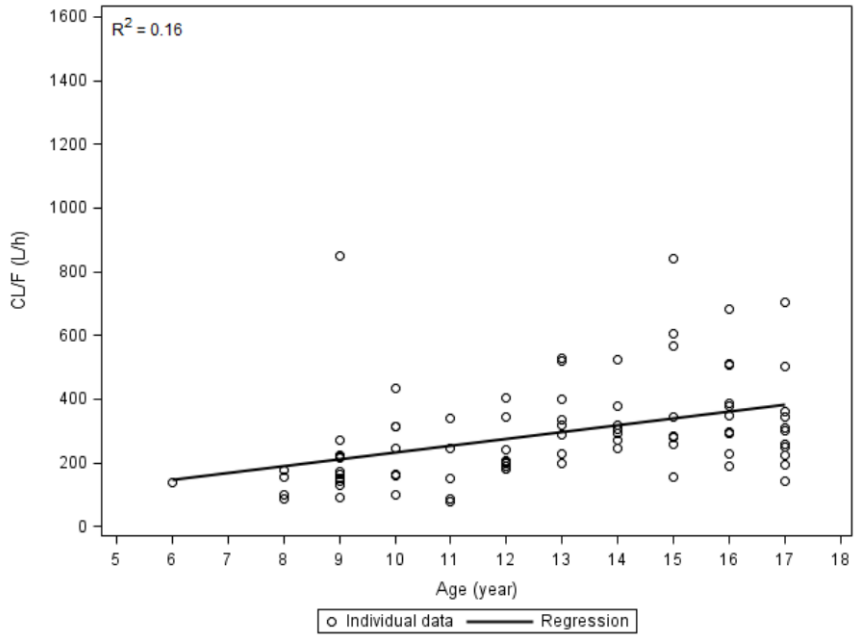
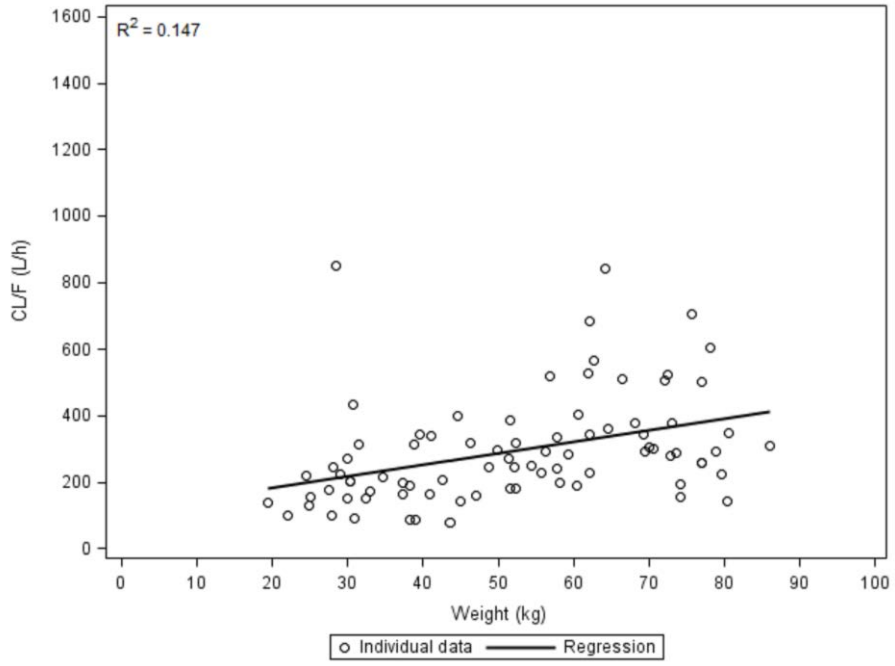


Figure 5. Individual CL/F for Lurasidone on Day 10 (or Day 12 for the 160 mg cohort) versus Weight with a Regression Line



Adult exposure

The MAH states that the observed lurasidone paediatric PK exposures (Cmax and AUC0-24) following multiple dose administration, in subjects age 6 to 17 years, across the daily dose range studied (20 to 160 mg) were generally similar to adult exposures previously observed at steady state (source: M1050005). However, the MAH did not supply the adult data referred to.

Assessor´s comment:
Several metabolites were determined and PK parameters were calculated. The active metabolite ID-14283 contributed to ca. 30% of parent exposure at steady state. This is similar to the found metabolite ratio found in adult population. The importance of the other metabolites has been shown to

be minor (Latuda EPAR – Public Assessment Report, Report date 08 April 2014) and is therefore not further assessed.

For lurasidone, the AUC(0-24) at last day of dosing increased approximately in proportion to dose while Cmax increased less than dose proportionally. There was no unexpected accumulation of lurasidone after multiple dosing.

It is agreed that CL/F appears to increase with increasing age and weight in the paediatric population. However, to better utilize the full data, PK modelling is encouraged for future submissions. This may facilitate assessment and also enable extrapolation of data.

The MAH states that the exposure is in general similar between paediatrics and adults. However, no data was presented to support this statement. The MAH should compile relevant exposure data and justify the choice of adult data used for comparison with paediatric data. In addition, if a difference in exposure is established between adults and paediatrics the MAH should aim to explain the possible underlying differences.

- Safety results

In Study D1050300, the most frequently observed AEs (≥10%) across the dose range in pediatric subjects were somnolence (42%), sedation (18%), nausea (17%), and vomiting (15%). The incidence of movement disorder AEs was 2.0% for akathisia and 1.0% for Parkinsonism. This pattern was consistent across all age groups.

All subjects in the 120 mg dose cohort in the 6 to 9 years age group experienced mild to moderate sedation or somnolence. The Cohort Review Team (CRT) therefore recommended not to dose escalate to 160 mg, despite not formally meeting the stopping rule, due to the negative impact this AE may have had on daily function.

The frequencies of treatment-emergent adverse events (TEAEs) were dose-related with the highest overall adverse event frequency observed in the 160 mg dose cohort. TEAEs were reported for 4 subjects (4/20, 20.0%) in the 20 mg cohort, 17 subjects (17/25, 68.0%) in the 40 mg cohort, 17 subjects (17/19, 89.5%) in the 80 mg cohort, 24 subjects (24/25, 96.0%) in the 120 mg cohort (includes 80 and 120 mg doses combined), and 16 subjects (16/16, 100%) in the 160 mg cohort (includes 80, 120, and 160 mg doses combined). In the 120 and 160 mg dosing schemes, in most cases, somnolence and sedation were initially observed at the 80 mg dose administered on Days 1, 4, and 5 of those schemes, but continued to be observed throughout administration of the 120 mg or 120 mg/160 mg doses. Most TEAEs of nausea, upper abdominal pain, and vomiting reported at the 120 and 160 mg dosing schemes began during the 80 mg dose administered on Days 1, 4, and 5.

Across all age groups and dose cohorts/levels, 5 of 105 subjects (4.8%) experienced TEAEs assessed by the investigator as severe. All other TEAEs were assessed as mild (22/105, 21.0%) or moderate (51/105, 48.6%) in severity.

Most TEAEs resolved for the majority of subjects, while 5 subjects (all TEAEs of somnolence) recovered with sequelae and 1 subject (TEAE of streptococcal pharyngitis) was recovering at the time of reporting. In the 5 subjects with TEAEs of somnolence, the duration of somnolence lasted between a few hours to 1 day after the event onset for 4 subjects. In the remaining subject, there was 1 TEAE of somnolence that lasted a maximum of 2 days.

A total of 2 serious adverse events (SAEs), parkinsonism (subject withdrawn due to SAE) and dystonia (with hospitalization, subject withdrawn due to sponsor decision), were reported and were assessed by the investigators as related to study drug.
Nine subjects were withdrawn from the study due to TEAEs: 1 subject with parkinsonism (SAE), somnolence (2 subjects), blurred vision (1 subject), dystonia (1 subject), vomiting (3 subjects), and akathisia (1 subject); all events were assessed by the investigators as possibly, probably, or related to study drug. There were no deaths during the study.

Of the 9 subjects aged 6 to 17 years who discontinued due to an AE, the majority (n=6) were treated with lurasidone doses ≥80 mg/day. The remaining 3 subjects discontinued at a dose of 40 mg/day. Six subjects aged between 6 to 12 years discontinued due to AEs (2 subjects at 40 mg, 3 subjects at 80

mg, and 1 subject at 120 mg [dose at onset]) and 3 subjects (1 at 40 mg and 2 at 80 mg [dose at onset]) aged between 13 and 17 years.
At screening, three (2.9 %) subjects reported a history of suicidal behavior and 10 (9.5 %)reported a history of suicidal ideation at the Columbia-Suicide Severity Rating Scale lifetime assessment, but no suicidality or suicidal ideation was detected during the study in any subject.
No clinically significant changes in laboratory tests (with the exception of prolactin elevation), vital sign measurements, or electrocardiogram findings were observed.

Assessors comment:
The types of the most frequently observed AEs in study D1050300 were similar to those reported in adults. However, across the dose range in pediatric subjects, the frequencies for some AEs were higher than has been reported in previous short-term placebo-controlled studies in adults (including somnolence, sedation, nausea, vomiting). There were no new or unexpected AEs reported. The lowest doses 20 mg/day and 40 mg/day were better tolerated than the 80 mg dose. Of the 9 subjects aged 6-17 years who discontinued due to an AE, the majority (n=6) were treated with lurasidone doses ≥ 80 mg/day. In the lowest age group 6-9 years, tolerability issues (moderate or severe vomiting, sedation and somnolence) were seen with the 120 mg/day dose and doses greater than 120 mg were therefore not evaluated in this age group. Taking these results for the lowest age group into account, it might be necessary to consider a lower maximum dose for younger children in the pediatric population than in adults.

2. Rapporteur's initial overall conclusion and recommendation

➢ Overall conclusion

The present study includes rich PK data in the paediatric population (6-17 years), but an adequate comparison to exposure in adults has not been presented. The MAH should compile and provide relevant adult exposure data and further compare with exposure in the paediatric population. The PIP is planned to be fulfilled in 2018, meanwhile it is considered relevant to update SmPC section 5.2 with paediatric exposure data.

➢ Recommendation

Before a final assessment of the study the MAH should respond to list of additional clarification in section IV. The MAH should propose a SmPC wording (Section 5.2) after a comparison to adult exposure data has been performed. An update of SmPC section 5.2 (and standard text in section 4.2 according to SmPC guideline) to include the paediatric data is recommended as a variation after completion of this procedure.

☐ **Fulfilled –**

☒ **Not fulfilled:**
Based on the data submitted, the MAH should provide additional clarifications as part of this procedure (see section 4 "Additional clarifications requested").

3. ADDITIONAL CLARIFICATIONS REQUESTED

1. It is stated that the plasma concentration were determined with validated methods, however bioanalytical reports are missing. The pre-study validation and the within study validation (analysis of the study samples) reports should be provided and the Guideline on the bioanalytical method validation (EMEA/CHMP/EWP/192217/2009) should be fulfilled.

2. The reasons for exclusion in the PK data set are acceptable in all cases except for subject 300013355. For this subject “An abnormal PK profile on day 10” was given as reason for exclusion. This is not acceptable and the MAH needs to discuss the PK of this subject or motivate whether the profile is implausible. It is important to understand if the exposure was unusually high or low and if so the possible underlying mechanistic reason.

3. The MAH states that the exposure is in general similar between paediatrics and adults. However, no data was presented to support this statement. The MAH should compile relevant adult exposure data and justify the choice of adult data used for comparison. In addition, if a difference in exposure is established between adult and paediatric population the MAH should aim to explain the possible underlying differences.

4. Based on the response on Question 3, a SmPC text in Section 5.2 regarding exposure in the paediatric population should be suggested by MAH.

The following timetable will apply:

Submission date	Start date	Preliminary Rapporteur's Assessment Report	Comments from CHMP Members	Final Rapporteur's Assessment Report	Adoption of Conclusions
10/09/2014	21/09/2014	21/10/2014	05/11/2014	10/11/2014	20/11/2014

4. Assessment of the responses to the List of Questions

Question 1
It is stated that the plasma concentration were determined with validated methods, however bioanalytical reports are missing. The pre-study validation and the within study validation (analysis of the study samples) reports should be provided and the Guideline on the bioanalytical method validation (EMEA/CHMP/EWP/192217/2009) should be fulfilled.

RESPONSE
The prestudy validation and within study validation sample analysis reports used to support Study D1050300 are attached (refer to Validation Report 8249-822, Validation Report 8249-822 Addendum I and Addendum II, Validation Report 7589-156, Validation Report 7589-156 Addendum I and Addendum II, and Bioanalytical Sample Analysis Report 8249-944).

The objective of Study 8249-822 was to validate a method for the determination of lurasidone (SM-13496) and its metabolites (ID-14283, ID-14326, and ID-11614) in human serum by high-performance liquid chromatography with tandem mass spectrometry detection. The sample extraction procedure and chromatographic conditions were very similar to those employed in the previously validated method Report 8200-092. The major modification from the 8200-092 method was the calibration curve range for each analyte. Reports 8249-822 Addendum I and II included extension of the stability period of the compounds in frozen matrix.

The objective of Study 7589-156 was to validate a method for the determination of lurasidone metabolites (ID-20219 and ID-20220) in human serum by high-performance liquid chromatography with tandem mass spectrometry detection. Validation Report 7589-156 Addendum I and II included extension of the stability period of the compounds in frozen matrix.

Analysis Report 8249-944 presented the analysis of samples from Study D1050300 for lurasidone and its metabolites ID-14283, ID-14326 and ID 11614 using the method validated in 8249-822 and for metabolites ID-20219 and ID-20220 using the method validated in 7589-156. A total of 1792 serum samples were successfully analyzed for lurasidone, ID-14283, ID-14326, ID-11614, ID-20219, and ID-20220. Incurred sample reproducibility (ISR) was evaluated. The ISR results were acceptable (within 20.0% of each other) for all analyzed with the respective pass rate for lurasidone (96%), ID-14283 (94%), ID-14326 (89%), ID-11614 (96%), ID-20219 (99%), and ID-20220 (98%).

All study samples were analyzed within the known stability period of 744 days for SM-13496, ID-14283, ID-14326, and ID-11614 and 1373 days for ID-20219 and ID-20220 when stored at - 10°C to -30°C.

The method validation and sample analysis reports are considered adequate to fulfill the criteria required by the guideline on bioanalytical method validation (1) and are presented for Agency review.

Assessor's comment:

The bioanalytical pre-study validation and within-study validation reports were submitted and performance of the analytical method was satisfactory.
Issue resolved

Question 2
The reasons for exclusion in the PK data set are acceptable in all cases except for subject 300013355. For this subject "An abnormal PK profile on day 10" was given as reason for exclusion. This is not acceptable and the MAH needs to discuss the PK of this subject or motivate whether the profile is implausible. It is important to understand if the exposure was unusually high or low and if so the possible underlying mechanistic reason.

RESPONSE
Subject 300013355 was excluded from the pharmacokinetic data set because lurasidone exposure on Day 10 was unusually low, and this was most likely due to noncompliance with lurasidone

administration. To respond to this question, the Marketing Authorisation Holder (MAH) has reviewed the study design, demographic data, dosing records, and sample analyses records of Subject 300013355, who was scheduled to receive lurasidone at a dose of 80mg. In addition to these other reviews, the plasma concentration-time profiles on Day 1 and Day 10 for Subject 300013355 were compared with the mean plasma concentration-time profiles for all subjects in the 80 mg lurasidone cohort. Following the review of this information, the MAH has concluded that the most probable reason for the difference in the pharmacokinetic profile on Day 1 and Day 10 in this subject is due to noncompliance with study medication during Days 4 to 10.

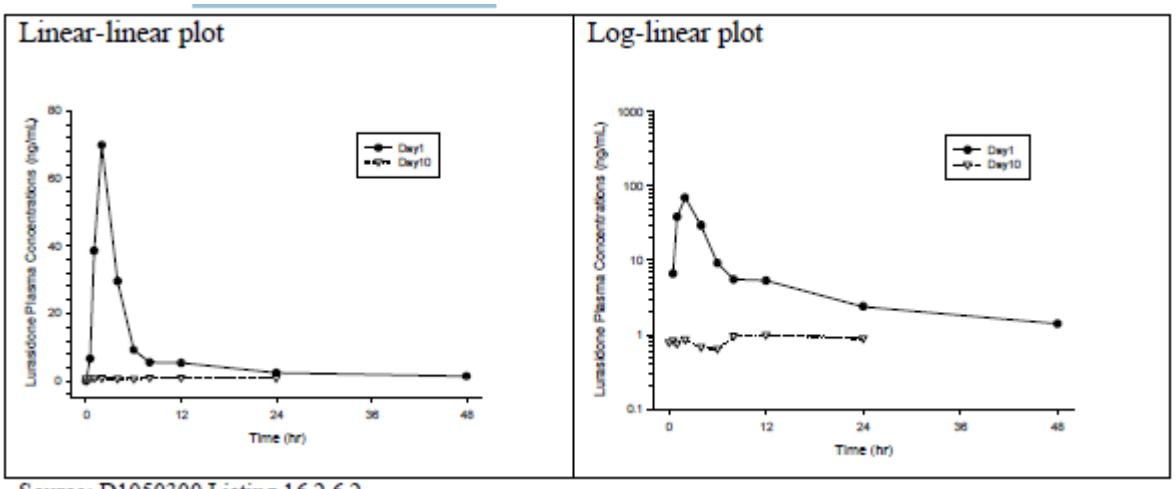
In this study, it was planned that all subjects would receive a single dose of lurasidone on Day 1 followed by a 2-day washout period (Days 2 and 3), then once-daily dosing of lurasidone for 7 days (Days 4 to 10). Blood samples for pharmacokinetic analysis were collected at predose and at 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 hours postdose on Day 1, as well as at predose and at 0.5, 1, 2, 4, 6, 8, 12, and 24 hours postdose on Day 10.

The subject with an abnormal pharmacokinetic profile on Day 10 (Subject 300013355) was a 13-year-old White male diagnosed with attention-deficit hyperactivity disorder (ADHD) with conduct disorder (refer to Study D1050300, Listing 16.2.4.5), who weighed 63.6 kg with a height of 165 cm at Screening (Listing 16.2.4.2).

Subject 300013355 reported taking study medication on Day 1 and Days 4 to 10 (Listing 16.2.5.1), generally within half an hour of eating breakfast (Listing 16.2.5.2), and returned only 1 of the 9 tablets that were provided (Listing 16.2.5.1). With the exception of 2 administrations of lorazepam for the treatment of anxiety (0.5 mg on 2 occasions on Day 1 and 1 mg on Day 4), the subject did not receive any concomitant medications (Listing 16.2.4.12). The pharmacokinetic blood sample collections were also collected at the appropriately nominated time (Listing 16.2.6.1), and concentrations from Day 10 blood samples were verified in ISR (see Analysis Report 8249-944).

On Day 1, the pharmacokinetic data for Subject 300013355 were similar to the mean data for the 80 mg Cohort. However, an analysis of the plasma concentration levels found that Subject 300013355 had low plasma concentrations of lurasidone on Day 10 (refer to Listing 16.2.6.2), and was subsequently excluded from the multiple-dose pharmacokinetic analyses on Day 10. To address this question, the MAH has plotted the plasma concentration-time profile for Subject 300013355 (as shown in Figure 1), and calculated individual pharmacokinetic parameters for this subject (as shown in Table 1).

Figure 1: Lurasidone Plasma Concentration-time Profiles for Subject 300013355 Following Single (Day 1) and Multiple-Dose (Day 10) Administration of 80 mg Lurasidone in Study



Source: D1050300 Listing 16.2.6.2.

Table 1: Comparison of Pharmacokinetic Data for Subject 300013355 With the Mean Data for the 80 mg Cohort in D1050300

	Day 1			
	C_{max} (ng/mL)	t_{max} (a) (hr)	AUC_{∞} (ng·hr/mL)	CL/F (L/hr)
Subject 300013355	69.8	2	359	223
Group mean	68.2	2.16	328	324
	Day 10			
	C_{max} (ng/mL)	t_{max} (a) (hr)	AUC_{24} (ng·hr/mL)	CL/F (L/hr)
Subject 300013355	1	12	21.3	3748
Group mean	80.0	2.24	387	262

Source: D1050300 Table 13, Table 14, Listing 16.2.6.8, and calculated from Listing 16.2.6.2 using WinNonlin Version 6.3.
AUC_{∞}=area under the serum concentration-time curve from time 0 to infinity, AUC_{24}=area under the serum concentration-time curve from the time 0 to 24 hours, C_{max}=maximum observed serum concentration, CL/F=apparent clearance after extravascular administration, t_{max}=time to reach C_{max}.
(a) Median.

As shown in Figure 1, the subject had markedly lower lurasidone plasma concentration on Day 10 versus Day 1. Table 1 indicates that although the Day 1 pharmacokinetic data for Subject 300013355 were similar to the mean data for the 80 mg Cohort, the Day 10 data were markedly lower.

Given that the plasma concentrations and pharmacokinetic profile of lurasidone on Day 1 were aligned with the group mean, the most likely reason for the low concentrations of lurasidone observed in this subject on Day 10 is noncompliance in taking study medication while the subject was an outpatient between Days 4 to 9, as well as on Day 10. Although the subject exhibited low concentrations of lurasidone on Day 10 (as shown in Figure 1), it could be expected that on Day 10 there would be residual systemic concentrations from dosing on Day 1 as lurasidone exhibits multi-compartmental pharmacokinetics with a long terminal elimination half-life (184 hours in adults). Therefore it would seem likely that the low concentrations of lurasidone observed on Day 10 for this subject are due to remaining concentrations from the Day 1 dose, and subsequent noncompliance with missed medication on Days 4 to 10.

Based on the overall assessment, subject 300013355 was excluded from the pharmacokinetic analyses due to noncompliance.

Assessor's comment:

The MAHs explanation for the abnormal PK profile in subject 300013355 was satisfactory and subsequent exclusion from PK analysis is acceptable.
Issue resolved

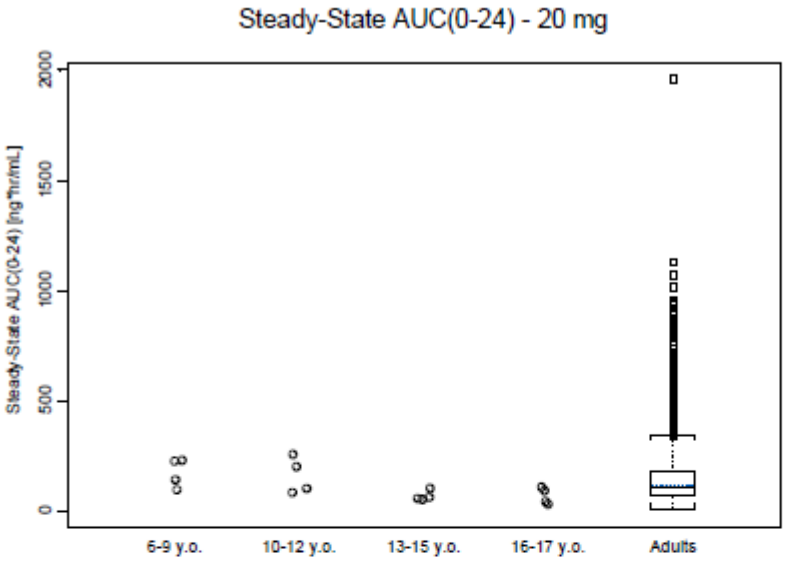
Question 3
The MAH states that the exposure is in general similar between paediatrics and adults. However, no data was presented to support this statement. The MAH should compile relevant adult exposure data and justify the choice of adult data used for comparison. In addition, if a difference in exposure is established between adult and paediatric population the MAH should aim to explain the possible underlying differences.

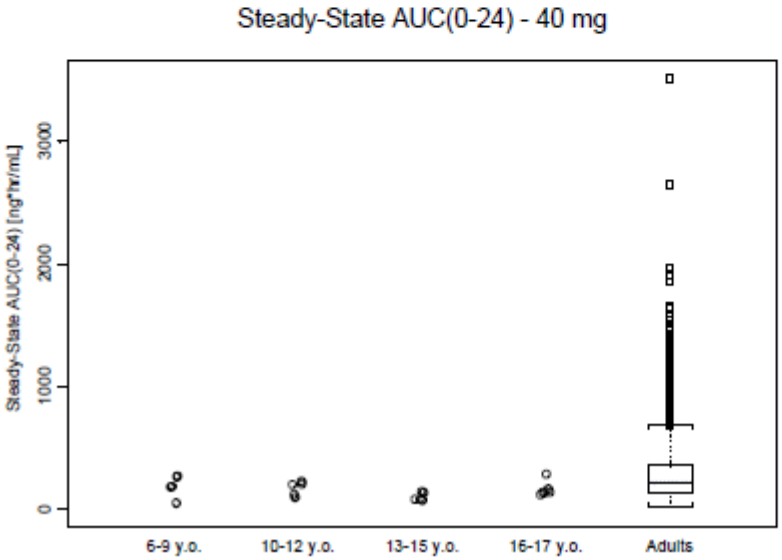
RESPONSE
The pharmacokinetic exposure data to lurasidone in paediatric subjects generated from Study D1050300 was compared with pharmacokinetic exposure data generated from an adult population pharmacokinetic model (M1050011). This population model was developed using subjects with schizophrenia, subjects with bipolar depression, and healthy volunteers. This is an update to the previously submitted population pharmacokinetic model (Report M1050005) to include subjects with bipolar depression. This updated adult pharmacokinetic population model found that the pharmacokinetics of lurasidone was not affected by disease type as shown by a similar

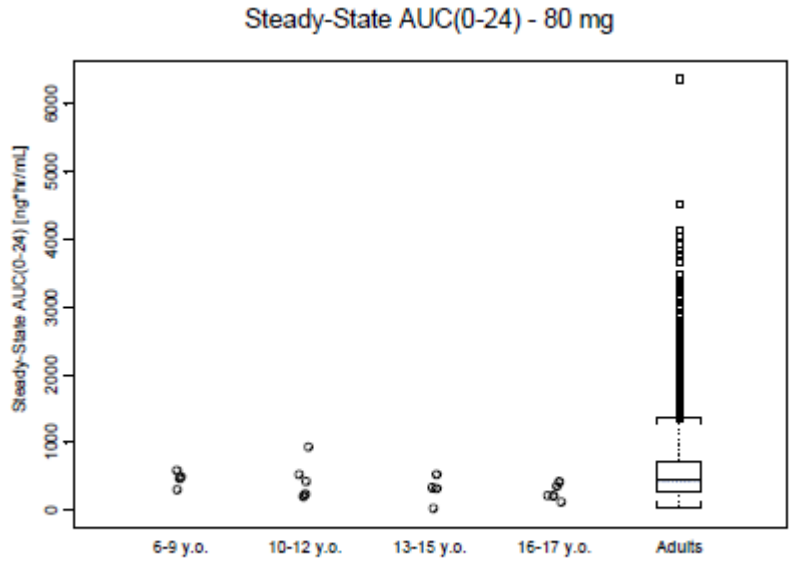
pharmacokinetic profile in healthy volunteers, as well as patients with schizophrenia or bipolar depression (M1050011).

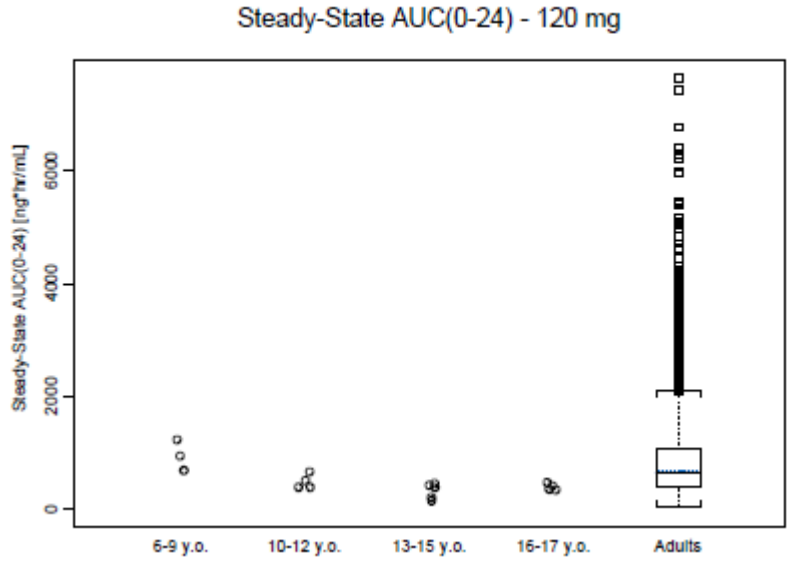
The results of this comparison of lurasidone in paediatric subjects generated from Study D1050300 with the adult population pharmacokinetic model are shown in Figure 2 for area under the serum concentration-time curve at steady state (AUCss) and Figure 3 for Cmax. In these figures, pediatric data are represented by open circles, and the adult data (based on simulations from 5000 adult subjects using the adult population pharmacokinetic model), are represented using box plots. The solid line in the center of the box represents the median of the simulated adult values, while the bottom and top of the box represent the 25th and 75th percentiles, respectively. Simulated values outside the span of the lower and upper whiskers (outliers) are represented by open squares.

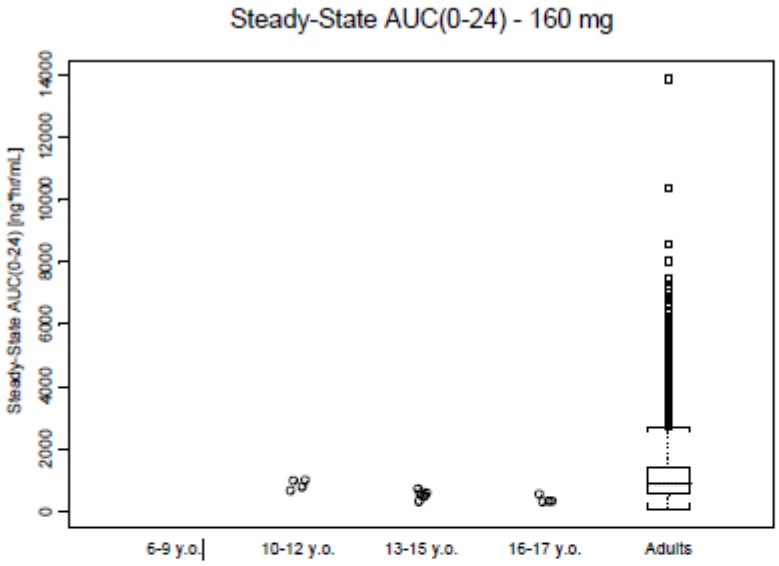
Figure 2: Lurasidone Exposure (AUCss) in Pediatric Subjects (D1050300) Compared With Simulated Exposure (AUCss) in Adult Subjects (100% Outliers)





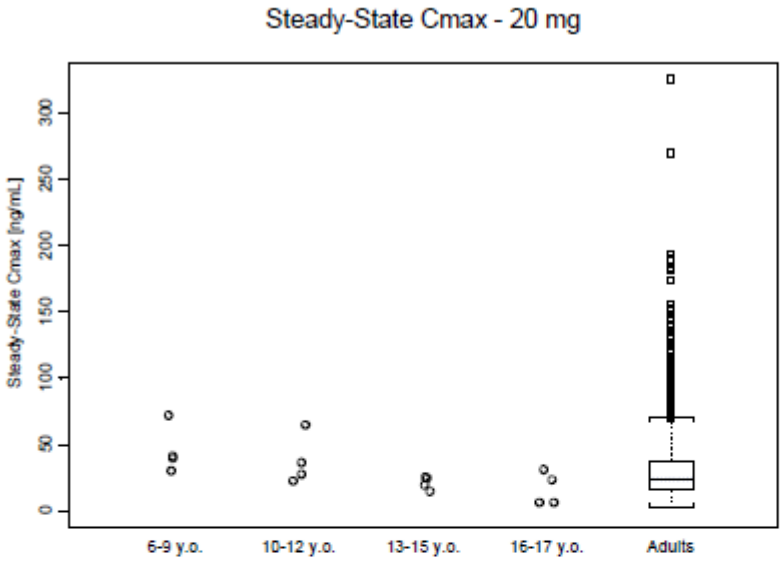

Steady-State AUC(0-24) - 80 mg
Steady-State AUC(0-24) [ng*hr/mL]
0
1000
2000
3000
4000
5000
6000
6-9 y.o.
10-12 y.o.
13-15 y.o.
16-17 y.o.
Adults

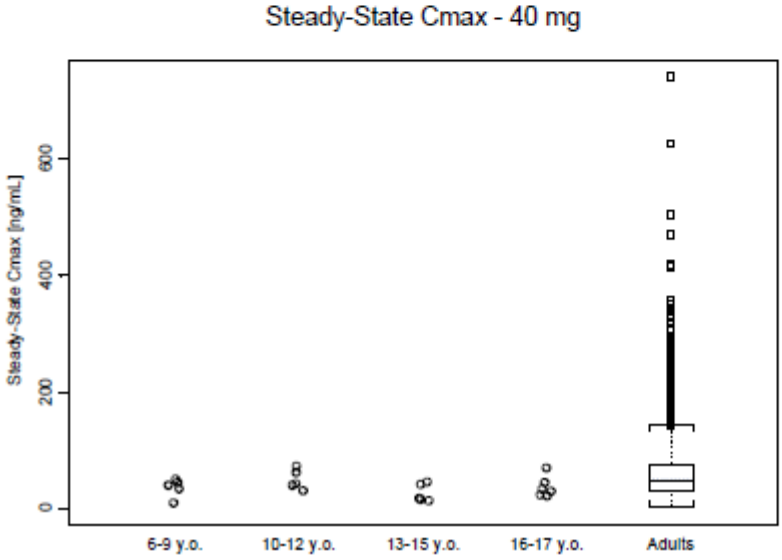

Steady-State AUC(0-24) - 120 mg
Steady-State AUC(0-24) [ng*hr/mL]
0
2000
4000
6000
6-9 y.o.
10-12 y.o.
13-15 y.o.
16-17 y.o.
Adults

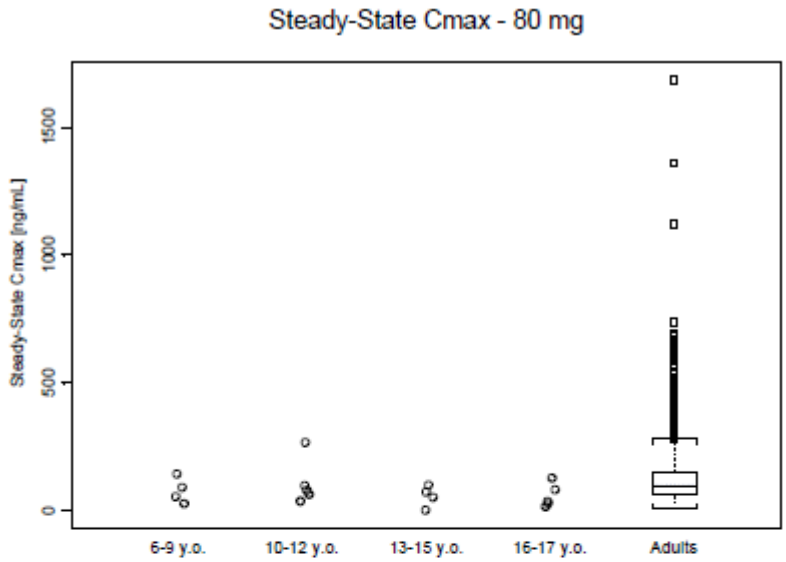


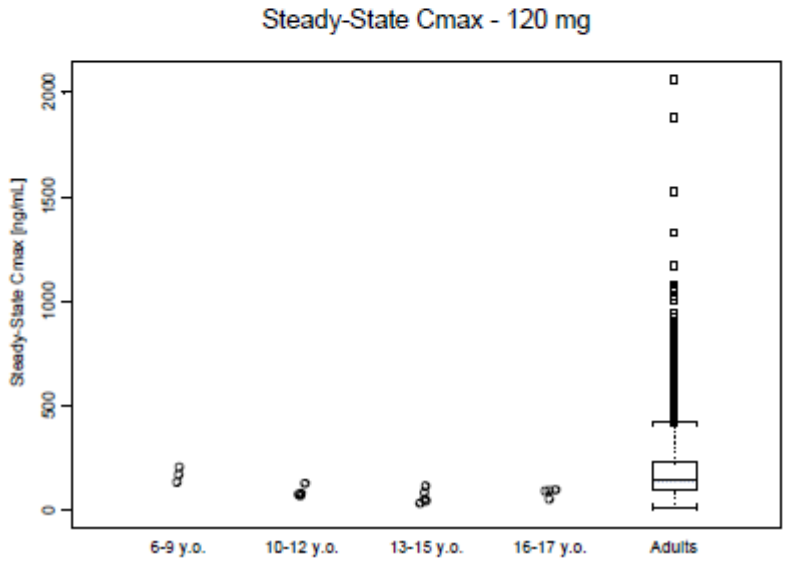
AUCss=AUC at steady state.
The open circles represent the observed steady-state AUC_{24} from the various age groups in the pediatric D1050300 study and the box plot represents the simulated distribution of steady-state AUC_{24} values from 5000 adult subjects using the adult population pharmacokinetic model. Demographic covariate vectors were sampled from the empiric distribution of the observed adult pharmacokinetic dataset. The solid line in the center of the box represents the median (shaded region represents the 95% confidence interval of the median) of the simulated adult values while the bottom and top of the box represent the 25th (Q1) and 75th (Q3) percentiles, respectively. The upper and lower whiskers represent a span equal to 1.5 times the interquartile range (75th percentile-25th percentile, ie, the length of the box plot). Simulated values outside the span of the lower and upper whiskers (i.e. below $Q_1 - 1.5 \times IQR$ or above $Q_3 + 1.5 \times IQR$) are outliers and these are represented by open squares.
Note: Subjects in the lowest age group (aged 6 to 9 years) were not administered the highest lurasidone dose (160 mg/day).

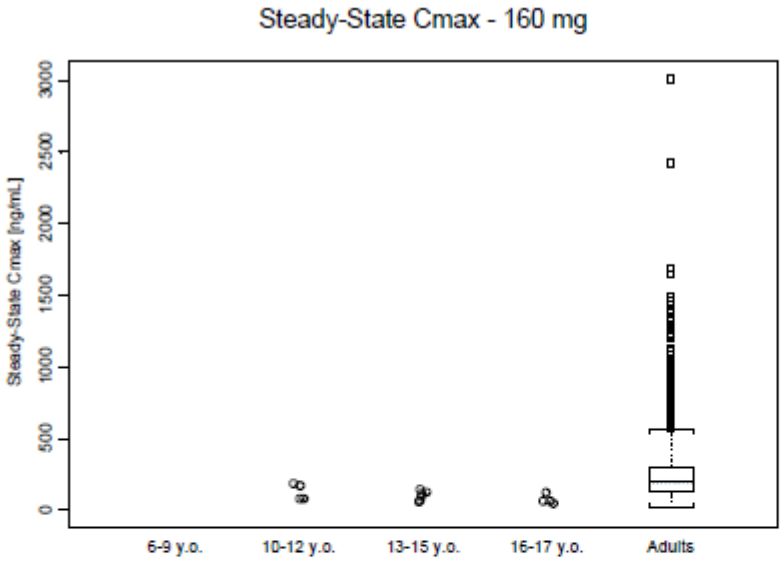
Figure 3: **Steady State Lurasidone C_{max} in Pediatric Subjects Compared With C_{max} in Adult Subjects**






Steady-State Cmax - 80 mg
Steady-State Cmax [ng/mL]
0
500
1000
1500
6-9 y.o.
10-12 y.o.
13-15 y.o.
16-17 y.o.
Adults


Steady-State Cmax - 120 mg
Steady-State Cmax [ng/mL]
0
500
1000
1500
2000
6-9 y.o.
10-12 y.o.
13-15 y.o.
16-17 y.o.
Adults



C_{max}= Maximum observed serum concentration
The open circles represent the observed steady-state C_{max} from the various age groups in pediatric Study D1050300 and the box plot represents the simulated distribution of steady-state C_{max} values from 5000 adult subjects using the adult population pharmacokinetic model. Demographic covariate vectors were sampled from the empiric distribution of the observed adult pharmacokinetic dataset. The solid line in the centre of the box represents the median (shaded region represents the 95% confidence interval of the median) of the simulated adult values while the bottom and top of the box represent the 25th (Q1) and 75th (Q3) percentiles, respectively. The upper and lower whiskers represent a span equal to 1.5 times the interquartile range (75th percentile-25th percentile, ie. the length of the box plot). Simulated values outside the span of the lower and upper whiskers (i.e. below $Q_1 - 1.5 \times IQR$ or above $Q_3 + 1.5 \times IQR$) are outliers and these are are represented by open squares.
Note: Subjects in the lowest age group (aged 6 to 9 years) were not administered the highest lurasidone dose (160 mg/day).

The observed steady-state paediatric lurasidone pharmacokinetic Cmax and area under the concentration-time curve following multiple-dose administration (for 7 days, from Day 4 to 10) across the dose range used (20 to 160 mg lurasidone), were generally within the simulated exposure ranges for the same dose range and durations in adults (see Table 2 and Table 3).

Table 2 **Steady State Median (and Range) Lurasidone AUC_{24} and C_{max} in Pediatric Subjects by Lurasidone Dose and Age Group**

	20 mg	40 mg	80 mg	120 mg	160 mg(a)
6-9 years	**N=4**	**N=5**	**N=4**	**N=3**	
AUC_{24} (ng•h/mL)					
Median	181	183	475	936	
Min, Max	93.5, 227	47.1, 267	296, 580	680, 1220	
C_{max} (ng/mL)					
Median	40.1	38.9	71.8	169	
Min, Max	29.9, 71.7	8.58, 49.2	26.1, 143	133, 205	
10-12 years	**N=4**	**N=5**	**N=5**	**N=4**	**N=4**
AUC_{24} (ng•h/mL)					
Median	149	197	418	443	872.0
Min, Max	81.1, 254	92.2, 223	199, 929	381, 658	652, 994
C_{max} (ng/mL)					
Median	31.6	41.3	78.2	76.6	122.0
Min, Max	22.2, 64.3	29.3, 71.7	35.9, 265	68.8, 126	74.4, 182
13-15 years	**N=4**	**N=5**	**N=3**	**N=5**	**N=6**
AUC_{24} (ng•h/mL)					
Median	56.4	77.2	325.0	375	525
Min, Max	50.2, 100	70.8, 139	313, 524	143.0, 447	307, 705
C_{max} (ng/mL)					
Median	21.8	16.4	71.0	49.5	101.0
Min, Max	14.4, 25.1	12.1, 44.9	51.9, 99.5	31.1, 114	54.9, 140
16-17 years	**N=4**	**N=6**	**N=5**	**N=4**	**N=3**
AUC_{24} (ng•h/mL)					
Median	64.4	135	212	377	319
Min, Max	28.4, 106	116, 284	117, 413	333, 466	312, 546
C_{max} (ng/mL)					
Median	14.5	30.2	34.9	92.0	59.3
Min, Max	5.90, 30.7	20.4, 68.7	15.2, 127	51.3, 96.4	41.3, 118

Source: D1050300 Table 14.2.7.
AUC_{24}=Area under the serum concentration-time curve from the time 0 to 24 hours, C_{max}=maximum observed serum concentration.
(a) Subjects in the lowest age group (aged 6 to 9 years) were not administered the highest lurasidone dose (160 mg/day).

Table 3 **Simulated Steady State Lurasidone AUC_{24} and C_{max} in Adult Subjects by Lurasidone Dose**

	20 mg (N=5000)	40 mg (N=5000)	80 mg (N=5000)	120 mg (N=5000)	160 mg (N=5000)
AUC_{24} (ng•h/mL)					
Upper whisker (a)	342.49	685.82	1358.49	2082.05	2712.83
Q3	177.72	355.68	706.79	1076.34	1411.60
Median	109.70	216.87	438.54	655.69	873.15
95% Confidence Interval	107.25, 112.15	211.96 221.78	428.87, 448.22	640.75, 670.62	853.80, 892.50
Q1	67.59	135.28	271.96	405.57	542.29
Lower whisker (a)	8.94	15.36	44.20	50.01	69.66
C_{max} (ng/mL)					
Upper whisker (a)	70.51	140.98	281.63	425.60	565.98
Q3	37.49	74.95	149.43	226.16	300.42
Median	23.71	47.62	95.88	142.87	191.93
95% Confidence Interval	23.22, 24.20	46.63, 48.60	93.92, 97.84	139.91, 145.83	187.99, 195.87
Q1	15.46	30.89	61.23	93.05	123.24
Lower whisker (a)	2.36	3.29	9.12	6.41	17.82

AUC_{24}=Area under the serum concentration-time curve from the time 0 to 24 hours, C_{max}=maximum observed serum concentration; Q1=25th percentile; Q3=75th percentile.
(a) The upper and lower whiskers represent a span equal to 1.5 times the interquartile range (75th percentile-25th percentile, i.e. the length of the box plot)

Study D1050300 was conducted in compliance with the agreed Paediatric Investigation Plan binding elements (ref: EMEA-001230-PIP01-M01) and the pediatric population (N=105) comprised of subjects with schizophrenia (n=4; 3.8%), schizoaffective disorder (n=1; 1.0%), ADHD with conduct disorder/disruptive behavior disorder not otherwise specified (n=78; 74.3% of patients), bipolar spectrum disorder (bipolar I) (n=16; 16.2%), bipolar spectrum disorder not otherwise specified (n=2; 1.9%), pervasive developmental disorders/autistic spectrum disorder (n=1; 1.0%), or Tourette's syndrome (n=2; 1.9%). The population used in the comparator adult population pharmacokinetic model (N=2077) was developed using data from healthy volunteers (n=131; 6.3%), as well as patients with schizophrenia (n=1492; 71.8%) or bipolar depression (n=454; 21.9%). There were no subjects with ADHD included in the adult model.

As previously described in the adult population pharmacokinetic model, the pharmacokinetic profile was not affected by disease type (refer to Report M1050011). Therefore, the comparison with this adult model was deemed to be justified on the basis that it is not expected that disease diagnosis would alter the pharmacokinetic properties of lurasidone in pediatric subjects.

On the basis of this comparison, the MAH have concluded that in general, the exposure is similar between pediatric and adult patients.

Assessor's comment:

The population pharmacokinetic model in adults was submitted in the initial MAA and includes healthy volunteers, schizophrenia and patients with bipolar depression. The pharmacokinetic profile was shown not to be affected by disease type in adults.
It is therefore acceptable to compare the exposure to lurasidone in paediatric subjects with several different diagnoses with the simulated adult data from the popPK model.

It is agreed that the observed steady-state paediatric lurasidone pharmacokinetic Cmax and AUC across the dose range used (20 to 160 mg lurasidone), were generally within the simulated exposure ranges for the same dose range and durations in adults. Lurasidone is mainly eliminated via CYP3A4 metabolism. The maturation of hepatic CYP3A4 is essentially complete at age 6, which support that exposure of lurasidone is similar in children and adolescents compared to adults. In addition, body weight has been found not to be a significant covariate in adults in the PopPK analysis.

Although no formal statistical analysis was performed for the paediatic data no clear correlation of obtained exposure to age or weight could be detected in the dose-normalized exposure vs. age or weight plots.

Issue resolved

Question 4
Based on the response on Question 3, a SmPC text in Section 5.2 regarding exposure in the paediatric population should be suggested by MAH.

RESPONSE
The MAH proposes the following text for inclusion into the Summary of Product Characteristics Section 5.2, which is based on the response for Question 3.

Paediatric population
The pharmacokinetics of lurasidone in paediatric patients was investigated in 49 children aged 6-12 years and 56 adolescents aged 13-17 years. Lurasidone was administered as lurasidone hydrochloride at daily doses of either 20, 40, 80, 120 mg (6-17 years) or 160 mg (10-17 years only) for 7 days. The pharmacokinetics of lurasidone in paediatric patients aged 6–17 years was generally comparable to those observed in adults.

Assessor's comment:

The proposed wording is acceptable with the following additions;

In Section 4.2

Paediatric population
The safety and efficacy of lurasidone in children aged less than 18 years have not been established. ~~No data are available.~~ ***Current available data are described in section 5.2, but no recommendation on a posology can be made.***
In Section 5.2

Paediatric population
The pharmacokinetics of lurasidone in paediatric patients was investigated in 49 children aged 6-12 years and 56 adolescents aged 13-17 years. Lurasidone was administered as lurasidone hydrochloride at daily doses of either 20, 40, 80, 120 mg (6-17 years) or 160 mg (10-17 years only) for 7 days. ***There was no clear correlation between obtained plasma exposure and age or body weight.*** The pharmacokinetics of lurasidone in paediatric patients aged 6–17 years was generally comparable to those observed in adults.

5. Rapporteur's updated overall conclusion and recommendation

➢ Overall conclusion

The present study includes rich PK data in the paediatric population (6-17 years). The MAH has provided acceptable responses to the list of questions, except for the SmPC text where the Rapporteur has additional proposals.

➢ Recommendation

Provided that the MAH agrees to implement the Rapporteur's proposed wording in SmPC sections 4.2 and 5.2 (see assessment of question 4 in section 5), this article 46 paediatric study is considered fulfilled. After completion of this procedure the MAH is requested to submit a type Ib variation to add the agreed wording to the SmPC.

APPENDIX 1

Sunovion Pharmaceuticals Inc.
Clinical Study: D1050300
Table 14.2.7. Descriptive Statistics for Lurasidone Serum Pharmacokinetic Parameters by Dose and Age Group (Pharmacokinetic Population)
Part I of II

Dose	Day	Age Group/ Statistic	AUC0-24 (ng*h/mL)	Cmax (ng/mL)	tmax (h)	Ctrough (ng/mL)
20 mg	10	6-9 Years				
		n	4	4	4	4
		Mean	171	45.4	2.00	2.05
		SD	65.5	18.2	1.41	1.11
		CV%	38.4	40.0	70.7	54.3
		Minimum	93.5	29.9	1.00	0.773
		Median	161	40.1	1.50	1.97
		Maximum	227	71.7	4.00	3.48
		Geo Mean	160	43.1	ND	1.79
		Geo Mean CV%	44.5	38.0	ND	68.9
		Geo Mean 95% CI	81.5, 315	24.0, 77.2	ND	0.665, 4.84
		Geo Mean 90% CI	97.2, 264	28.0, 66.3	ND	0.862, 3.74
		10-12 Years				
		n	4	4	4	4
		Mean	158	37.4	2.75	2.11
		SD	82.1	18.8	2.22	1.36
		CV%	51.9	50.2	80.6	64.5
		Minimum	81.1	22.2	1.00	0.846
		Median	149	31.6	2.00	1.97
		Maximum	254	64.3	6.00	3.65
		Geo Mean	142	34.4	ND	1.76
		Geo Mean CV%	58.8	48.8	ND	81.6
		Geo Mean 95% CI	59.5, 338	16.5, 71.7	ND	0.565, 5.48
		Geo Mean 90% CI	74.6, 269	20.0, 59.2	ND	0.759, 4.08

Note(s): CI = confidence interval; CV% = coefficient of variation; Geo = geometric; ND = not determined; SD = standard deviation.
If a value is missing or 0 in a group, geometric mean is set to ND.
Source: Listing 16.2.6.8

Table 14.2.7. Descriptive Statistics for Lurasidone Serum Pharmacokinetic Parameters by Dose and Age Group (Pharmacokinetic Population)
Part I of II

Dose	Day	Age Group/ Statistic	AUC0-24 (ng*h/mL)	Cmax (ng/mL)	tmax (h)	Ctrough (ng/mL)
20 mg	10	13-15 Years				
		n	4	4	4	4
		Mean	65.8	20.8	2.00	0.664
		SD	23.2	5.05	0.00	0.571
		CV%	35.2	24.3	0.0	86.0
		Minimum	50.2	14.4	2.00	0.333
		Median	56.4	21.8	2.00	0.402
		Maximum	100	25.1	2.00	1.52
		Geo Mean	63.2	20.3	ND	0.535
		Geo Mean CV%	32.3	26.4	ND	79.8
		Geo Mean 95% CI	38.3, 104	13.4, 30.6	ND	0.175, 1.63
		Geo Mean 90% CI	43.6, 91.5	14.9, 27.5	ND	0.234, 1.22
		16-17 Years				
		n	4	4	4	4
		Mean	65.8	16.4	2.25	0.987
		SD	37.6	12.5	1.26	0.582
		CV%	57.2	76.1	55.9	59.0
		Minimum	28.4	5.90	1.00	0.420
		Median	64.4	14.5	2.00	0.864
		Maximum	106	30.7	4.00	1.80
		Geo Mean	57.1	12.6	ND	0.866
		Geo Mean CV%	70.3	107.0	ND	65.3
		Geo Mean 95% CI	20.8, 156	3.13, 50.4	ND	0.336, 2.23
		Geo Mean 90% CI	27.1, 120	4.49, 35.1	ND	0.430, 1.75

Note(s): CI = confidence interval; CV% = coefficient of variation; Geo = geometric; ND = not determined; SD = standard deviation.
If a value is missing or 0 in a group, geometric mean is set to ND.
Source: Listing 16.2.6.8

Table 14.2.7. Descriptive Statistics for Lurasidone Serum Pharmacokinetic Parameters by Dose and Age Group (Pharmacokinetic Population)
Part I of II

Dose	Day	Age Group/ Statistic	AUC0-24 (ng*h/mL)	Cmax (ng/mL)	tmax (h)	Ctrough (ng/mL)
40 mg	10	6-9 Years				
		n	5	5	5	5
		Mean	188	34.7	1.00	2.28
		SD	89.0	15.7	0.00	1.26
		CV%	47.4	45.4	0.0	55.4
		Minimum	47.1	8.58	1.00	0.529
		Median	183	38.9	1.00	2.01
		Maximum	267	49.2	1.00	3.68
		Geo Mean	161	29.8	ND	1.89
		Geo Mean CV%	81.3	81.2	ND	90.4
		Geo Mean 95% CI	66.4, 390	12.3, 72.2	ND	0.724, 4.94
		Geo Mean 90% CI	81.6, 317	15.1, 58.8	ND	0.904, 3.95
		10-12 Years				
		n	5	5	5	5
		Mean	167	48.5	1.10	2.47
		SD	57.7	17.4	0.55	1.41
		CV%	34.6	35.9	49.8	56.9
		Minimum	92.2	29.3	0.50	1.10
		Median	197	41.3	1.00	1.85
		Maximum	223	71.7	2.00	4.70
		Geo Mean	158	46.1	ND	2.19
		Geo Mean CV%	40.4	37.3	ND	59.5
		Geo Mean 95% CI	97.2, 255	29.4, 72.1	ND	1.10, 4.33
		Geo Mean 90% CI	109, 228	32.6, 65.0	ND	1.29, 3.70

Note(s): CI = confidence interval; CV% = coefficient of variation; Geo = geometric; ND = not determined; SD = standard deviation.
If a value is missing or 0 in a group, geometric mean is set to ND.
Source: Listing 16.2.6.8

Table 14.2.7. Descriptive Statistics for Lurasidone Serum Pharmacokinetic Parameters by Dose and Age Group (Pharmacokinetic Population)
Part I of II

Dose	Day	Age Group/ Statistic	AUC0-24 (ng*h/mL)	Cmax (ng/mL)	tmax (h)	Ctrough (ng/mL)
40 mg	10	13-15 Years				
		n	5	5	5	5
		Mean	99.0	25.5	2.20	1.48
		SD	33.5	15.7	1.10	0.463
		CV%	33.8	61.4	49.8	31.4
		Minimum	70.8	12.1	1.00	1.02
		Median	77.2	16.4	2.00	1.23
		Maximum	139	44.9	4.00	2.12
		Geo Mean	94.7	21.9	ND	1.42
		Geo Mean CV%	33.8	67.8	ND	31.2
		Geo Mean 95% CI	63.0, 142	10.2, 47.0	ND	0.973, 2.08
		Geo Mean 90% CI	69.3, 130	12.2, 39.4	ND	1.06, 1.90
		16-17 Years				
		n	6	6	6	6
		Mean	160	36.0	2.17	1.94
		SD	62.5	18.0	0.98	0.710
		CV%	39.1	50.1	45.4	36.6
		Minimum	116	20.4	1.00	1.47
		Median	135	30.2	2.00	1.65
		Maximum	284	68.7	4.00	3.33
		Geo Mean	152	32.9	ND	1.86
		Geo Mean CV%	33.1	47.3	ND	31.6
		Geo Mean 95% CI	108, 213	20.5, 52.7	ND	1.34, 2.56
		Geo Mean 90% CI	117, 198	22.7, 47.6	ND	1.44, 2.39

Note(s): CI = confidence interval; CV% = coefficient of variation; Geo = geometric; ND = not determined; SD = standard deviation.
If a value is missing or 0 in a group, geometric mean is set to ND.

Table 14.2.7. Descriptive Statistics for Lurasidone Serum Pharmacokinetic Parameters by Dose and Age Group (Pharmacokinetic Population)
Part I of II

Dose	Day	Age Group/ Statistic	AUC0-24 (ng*h/mL)	Cmax (ng/mL)	tmax (h)	Ctrough (ng/mL)
80 mg	10	6-9 Years				
		n	4	4	4	4
		Mean	456	78.2	2.50	6.56
		SD	118	50.5	2.38	2.88
		CV%	25.9	64.6	95.2	43.8
		Minimum	296	26.1	1.00	2.84
		Median	475	71.8	1.50	6.84
		Maximum	580	143	6.00	9.74
		Geo Mean	443	65.1	ND	5.98
		Geo Mean CV%	29.2	83.8	ND	56.9
		Geo Mean 95% CI	281, 699	20.4, 208	ND	2.58, 13.9
		Geo Mean 90% CI	317, 621	27.6, 154	ND	3.21, 11.2
		10-12 Years				
		n	5	5	5	5
		Mean	461	108	1.80	6.40
		SD	294	90.8	1.30	3.96
		CV%	63.9	84.3	72.4	61.9
		Minimum	199	35.9	1.00	2.12
		Median	418	78.2	1.00	6.34
		Maximum	929	265	4.00	12.6
		Geo Mean	393	85.2	ND	5.43
		Geo Mean CV%	69.3	84.7	ND	74.6
		Geo Mean 95% CI	181, 856	34.2, 212	ND	2.38, 12.4
		Geo Mean 90% CI	216, 715	42.3, 172	ND	2.88, 10.2

Table 14.2.7. Descriptive Statistics for Lurasidone Serum Pharmacokinetic Parameters by Dose and Age Group (Pharmacokinetic Population)
Part I of II

Dose	Day	Age Group/ Statistic	AUC0-24 (ng*h/mL)	Cmax (ng/mL)	tmax (h)	Ctrough (ng/mL)
80 mg	10	13-15 Years				
		n	3	3	3	3
		Mean	387	74.1	2.33	4.01
		SD	119	24.0	1.53	2.66
		CV%	30.6	32.3	65.5	66.4
		Minimum	313	51.9	1.00	1.19
		Median	325	71.0	2.00	4.36
		Maximum	524	99.5	4.00	6.48
		Geo Mean	376	71.6	ND	3.23
		Geo Mean CV%	29.3	33.4	ND	109.3
		Geo Mean 95% CI	184, 768	31.9, 161	ND	0.357, 29.2
		Geo Mean 90% CI	232, 611	41.3, 124	ND	0.724, 14.4
		16-17 Years				
		n	5	5	5	5
		Mean	259	57.2	2.40	3.06
		SD	119	46.1	1.52	1.11
		CV%	46.0	80.7	63.2	36.3
		Minimum	117	15.2	1.00	1.69
		Median	212	34.9	2.00	2.92
		Maximum	413	127	4.00	4.68
		Geo Mean	236	43.4	ND	2.89
		Geo Mean CV%	52.9	102.4	ND	39.0
		Geo Mean 95% CI	127, 437	15.2, 124	ND	1.81, 4.62
		Geo Mean 90% CI	147, 379	19.4, 97.2	ND	2.02, 4.14

Note(s): CI = confidence interval; CV% = coefficient of variation; Geo = geometric; ND = not determined; SD = standard deviation.
If a value is missing or 0 in a group, geometric mean is set to ND.
Source: Listing 16.2.6.8

Table 14.2.7. Descriptive Statistics for Lurasidone Serum Pharmacokinetic Parameters by Dose and Age Group (Pharmacokinetic Population)
Part I of II

Dose	Day	Age Group/ Statistic	AUC0-24 (ng*h/mL)	Cmax (ng/mL)	tmax (h)	Ctrough (ng/mL)
120 mg	10	6-9 Years				
		n	3	3	3	3
		Mean	945	169	2.67	10.1
		SD	270	36.0	1.15	1.74
		CV%	28.6	21.3	43.3	17.2
		Minimum	680	133	2.00	8.82
		Median	936	169	2.00	9.46
		Maximum	1220	205	4.00	12.1
		Geo Mean	919	166	ND	10.0
		Geo Mean CV%	29.9	21.9	ND	16.7
		Geo Mean 95% CI	444, 1900	97.1, 285	ND	6.64, 15.2
		Geo Mean 90% CI	561, 1510	115, 240	ND	7.58, 13.3
		10-12 Years				
		n	4	4	4	4
		Mean	481	87.0	2.00	6.71
		SD	131	26.3	0.00	2.85
		CV%	27.2	30.3	0.0	42.5
		Minimum	381	68.8	2.00	4.83
		Median	443	76.6	2.00	5.56
		Maximum	658	126	2.00	10.9
		Geo Mean	469	84.4	ND	6.33
		Geo Mean CV%	26.5	27.8	ND	39.1
		Geo Mean 95% CI	310, 709	54.7, 130	ND	3.48, 11.5
		Geo Mean 90% CI	345, 637	61.3, 116	ND	4.06, 9.87

Table 14.2.7. Descriptive Statistics for Lurasidone Serum Pharmacokinetic Parameters by Dose and Age Group (Pharmacokinetic Population)
Part I of II

Dose	Day	Age Group/ Statistic	AUC0-24 (ng*h/mL)	Cmax (ng/mL)	tmax (h)	Ctrough (ng/mL)
120 mg	10	13-15 Years				
		n	5	5	5	5
		Mean	317	64.1	2.60	3.69
		SD	138	33.8	1.34	1.72
		CV%	43.4	52.8	51.6	46.5
		Minimum	143	31.1	1.00	1.84
		Median	375	49.5	2.00	4.16
		Maximum	447	114	4.00	5.99
		Geo Mean	289	57.4	ND	3.35
		Geo Mean CV%	54.5	55.7	ND	53.7
		Geo Mean 95% CI	153, 544	30.1, 110	ND	1.79, 6.26
		Geo Mean 90% CI	178, 469	35.0, 94.3	ND	2.07, 5.42
		16-17 Years				
		n	4	4	4	4
		Mean	388	82.9	2.00	3.58
		SD	61.6	21.2	1.41	0.775
		CV%	15.9	25.6	70.7	21.7
		Minimum	333	51.3	1.00	2.66
		Median	377	92.0	1.50	3.55
		Maximum	466	96.4	4.00	4.55
		Geo Mean	385	80.4	ND	3.51
		Geo Mean CV%	15.7	30.8	ND	22.3
		Geo Mean 95% CI	300, 493	49.8, 130	ND	2.48, 4.99
		Geo Mean 90% CI	320, 462	56.5, 115	ND	2.71, 4.55

Note(s): CI = confidence interval; CV% = coefficient of variation; Geo = geometric; ND = not determined; SD = standard deviation.
If a value is missing or 0 in a group, geometric mean is set to ND.
Source: Listing 16.2.6.8

Table 14.2.7. Descriptive Statistics for Lurasidone Serum Pharmacokinetic Parameters by Dose and Age Group (Pharmacokinetic Population)
Part I of II

Dose	Day	Age Group/ Statistic	AUC0-24 (ng*h/mL)	Cmax (ng/mL)	tmax (h)	Ctrough (ng/mL)
160 mg	12	10-12 Years				
		n	4	4	4	4
		Mean	848	125	2.25	9.84
		SD	163	57.5	1.26	1.53
		CV%	19.2	46.1	55.9	15.6
		Minimum	652	74.4	1.00	8.15
		Median	872	122	2.00	9.70
		Maximum	994	182	4.00	11.8
		Geo Mean	835	115	ND	9.75
		Geo Mean CV%	20.1	51.5	ND	15.6
		Geo Mean 95% CI	608, 1150	53.0, 248	ND	7.62, 12.5
		Geo Mean 90% CI	661, 1060	64.8, 203	ND	8.12, 11.7
		13-15 Years				
		n	6	6	6	6
		Mean	517	96.3	2.17	7.42
		SD	131	33.4	0.98	1.92
		CV%	25.4	34.7	45.4	25.9
		Minimum	307	54.9	1.00	4.42
		Median	525	101	2.00	7.94
		Maximum	705	140	4.00	9.44
		Geo Mean	502	91.0	ND	7.18
		Geo Mean CV%	28.4	38.9	ND	29.6
		Geo Mean 95% CI	375, 672	61.4, 135	ND	5.30, 9.74
		Geo Mean 90% CI	399, 631	66.9, 124	ND	5.66, 9.12

Note(s): CI = confidence interval; CV% = coefficient of variation; Geo = geometric; ND = not determined; SD = standard deviation.
If a value is missing or 0 in a group, geometric mean is set to ND.
Source: Listing 16.2.6.8

Table 14.2.7. Descriptive Statistics for Lurasidone Serum Pharmacokinetic Parameters by Dose and Age Group (Pharmacokinetic Population)
Part I of II

Dose	Day	Age Group/ Statistic	AUC0-24 (ng*h/mL)	Cmax (ng/mL)	tmax (h)	Ctrough (ng/mL)
160 mg	12	16-17 Years				
		n	3	3	3	3
		Mean	392	72.9	2.67	5.81
		SD	133	40.1	1.15	0.266
		CV%	33.9	55.0	43.3	4.6
		Minimum	312	41.3	2.00	5.58
		Median	319	59.3	2.00	5.74
		Maximum	546	118	4.00	6.10
		Geo Mean	379	66.1	ND	5.80
		Geo Mean CV%	32.5	57.4	ND	4.6
		Geo Mean 95% CI	172, 832	17.6, 249	ND	5.18, 6.50
		Geo Mean 90% CI	222, 646	26.9, 162	ND	5.37, 6.27