Clinical Pharmacology Review

NDA:	200603
Generic Name:	Lurasidone HCL
Trade Name:	LATUDA
Strength and Dosage Form:	Oral Tablets; 20 mg, 40 mg, 60 mg, 80 mg and 120 mg
Route of administration	Oral
Indication:	Schizophrenia
Mechanism of action:	Atypical antipsychotic
Sponsor:	Sunovion
Submission Type/SDN#:	(b) (4) Supp.# 26, Schizophrenia in adolescents- SDN # 1080 (b) (4) Supp.# 27, Irritability with Autism in children and adolescents- SDN # 1081
Relevant IND:	IND 61292
Priority Classification:	Standard
Submission Date:	7/29/2016 (for Supp. # 26) 8/1/2016 (for Supp. #27)
PDUFA date:	1/27/2017 (for both supplements)
OCP Division:	DCP1
OND Division:	DPP
Reviewer:	Praveen Balimane, Ph.D.
Team Leader:	Hao Zhu, Ph.D.

Executive Summary

Sunovion has submitted two separate supplements to the original NDA (S26 and S27; for Latuda, lurasidone oral tablets) both as a Prior Approval Supplement (PAS) and a Submission of Pediatric Study Reports-Exclusivity Determination. The two supplements included the same pharmacokinetic (PK) study report in children and adolescents 6-17 years (Study D1050300). The PK study was submitted to fulfill the post-marketing requirement (PMR) listed as 1701-1 in the original approval letter (dated 10/28/2010). The PK study is also used to satisfy the written request (WR) issued by the agency (dated 04/20/2012). In addition, the following studies were submitted in each supplement.

- Study D1050301 was submitted in S26, which provides clinical efficacy and safety information to support the approval of lurasidone in the treatment of adolescent patients with schizophrenia.
- Study D1050325 was submitted in S27, which provides clinical efficacy and safety information in children and adolescents with irritability associated with autistic disorder.

The office of Clinical Pharmacology finds that the (b) (4) supplements are acceptable from the clinical pharmacology's point of view. The design and conduct of the pediatric pharmacokinetic study (Study D1050300) are consistent with the requirements listed under the issued WR and this study has fulfilled the PMR. There are no additionally identified PMR studies at this time.

The PK study indicated that:

- The exposure of lurasidone (i.e., steady-state Cmax and AUC: Figure 1 and Figure 2) was similar in children and adolescents 10 – 17 years and adult patients for doses from 40 mg to 160 mg without adjusting for body weight.
- For the younger children (i.e., 6-9 year), the exposure of lurasidone (i.e., steady-state Cmax and AUC) was found to be similar to adult patients for doses from 40 mg to 80 mg, even though there seemed to be a higher exposures (steady-state Cmax and AUC) in younger children (i.e., 6- 9 years) both at the 20 mg and at 120 mg dose level.

Based on these results, the intended doses of 40 mg and 80 mg for the treatment of schizophrenia in adolescents yielded similar exposure to adults, and hence are acceptable from the OCP's point of view.

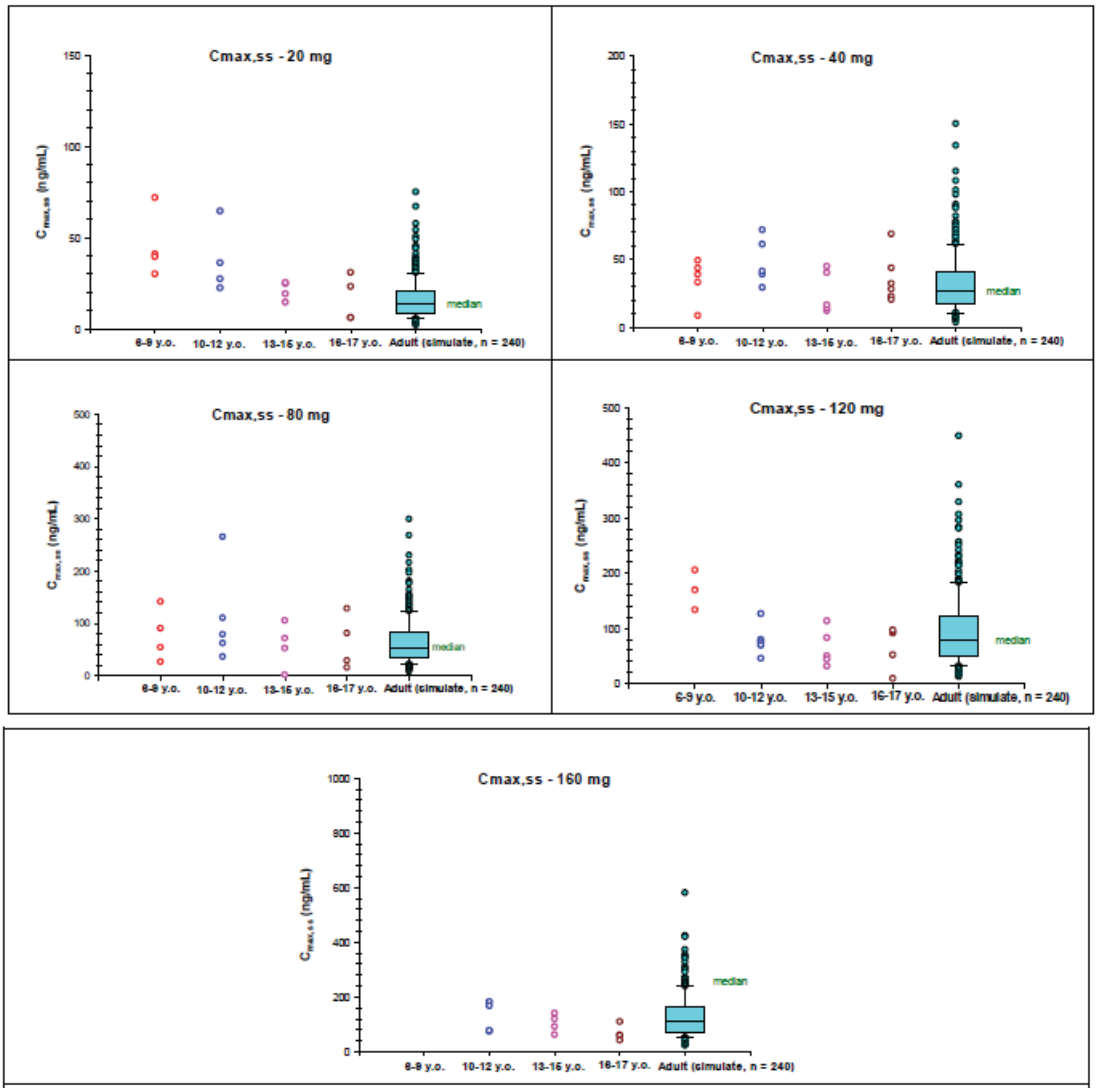
Labeling Recommendations:

Label language change to section 12.3:

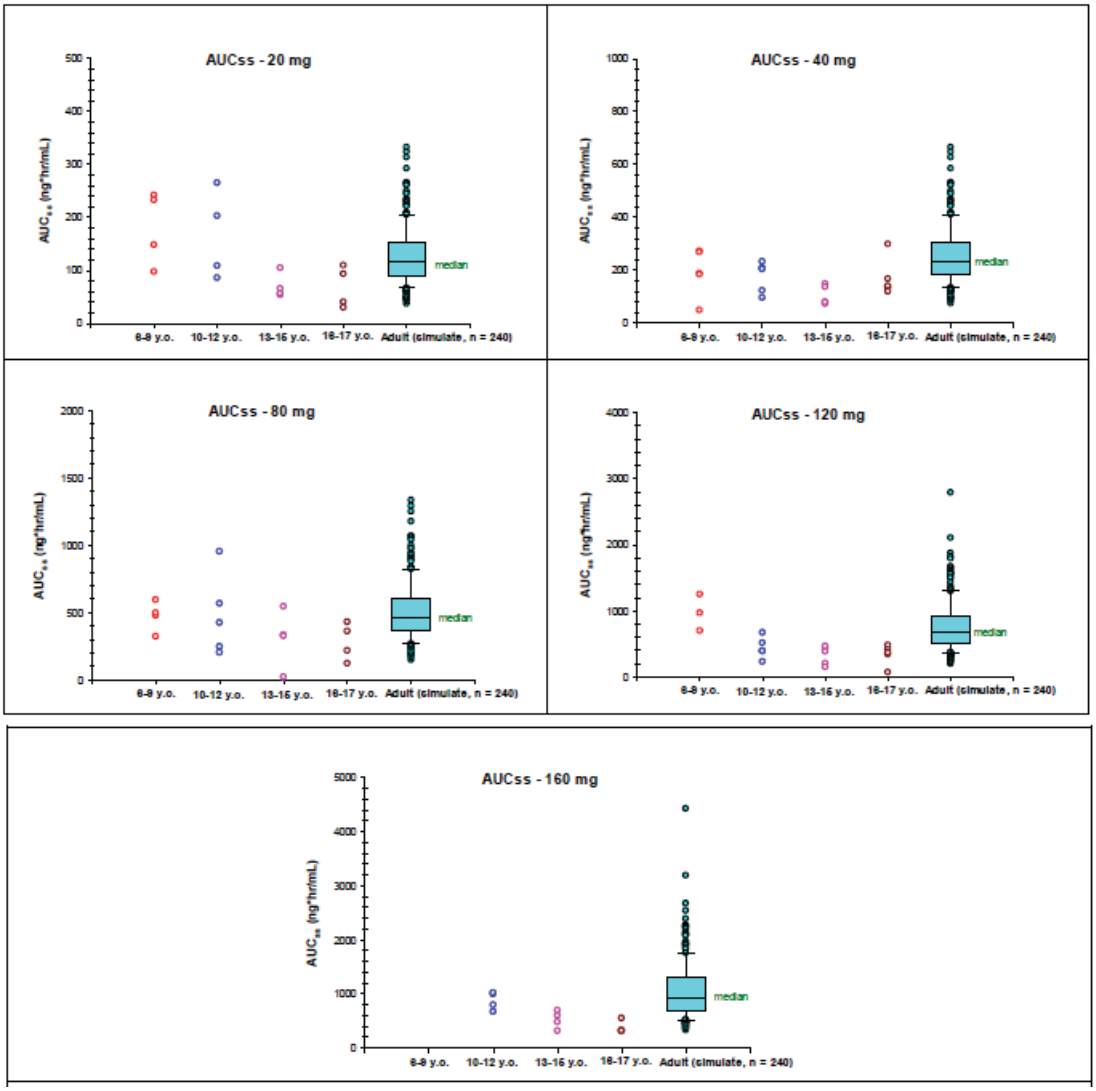
- Sponsor's version: (b) (4)
- Reviewer recommendation: (b) (4)

  The LATUDA exposure (i.e., steady-state Cmax and AUC) in children and adolescent patients (10 to 17 years of age) was generally similar to (b) (4) in adults when administered the same dose from 40 to 160 mg without adjusting for body weight.

Figure 1: Lurasidone Exposure (Cmax) in Pediatric Subjects (Different Age Strata's) compared to Adult Subjects for Various Doses (20 mg to 160 mg)



<u>Figure 2:</u> Lurasidone Exposure (<u>AUC</u>) in Pediatric Subjects (Different Age Strata's) compared to Adult Subjects for Various Doses (20 mg to 160 mg)



Appendix: Review of Individual Study Report

CLINICAL PHARMACOLOGY STUDY REVIEW

Pharmacokinetic Study

Report # D1050300 **Study Period:** 19-June-2012 to 06-May-2013

IND 61292 / NDA 200603

Title	**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**
Objectives :	**8. STUDY OBJECTIVES** This study evaluated the PK profiles of lurasidone administered at doses of 20, 40, 80, 120, and 160 mg/day to pediatric subjects aged 6 to 17 years. The safety and tolerability of these doses were also assessed. **8.1. 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. **8.2. 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:

- Open label, single-dose and multiple-dose lurasidone PK study.
- Male and female subjects from 6 to 17 year years old with schizophrenia spectrum, bipolar spectrum, autistic spectrum disorder, or other psychiatric disorders.
- Sequential escalating doses of lurasidone (20, 40, 80, 120, or 160 mg/day) were administered to the four age groups (6 to 9, 10 to 12, 13 to 15, and 16 to 17 years) of subjects.
- Thus, all dose levels (i.e., 20 mg to 160 mg) were dosed to all age groups except the highest dose of 160 mg which was not dosed to the youngest cohort of 6-9 year subjects.

This was a Phase 1, open-label, multicenter, single- and multiple-ascending lurasidone dose study in subjects from 6 to 17 years old with schizophrenia spectrum, bipolar spectrum, autistic spectrum disorder, or other psychiatric disorders. 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).

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 (ie, 4 subjects/age group/dose level × 5 doses), clinical sites were to collectively enroll approximately 25 subjects per age group.

For subjects in the 20 to 120 mg cohorts, there was a screening period (Day -28 to Day -2), followed by a study period (Day -1 to Day 11), and a follow-up period (7 [±3] days after discharge on Day 11, ie, Day 18 [±3]). During the study period, subjects had 2 inpatient visits (Day -1 to Day 2, and Day 9 to Day 11) for dosing and study assessments, 3 outpatient visits (Days 3, 5 and 7), and a telephone contact (Day 6) for assessment of safety and study drug compliance. At the discretion of the investigator, subjects were allowed to remain inpatient from Day -1 through Day 11. Subjects who met study entry criteria but were not enrolled into the study could have been rescreened once more for possible enrollment into this study.

The total study participation for subjects in the 20 to 120 mg cohorts could have lasted up to approximately 49 days.

For subjects in the 160 mg cohort only, there was a screening period (Day -28 to Day -2), followed by a study period (Day -1 to Day 13), and a follow-up period (7 [±3] after discharge on Day 13, ie, Day 20 [±3]). During the study period, subjects had 2 inpatient visits (Day -1 to Day 2, and Day 11 to Day 13) for dosing and study assessments, 3 outpatient visits (Days 3, 5 and 7), and a telephone contact (Day 6) for assessment of safety and study drug compliance. At the discretion of the investigator, subjects were allowed to remain inpatient from Day -1 through Day 13.

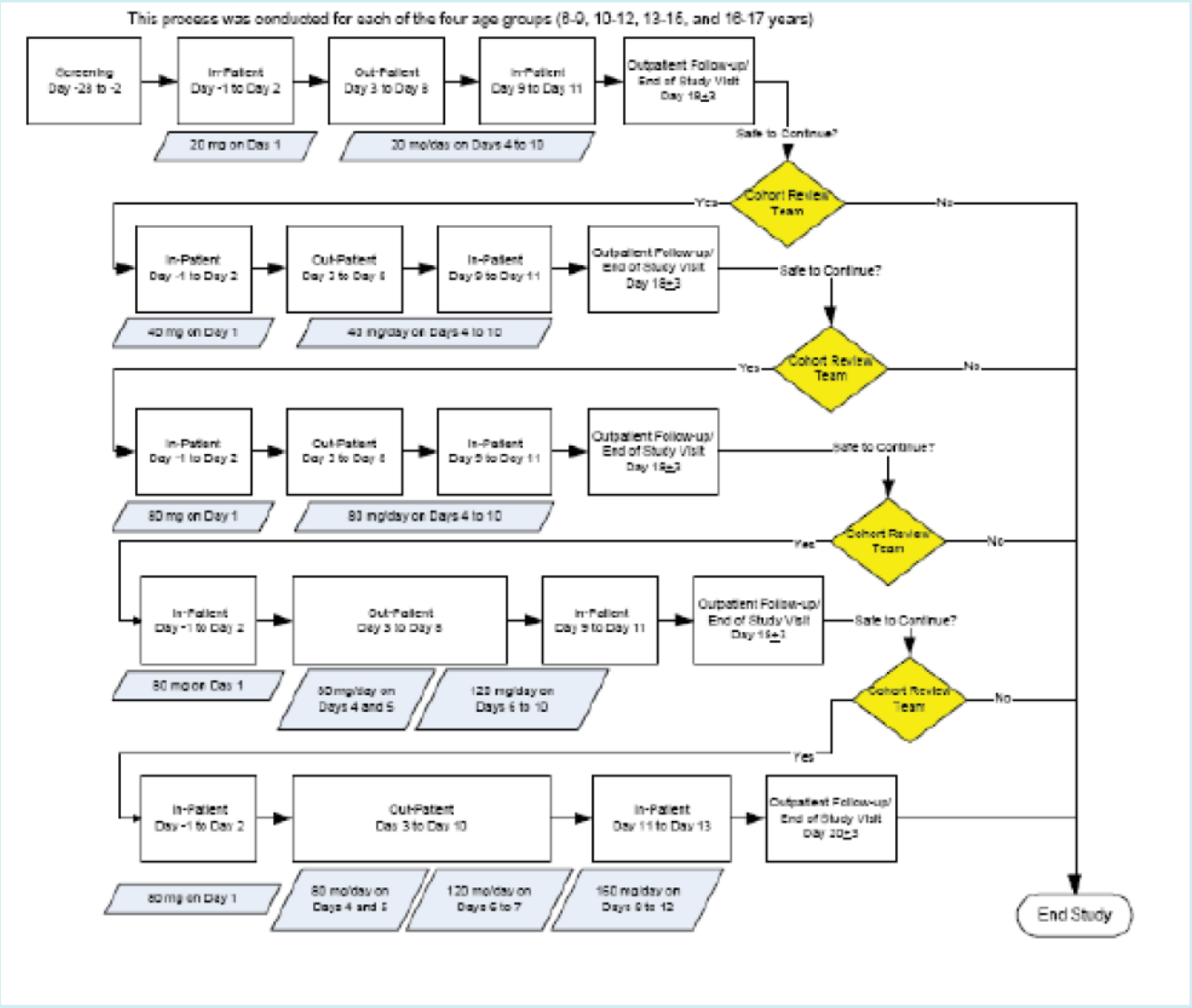
The total study participation for subjects in the 160 mg cohort could have lasted up to approximately 51 days.

Dosing was initiated at the 20 mg cohort for each age group. Dosing of subsequent dose cohorts in each age group did not occur until a review of safety data from the prior dose level for each age group had been completed (see Section 9.1.2). Dosing was initiated and maintained at the same dose for each dose cohort (eg, the 20 mg/day dose cohort was initiated and continued at 20 mg/day) except for the 120 and 160 mg cohorts.

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

Figure 1: Schematic of the study design



Administration	Oral
Sampling Times	Blood was collected for measurement of lurasidone and its metabolite concentrations at predose and at 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 hours post Day 1 dose administration; and predose and at 0.5, 1, 2, 4, 6, 8, 12, and 24 hours post Day 10 dose administration.

PK Parameters	Pharmacokinetic assessments for serum lurasidone and its metabolite concentrations included the following: 48 hour serial blood sampling following Day 1 dose administration (predose, 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 hours postdose); and 24 hour serial blood sampling following Day 10 (or Day 12) dose administration (predose, 0.5, 1, 2, 4, 6, 8, 12, and 24 hours postdose). Collected serum samples were analyzed by validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods. Pharmacokinetic parameters were derived using noncompartmental methods with WinNonlin® Professional version 5.2 (Pharsight Corp., Mountain View, California, US). All PK computations were performed using WinNonlin Professional 5.2 or SAS® version 9.2 (SAS Institute, Inc., Cary, North Carolina, US). Graphics were prepared with SAS version 9.2; SigmaPlot® 9.0 (Systat Software, Inc., San Jose, California, US); or WinNonlin Professional 5.2. The following PK parameters for lurasidone and its metabolites (ID-14283, ID-14326, ID-11614, ID-20219, and ID-20220) were estimated by noncompartmental methods using actual elapsed time from dosing on Day 1 and Day 10 (or Day 12 for the 160 mg cohort). If actual times were not available, nominal times were used. C_{max} — Maximum concentration in the sampled matrix (ng/mL), obtained directly from the observed concentration versus time data. t_{max} — Time of maximum concentration (h), obtained directly from the observed concentration versus time data. C_{trough} — Concentration in the sampled matrix (ng/mL) at 24 hours postdose on Day 10 (or Day 12 for the 160 mg cohort), obtained directly from the observed concentration versus time data. AUC_{0-24} — Area under the concentration-time curve in the sampled matrix from zero (predose) to 24 hours (ng·h/mL), calculated by linear up/log down trapezoidal summation.

	AUC_{last} Area under the concentration-time curve in the sampled matrix from zero (predose) to time of last quantifiable concentration (ng·h/mL) on Day 1 only, calculated by linear up/log down trapezoidal summation. $AUC_{0-\infty}$ Area under the concentration-time curve in the sampled matrix from zero (predose) extrapolated to infinite time (ng·h/mL) on Day 1 only, calculated by linear up/log down trapezoidal summation and extrapolated to infinity by addition of the last quantifiable concentration divided by the terminal elimination rate constant: $AUC_{last} + C_{last}/\lambda_z$. RC_{max} Accumulation ratio, calculated for C_{max} as (C_{max} on Day 10/C_{max} on Day 1), when applicable. $RAUC_{0-24}$ Accumulation ratio, calculated for AUC_{0-24} as [AUC_{0-24} on Day 10/AUC_{0-24} on Day 1], when applicable. λ_z Apparent terminal rate constant (1/h) on Day 1 only, determined by linear regression of the terminal points of the log-linear concentration-time curve. Visual assessment was used to identify the terminal linear phase of the concentration-time profile. A minimum of 3 data points was used for determination. $t_{1/2}$ Terminal elimination half-life (h) on Day 1 only, determined as $\ln 2/\lambda_z$. CL/F Apparent oral clearance (L/h), calculated for lurasidone only as [dose/$AUC_{0-\infty}$] on Day 1 or [dose/AUC_{0-24}] on Day 10 or Day 12. Vz/F Apparent volume of distribution at terminal phase (L), calculated for lurasidone only as [dose/(λ_z*$AUC_{0-\infty}$)] on Day 1 and [dose/(λ_z*AUC_{0-24})] on Day 10 or Day 12. MRC_{max} Ratio of metabolite C_{max} to lurasidone C_{max}, calculated for all metabolites. $MRAUC_{last}$ Ratio of metabolite AUC_{last} to lurasidone AUC_{last}, calculated for all metabolites on Day 1. $MRAUC_{0-\infty}$ Ratio of metabolite $AUC_{0-\infty}$ to lurasidone $AUC_{0-\infty}$, calculated for all metabolites on Day 1. $MRAUC_{0-24}$ Ratio of metabolite AUC_{0-24} to lurasidone AUC_{0-24}, calculated for all metabolites on Day 10 or Day 12. The following PK parameters were calculated for diagnostic purposes and listed, but were not summarized. $t_{1/2}$, Interval The time interval (h) of the log-linear regression to determine $t_{1/2}$. $t_{1/2}$, N Number of data points included in the log-linear regression analysis. Rsq Goodness of fit statistic for calculation of λ_z (Regression coefficient). If Rsq was less than 0.800, λ_z and related parameters were not reported. $\%AUC_{ex}$ Percentage of $AUC_{0-\infty}$ obtained by extrapolation, calculated as [(C_{last}/λ_z)/ $AUC_{0-\infty} \times 100$]. If the extrapolated area was greater than 30% of $AUC_{0-\infty}$, then $AUC_{0-\infty}$ was listed but not included in any summary or inferential statistics.
PK Moieties	Blood samples were collected and processed to obtain serum samples for the concentration measurements of lurasidone and its major metabolites (ID-14283, ID-14326, ID-11614, ID-20219, and ID-20220)
PD Endpoint(s)	Pharmacodynamics were not assessed for this study.
PD Parameters	Pharmacodynamics were not assessed for this study.

Safety Measures

9.5.1.6.1.2. Collecting and Recording Adverse Events

Adverse events were collected and recorded for each subject from the date informed consent/assent was signed until the end of their participation in the study, ie, the subject discontinued or completed the study.

Following the end of the subject's participation in the study, the investigator or an authorized delegate reported SAEs 'spontaneously' if considered at least possibly related to study drug (see Section 9.5.1.6.1.4).

Adverse events were volunteered spontaneously by the study subject, or discovered by the study staff during physical examinations or by asking an open, nonleading question such as 'How have you been feeling since you were last asked?' All AEs and any required remedial action were recorded in the subject's source documentation and transcribed onto the appropriate eCRF page for the treatment period indicated. The nature of the AE, date (and time, if known) of AE onset, date (and time, if known) of AE outcome to date, severity, and action taken of the AE were documented together with the investigator's (or a physician listed on the Form FDA 1572) assessment of the seriousness of the AE and causal relationship to study drug and/or study procedure (at the time of assessment).

All AEs were recorded individually in the study subject's own words (verbatim) unless, in the opinion of the investigator, the AEs constituted components of a recognized condition, disease or syndrome. In the latter case, the condition, disease, or syndrome was named rather than each individual sign and/or symptom. Rashes were identified as type, extent, and location.

9.5.1.6.1.3. Assessment of Adverse Events

The investigator or a physician listed on the Form FDA 1572 assessed all AEs for severity, relationship with study drug, and for whether it met the criteria for classification as an SAE, requiring immediate notification to the sponsor (see Section 9.5.1.6.1.8). These assessments were made in accordance with the standard ratings detailed in Table 6 (severity) and Table 7 (causality).

Table 6: Severity Assessment

Mild	Ordinarily transient symptoms did not influence performance of subject's daily activities. Treatment was not ordinarily indicated.
Moderate	Marked symptoms, sufficient to make the subject uncomfortable. Moderate influence on performance of subject's daily activities. Treatment could have been necessary.
Severe	Symptoms caused considerable discomfort. Substantial influence on subject's daily activities. May have been unable to continue in the study and treatment was necessary.

When changes in the intensity of an AE occurred more frequently than once a day, the maximum intensity for the event was noted for that day. Any change in severity of signs and symptoms over a number of days was captured by recording a new AE, with the amended severity grade, and the date (and time, if known) of the change.

Analytical Method

Method Type	LC/MS/MS	Matrix	Plasma
Analytes	lurasidone and its major metabolites (ID-14283, ID-14326, ID-11614, ID-20219, and ID-20220)		

Validation	▪ Method validated prior to use	☑ Yes	☐ No
	▪ Method validation acceptable	☑ Yes	☐ No
Study Sample Analysis	▪ Samples analyzed within the established stability period	☑ Yes	☐ No
	▪ Quality control samples range acceptable	☑ Yes	☐ No
	▪ Chromatograms provided	☑ Yes	☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☑ Yes	☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☑ Yes	☐ No
	▪ Overall performance acceptable	☑ Yes	☐ No

Study Population

A total of 105 subjects (males and females patients between the age of 6-17 year) participated in the study and received at least 1 dose of study drug; therefore, 105 subjects were included in the safety population. Of these, 90 (85.7%) subjects completed all study procedures per protocol and received all planned doses of study drug.

Summary of demographics

Table 1: Demographics and baseline characteristics of all subjects (ages 6-17 year)

Parameter	Pharmacokinetic Population						Safety Population					
	Dose Cohort – All Age Groups (6-17 Years) Combined					All Subjects N=102	Dose Cohort – All Age Groups (6-17 Years) Combined					All Subjects N=105
	20 mg N=17	40 mg N=25	80 mg N=19	120 mg N=25	160 mg N=16		20 mg N=20	40 mg N=25	80 mg N=19	120 mg N=25	160 mg N=16	
Age (years)												
Mean (SD)	12.1 (3.06)	12.8 (2.96)	12.7 (3.05)	12.6 (3.44)	13.4 (2.42)	12.7 (3.01)	12.1 (2.83)	12.8 (2.96)	12.7 (3.05)	12.6 (3.44)	13.4 (2.42)	12.7 (2.97)
Sex, n (%)												
Male	11 (64.7)	15 (60.0)	13 (68.4)	17 (68.0)	11 (68.8)	67 (65.7)	12 (60.0)	15 (60.0)	13 (68.4)	17 (68.0)	11 (68.8)	68 (64.8)
Female	6 (35.3)	10 (40.0)	6 (31.6)	8 (32.0)	5 (31.3)	35 (34.3)	8 (40.0)	10 (40.0)	6 (31.6)	8 (32.0)	5 (31.3)	37 (35.2)
Race, n (%)												
White	15 (88.2)	17 (68.0)	16 (84.2)	18 (72.0)	13 (81.3)	79 (77.5)	18 (90.0)	17 (68.0)	16 (84.2)	18 (72.0)	13 (81.3)	82 (78.1)
Black or Afr Am	2 (11.8)	8 (32.0)	3 (15.8)	7 (28.0)	3 (18.8)	23 (22.5)	2 (10.0)	8 (32.0)	3 (15.8)	7 (28.0)	3 (18.8)	23 (21.9)
Ethnicity, n (%)												
Hisp or Lat	12 (70.6)	2 (8.0)	1 (5.3)	12 (48.0)	0	27 (26.5)	13 (65.0)	2 (8.0)	1 (5.3)	12 (48.0)	0	28 (26.7)
Not Hisp or Lat	5 (29.4)	23 (92.0)	18 (94.7)	13 (52.0)	16 (100.0)	75 (73.5)	7 (35.0)	23 (92.0)	18 (94.7)	13 (52.0)	16 (100.0)	77 (73.3)
Height (cm)												
Mean (SD)	151.55 (20.087)	155.57 (16.032)	156.19 (17.515)	154.56 (17.493)	160.56 (13.898)	155.55 (16.972)	152.04 (18.527)	155.57 (16.032)	156.19 (17.515)	154.56 (17.493)	160.56 (13.898)	155.53 (16.738)
Weight (kg)												
Mean (SD)	48.34 (18.165)	50.90 (18.745)	52.03 (17.892)	49.94 (19.261)	57.96 (14.414)	51.56 (17.913)	48.36 (16.870)	50.90 (18.745)	52.03 (17.892)	49.94 (19.261)	57.96 (14.414)	51.47 (17.695)
BMI (kg/m^2)												
Mean (SD)	20.24 (3.259)	20.39 (5.009)	20.54 (3.586)	19.94 (4.210)	22.24 (3.824)	20.57 (4.109)	20.23 (3.110)	20.39 (5.009)	20.54 (3.586)	19.94 (4.210)	22.24 (3.824)	20.56 (4.066)

Abbreviations: Afr Am = African American; BMI = body mass index; Hisp = Hispanic; Lat = Latino; N = number of subject enrolled; n = number of subjects in demographic category; SD = standard deviation.

Table 2: Primary psychiatric history by dose cohorts for all subjects (ages 6-17 year)

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.

Results

Pharmacokinetic Results

Figure 2: Mean (SD) Lurasidone Serum Concentration-time Profiles on Day 1

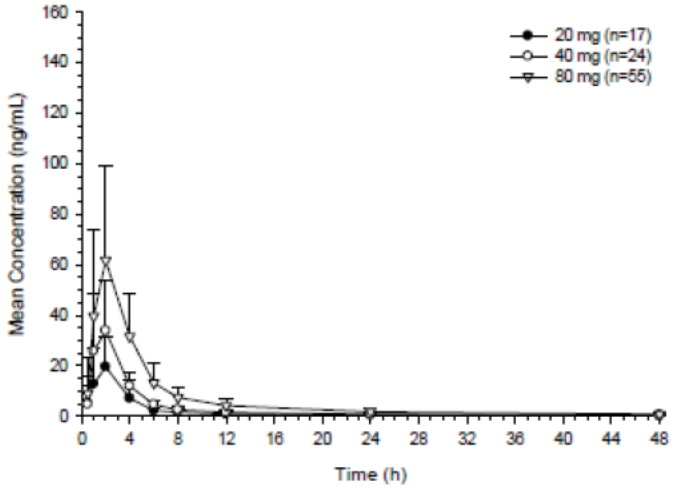


Figure 3: Mean (SD) Lurasidone Serum Concentration-time Profiles on Day 10 (or Day 12 for the 160 mg cohort)

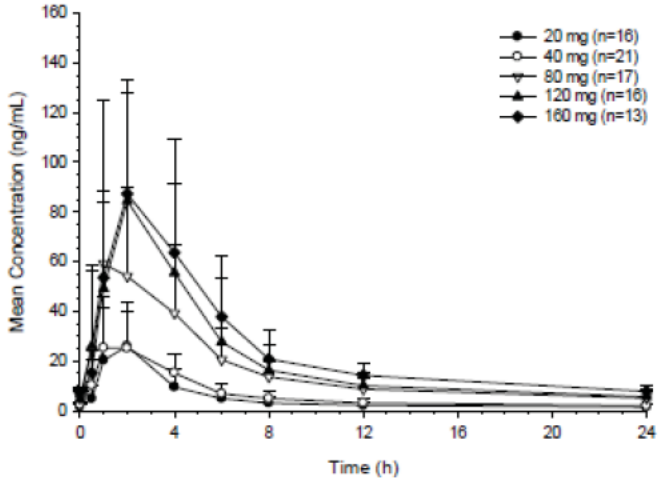


Table 3: Summary of Lurasidone Key Pharmacokinetics Parameters for All Age Groups on Day 1

Dose	Statistic	AUC_{last} (ng·h/mL)	$AUC_{\beta-\infty}$ (ng·h/mL)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)
20 mg	n	16	16	16	16	16	16	16
	Mean	78.0	83.8	24.4	1.97	16.2	346	6940
	SD	44.9	48.3	14.1	0.94	4.68	245	3030
	Min	18.5	19.5	4.63	0.50	6.27	104	2630
	Median	64.8	69.1	22.8	2.00	17.2	290	5930
	Max	179	192	53.8	4.00	25.4	1020	11800
40 mg	n	24	19	24	24	20	19	19
	Mean	140	153	38.4	1.83	21.3	317	8700
	SD	65.4	69.8	22.4	0.82	7.26	144	3500
	Min	36.8	58.1	5.10	1.00	11.1	134	4740
	Median	128	134	32.9	2.00	18.8	299	7740
	Max	292	299	94.2	4.00	38.4	689	17300
80 mg	n	54	50	55	55	50	50	50
	Mean	300	328	68.2	2.16	16.8	324	7640
	SD	140	163	37.5	1.01	5.42	240	5390
	Min	47.8	51.6	6.33	0.50	8.17	82.3	2010
	Median	276	299	58.3	2.00	16.4	269	6490
	Max	770	972	197	6.00	32.7	1550	31800

Abbreviations: SD = standard deviation; Min = minimum; Max = maximum.
Source: Table 14.2.7.

Table 4: Summary of Lurasidone Key Pharmacokinetics Parameters for All Age Groups on Day 10 (or Day 12 for 160 mg)

Dose	Statistic	$AUC_{0\text{-}24}$ (ng·h/mL)	C_{max} (ng/mL)	t_{max} (h)	CL/F (L/h)	$RAUC_{0\text{-}24}$	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.
Source: Table 14.2.7.

The observed lurasidone pediatric pharmacokinetic exposures following multiple-dose administration (Cmax and AUC0-tau) across the dose range studied (20-160 mg) were generally within the simulated adult exposure ranges for the same dose and durations in adults.

<u>Figure 4</u>: Lurasidone Exposure (<u>Cmax</u>) in Pediatric Subjects (different age strata's) compared to Adult Subjects for various doses (20 mg to 160 mg)

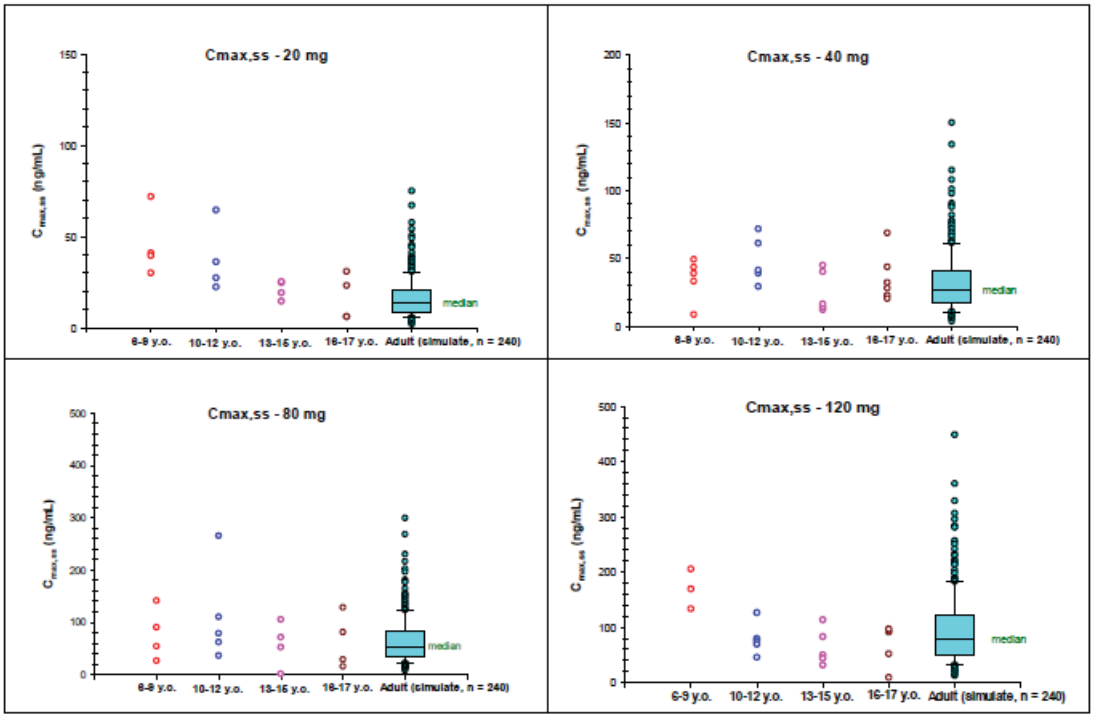
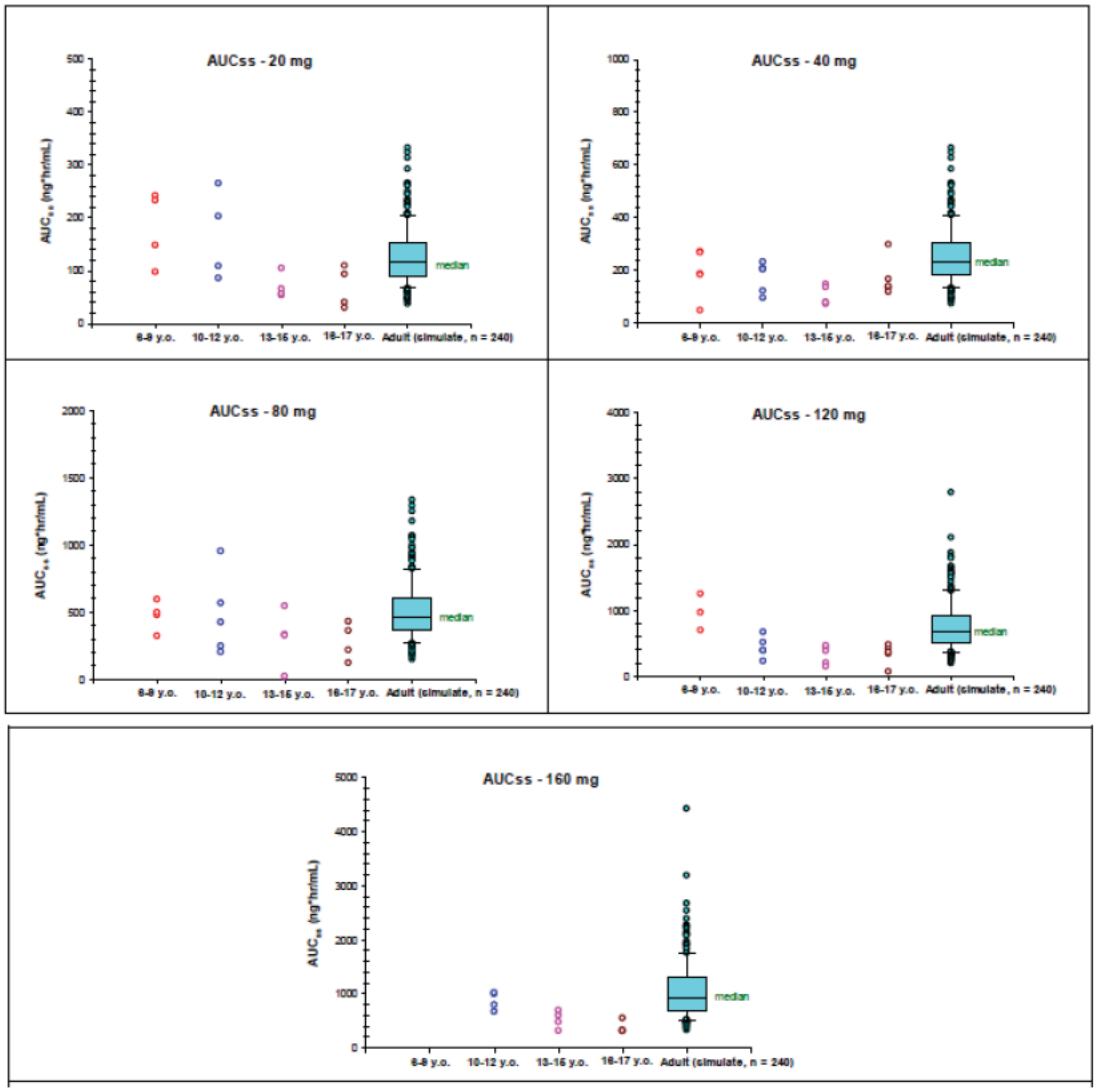


Figure 5: Lurasidone Exposure (AUC) in Pediatric Subjects (different age strata's) compared to Adult Subjects for various doses (20 mg to 160 mg)



Therefore, the overall exposure (i.e., both Cmax and AUC values) for lursoidone remain similar in all age strata (i.e., across all age groups from 6 years up to adults) when they get administered the same dose in mg. Thus, no dose adjustment based on weight was required to match the exposures in efficacy studies conducted in children and adolescents.

Safety Results

Was there any death or serious adverse events?	☐ Yes ☑ No ☐ NA

- A total of 2 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 of parkinsonism (SAE), somnolence (2 subjects), blurred vision, dystonia, vomiting (3 subjects), and akathisia; all events were assessed by the investigators as possibly, probably, or related to study drug. There were no deaths during study conduct.
- The 20 mg dose of lurasidone was well tolerated by all age groups when administered orally once daily on Day 1 and Days 4 through 10.
- The 40 mg and 80 mg doses of lurasidone were moderately well tolerated by all age groups when administered orally once daily on Day 1 and Days 4 through 10 with the most frequently reported TEAEs being somnolence, sedation, nausea, and vomiting, which are consistent with the lurasidone safety profile in adults.
- The 120 mg dosing scheme (ie, lurasidone given orally once daily on Days 1, 4, and 5 as 80 mg; and on Days 6 to 10 as 120 mg) was moderately well tolerated in subjects from 10 to 17 years old. Subjects in the 6 to 9 year age group experienced tolerability difficulties (moderate or severe vomiting, sedation, and somnolence) during the 120 mg dosing scheme. Doses greater than 120 mg were therefore not evaluated in the 6 to 9 year age group.
- The 160 mg dosing scheme (lurasidone given orally once daily on Days 1, 4, and 5 as 80 mg; Days 6 to 7 as 120 mg; and on Days 8 to 12 as 160 mg) was moderately well tolerated in subjects from 10 to 17 years old with the most frequently reported TEAEs being somnolence, sedation, vomiting, nausea, upper abdominal pain, and dystonia. The majority of TEAEs reported for the 120 and 160 mg dosing schemes began during initial 80 mg dosing on Days 1, 4, and 5.
- Mean CGI-S scores decreased for all treatments from baseline to Day 10/Day 12 (decrease ranged from 0.2 to 0.6), with the largest change from baseline observed for the 120 mg cohort. Mean CGI-S scores decreased for all age groups from baseline to Day 10/Day 12 (decrease ranged from 0.1 to 0.5), with the largest change from baseline observed for the 13 to 15, 16 to 17, and 13 to 17 year age groups.
- No mean or median changes from baseline in the AIMS, BAS, or SAS were observed across the different dose cohorts or age groups. No suicidal ideation or behavior as assessed by C-SSRS was detected during the study.
- Overall, there were no trends or clinically relevant changes noted in mean, median, or individual clinical laboratory (with the exception of prolactin elevation), vital sign, or ECG data following dose administration.

Overall Sponsor Conslusions

The observed lurasidone pediatric PK exposures (C_{max} and AUC_{0-24}) 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. Overall, lurasidone was generally tolerated by all age groups at daily doses of up to 80 mg with an adverse event profile that was similar to prior studies in adults.

Reviewer's Comments

1. *Study Design:*

An open label single and multiple dose PK study in *subjects from 6 to 17 years old with schizophrenia spectrum, bipolar spectrum, autistic spectrum disorder, or other psychiatric disorders was an appropriate study design to assess the PK of lurasidone (and its metabolites) in the patients of various age strata (i.e., 6 to 17 years). The study provided PK on both day 1 as well as on steady state (day 10) for children and adolescents. The sequential escalating doses of lurasidone made the design safe and prudent design in children.*

- *Dose: Sequential escalating doses of lurasidone (20, 40, 80, 120, or 160 mg/day) were administered to the four age groups (6 to 9, 10 to 12, 13 to 15, and 16 to 17 years) of subjects. Thus, all dose levels (i.e., 20 mg to 160 mg) were dosed to all age groups except the highest dose of 160 mg which was not dosed to the youngest cohort of 6-9 year subjects.*
- *Sample Size: A total of 105 subjects (males and females patients between the ages of 6-17 year) participated in the study, which is considered acceptable to assess the PK.*
- *Age range and gender representation of the patients: The study included 20 or more patients in each of the age strata's: 6-9 year, 10-12 year, 13-15 year and 16-17 year. It had representation from both genders: 65% males and 35% female and included 78% whites and 22% blacks/African Americans.*
- *PK samples: Complete PK profiles were obtained on day 1 as well as at steady state at all dose levels for all age strata's.*
- *Restrictions on co-medication that may affect PK: Excluded use of inhibitors or inducers of CYP3A4's.*
- *Restrictions on organ dysfunction patients: Excluded any subjects with hepatic impairments.*
- *Moieties measured: lurasidone and its major metabolites (ID-14283, ID-14326, ID-11614, ID-20219, and ID-20220) are all measured in the pediatric PK study.*
- *Data Analysis: NCA analysis was performed. Major PK parameters including Cmax, Tmax, AUC0-24 (at steady state and Day 1) and AUC 0-inf are all assessed.*

2. *Protocol deviation:*

No significant deviations were observed which could impact the quality of PK data.

3. *Subject Exclusion:*

Three subjects (Subjects 300013225, 300013226, and 300013251) were excluded from the pharmacokinetic analysis for Study D1050300. Blood samples for these 3 subjects were collected but not analyzed due to the samples being stored at inappropriate condition. We agree that the samples that are inappropriately handled may yield inaccurate results. Given that the storage issue occurred randomly in the three subjects, we do not expect the final conclusion on PK should be affected in any way after the three subjects are excluded.

4. *Bioanalytical Method:*

An acceptable and validated LC/MS/MS methodology with rigorous quality control and calibration data for all moieties of interest provides assurance for the quality of the PK data.

5. *Pharmacokinetic findings:*

The PK study indicated that:

- *The exposure of lurasidone (i.e., steady-state Cmax and AUC: Figure 4 and Figure 5) was similar in children and adolescents 10 – 17 years and adult patients for doses from 40 mg to 160 mg without adjusting for body weight.*
- *For the younger children (i.e., 6-9 year), the exposure of lurasidone (i.e., steady-state Cmax and*

AUC) was found to be similar to adult patients for doses from 40 mg to 80 mg, even though there seemed to be a higher exposures (steady-state Cmax and AUC) in younger children (i.e., 6- 9 years) both at the 20 mg and at 120 mg dose level.

Based on these results, the intended doses of 40 mg and 80 mg for the treatment of schizophrenia in adolescents yielded similar exposure to adults, and hence are acceptable from the OCP's point of view.

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/s/

PRAVEEN BALIMANE
12/23/2016

HAO ZHU
12/23/2016