CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	200603 S-026
Priority or Standard	Priority
Submit Date(s)	July 29, 2016
Received Date(s)	July 29, 2016
PDUFA Goal Date	January 29, 2017
Division / Office	DPP/ODE I
Reviewer Name(s)	Jean Kim, MD, MA
Review Completion Date	January 27, 2017
Established Name	Lurasidone
Trade Name	Latuda
Therapeutic Class	Antipsychotic
Applicant	Sunovion
Formulation(s)	Oral Tablets
Dosing Regimen	40mg daily or 80mg daily, po
Indication(s)	Schizophrenia
Intended Population(s)	Adolescents (13 to 17 years old)

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

For the indication of lurasidone for the treatment of adolescents (ages 13 to 17) with schizophrenia, this reviewer recommends approval at 40mg and 80mg. The study showed overall statistical efficacy on their primary endpoint for lurasidone in this patient population at both dosages.

1.2 Risk Benefit Assessment

The benefits of lurasidone treatment outweigh the potential risks in the treatment of pediatric patients with schizophrenia at both the 40mg and 80mg doses given that both showed significant efficacy in the study, and safety issues were within expected limits for this drug from prior studies. Of note, the 80mg did not show additional efficacy over the 40mg dose in terms of overall endpoint numerical results, and there were concerns about lack of significant efficacy at the 80mg dose when the Ukraine subgroup was excluded. The U.S. subgroup did not show significant efficacy at either dose but still showed endpoint numerical improvement in both. See Section 6.1.7 for more discussion.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None are recommended at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

None are recommended at this time.

2 Introduction and Regulatory Background

2.1 Product Information

Lurasidone hydrochloride is an atypical antipsychotic that was first approved in the United States on October 28, 2010, under the tradename Latuda. It is an antagonist with high affinity at the dopamine D_2 receptor, 5-hydroxytryptamine (5-HT) receptors 5-HT_{2A} and 5-HT_7. Lurasidone is currently approved for the treatment of schizophrenia, the treatment of depressive episodes associated with bipolar I disorder as monotherapy or as adjunctive therapy with lithium or valproate (approval for the bipolar supplemental

indications occurred on July 1, 2013). Several 6-week clinical trials were the basis of approval for all indications.

2.2 Tables of Currently Available Treatments for Proposed Indications

FDA-Approved Available Medications for Treatment of Schizophrenia in Adolescents via BPCA/PREA Studies:
Risperidone (Risperdal), August 2007 (ages 13-17)
Aripiprazole (Abilify), October 2007 (ages 13-17)
Olanzapine (Zyprexa), December 2009 (ages 13-17)
Quetiapine (Seroquel), December 2009 (ages 13-17)
Paliperidone (Invega), April 2011 (ages 12-17)

Via Extrapolation Data:
Haloperidol (Haldol)
Molindone (Moban)
Perphenazine (Trilafon)
Trifluoperazine (Stelazine)
Thiothixene (Navane)

2.3 Availability of Proposed Active Ingredient in the United States

Lurasidone has been available in the U.S. since 2010.

2.4 Important Safety Issues With Consideration to Related Drugs

Important risks associated with the use of atypical antipsychotics are:

- metabolic changes including hyperglycemia and diabetes mellitus, dyslipidemia, and weight gain
- cerebrovascular events (e.g., stroke) in elderly patients with dementia-related psychosis
- increased mortality in elderly patients with dementia-related psychosis
- orthostatic hypotension and syncope
- neuroleptic malignant syndrome
- tardive dyskinesia
- leukopenia, neutropenia, and agranulocytosis

2.5 Summary of Presubmission Regulatory Activity Related to Submission

In the original NDA approval letter for lurasidone from October 2010, post-marketing commitment (PMC) 1701-1 and 1701-2 both discussed deferred pediatric studies under PREA for the treatment of schizophrenia in patients aged 13 to 17 years:

- D1050300: for pharmacokinetic data and dosing to be completed by late December 2012.
- D1050301: for efficacy and safety to be completed by late April 2015, with final report submission by October 30, 2015.

In a subsequent Written Request (WR) from April 20, 2012, the FDA clarified the pediatric study requirements to qualify for exclusivity under 505A of the Federal Food, Drug, and Cosmetic Act. The WR required the two trials as per the prior PMCs, as well as:

- D1050302: an additional pediatric long-term safety study of at least 6 months duration.
- D1050325: an additional study in irritability in patients with autistic disorder (see Supplement 27) in children ages 6 to 17 years because lurasidone might be used off-label for that indication.

The pharmacokinetic and long-term safety trials could enroll patients with either schizophrenia or autism.

The Sponsor agreed to this WR. The protocol for study D1050301 was submitted to NDA 200603 originally on July 13, 2013, and was amended 3 times afterwards with 4 subsequent amendments, last in November 2014, including two sample size adjustments.

2.6 Other Relevant Background Information

N/A

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The consistency of adverse event information in this application was evaluated by comparing information across the following documents for a sample of 6 patients: Case Report Forms (CRFs), Narrative Summaries (NSs),
and adverse event data listings (ae.xpt files). The 6 patients audited were:

301006001
301032001
301035001
301682001
301687010
301857001

Adverse event data was found to be consistently documented for these patients. Additionally, the Sponsor's coding of adverse event verbatim terms (AETERM) to preferred terms (AEDECOD) as documented in the adae.xpt database was audited. No overt inaccuracies in adverse event coding were detected. However, as will be discussed in Section 7.1.2, because MedDRA allows splitting of closely related verbatim terms to multiple coded terms, related preferred terms have been combined into common terms for purposes of this review.

3.2 Compliance with Good Clinical Practices

Study D1050301 was conducted in accordance with Good Clinical Practice standards. An Office of Scientific Investigations (OSI) inspection was deferred due to no overtly unusual safety or efficacy signals from clinical study sites that were FDA-accessible. (Per our statistics reviewer, Ukraine sites showed somewhat higher efficacy data than the other sites, but were not accessible for inspection.)

3.3 Financial Disclosures

Clinical Investigator Financial Disclosure
Review Template

Application Number: NDA 200603, Supplement 26

Submission Date(s): 7/29/16

Applicant: Sunovion

Product: Latuda (lurasidone)

Reviewer: Jean Kim MD, MA

Date of Review: 8/30/16

Covered Clinical Study (Name and/or Number): D1050301

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from applicant)
Total number of investigators identified: 101 principal, 325 subinvestigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the		

number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: see below Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

There were three investigators who disclosed amounts of $306,612.50, $106,277.50, and $76,212.50 from 2011-2015 respectively. However, they were all sub-investigators, and the number of subjects at the sites where they worked was miniscule (b) (6) each.) Therefore, it is unlikely that financial interests would have impacted the overall results of this study.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Refer to original NDA 200603. No new information noted.

4.2 Clinical Microbiology

Refer to original NDA 200603. No new information noted.

4.3 Preclinical Pharmacology/Toxicology

Refer to original NDA 200603. No new information noted.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

There is no new information in this supplement regarding the mechanism of action of lurasidone in treating schizophrenia.

4.4.2 Pharmacodynamics

There is no new information regarding the pharmacodynamics of lurasidone.

4.4.3 Pharmacokinetics

Study D1050300 reviewed the pharmacokinetics of lurasidone in the adolescent population. (See Module 5.3.3.2). This was a Phase 1 open-label, multicenter, single and multiple-ascending dose trial, to characterize the lurasidone PK profile, safety, and tolerability in subjects ages 6 to 17 years old with schizophrenia spectrum, bipolar spectrum, autistic spectrum, or other psychiatric disorders. Doses of 20, 40, 80, 120 and 160mg daily were used. Lurasidone metabolites' PK was also characterized.

Sequential escalating doses of lurasidone were administered to four pediatric age groups, with a total of 90 subjects completing the study (out of 105 who participated). All subjects received a single dose of drug followed by a 2-day washout period, then once-daily dosing of drug for 7 days (20 to 120mg cohorts) or 9 days (160mg cohort), with dose titration occurring during the daily dosing period for 120mg and 160mg cohorts only.

There were 102 subjects included in the PK analysis (3 had unusable samples and had to be excluded.) The Sponsor noted that the 40 and 80mg daily doses were safe and well-tolerated in Study D1050300 and demonstrated similar exposure parameters between the pediatric and adult populations. Overall PK exposure parameters (C_{max} and AUC_{0-24} for 20 to 160mg were generally similar to adult exposures previously observed at steady state (as in Study M1050005). 20 and 40mg doses were noted to be better tolerated than the 80mg dose and higher, although 80mg was felt to be reasonably tolerated (although with marked sedation). Children ages 6 to 9 had marked difficulty tolerating 120mg due to sedation and vomiting issues, so higher doses were not studied in that group, only in adolescents.

The Clinical Pharmacology reviewer notes that based on the study's PK results, the dosing was appropriate.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The studies done by the Sponsor to support a claim for schizophrenia in the adolescent population are:

Table 1 Lurasidone Studies for Adolescent Schizophrenia

Study	Design
Phase 1: D1050300	Open-label, rising single and multiple-dose PK and safety study in pediatric subjects with psychotic disorder. See 4.4.3.
Phase 3: D1050301	6-week randomized double-blind placebo-controlled efficacy and safety study in adolescent subjects with schizophrenia at 40 to 80mg lurasidone.
Phase 3: D1050302	6-month open-label extension safety study for completers of D1050301 and D1050325 (see Supplement 27) on lurasidone.

5.2 Review Strategy

The efficacy review of this supplement is solely based on the results of Study D1050301.

The safety review of this supplement is based on serious adverse events (SAEs) and adverse events (AEs) from Study D1050301 and D1050302 and an evaluation of supportive safety findings from safety assessment data (laboratory tests, vital signs, ECGs.)

Table 2 Sponsor Updates for this sNDA

Date	eCTD #	Content
7/29/16	142	Original sNDA Submission for Supplement 26
9/7/16	146	Sponsor provided updated labeling as requested to incorporate PLLR standards
9/12/16	147	Response to IR re: protocol violations at a site in Romania. Study D1050301 did not use the site in question. (D1050300 also did not.)
11/4/16	151	Response to IR requesting updated Literature Search review
11/25/16	155	Response to IR providing targeted exposure table and clarification of D1050302 assessment protocol (especially C-SSRS) and age subgroup analyses for selected lab parameters

12/21/16	158/159	Response to IR with Annual Report and Periodic Adverse Drug Experience Report (PADER)
1/5/17	160	120-Day Safety Update submission
1/11/17, 1/13/17	161/162	Response to IR providing additional PADER info on SAEs and deaths

5.3 Discussion of Individual Studies/Clinical Trials

N/A (There was only one study for this supplement, Section 5.1).

6 Review of Efficacy

Efficacy Summary

The efficacy of lurasidone at 40 to 80mg daily for the treatment of schizophrenia in adolescents was evaluated in one clinical trial, D1050301. Two different doses (40mg and 80mg) were compared to placebo using the primary endpoint of change in baseline to Week 6 on the PANSS total score. Superiority over placebo was demonstrated at both doses, but was not statistically significant in the U.S. sites versus the rest of the world. There are some concerns that the results were primarily driven by the sites in Ukraine, which were not available for OSI inspection due to current travel restrictions, although there was still statistical significance at 40mg after excluding Ukraine site results; also subgroup analyses are of limited interpretability since the overall statistical analysis should be based on the total study. Ukraine site subgroup efficacy analyses did not note unusual outliers driving results within the country. There was no significant additional efficacy noted for the 80mg versus the 40mg dose in this study, although the study was not designed to compare the doses, only each dose versus placebo. The biometrics reviewer Kelly Yang completed a Statistical Review and Evaluation and agrees with this conclusion.

6.1 Indication

Treatment of schizophrenia in adolescents.

6.1.1 Methods

The demonstration of efficacy of lurasidone in adolescents is based on a single clinical trial (D1050301). Because efficacy has already been established in adults with schizophrenia, which is considered essentially the same illness in the adolescent population as well, a single efficacy trial was deemed sufficient to fulfill this PREA requirement for lurasidone.

D1050301 was a 6-week randomized, double-blind, placebo-controlled, parallel group trial. This study was conducted at 72 (27 domestic) centers with 327 randomized total

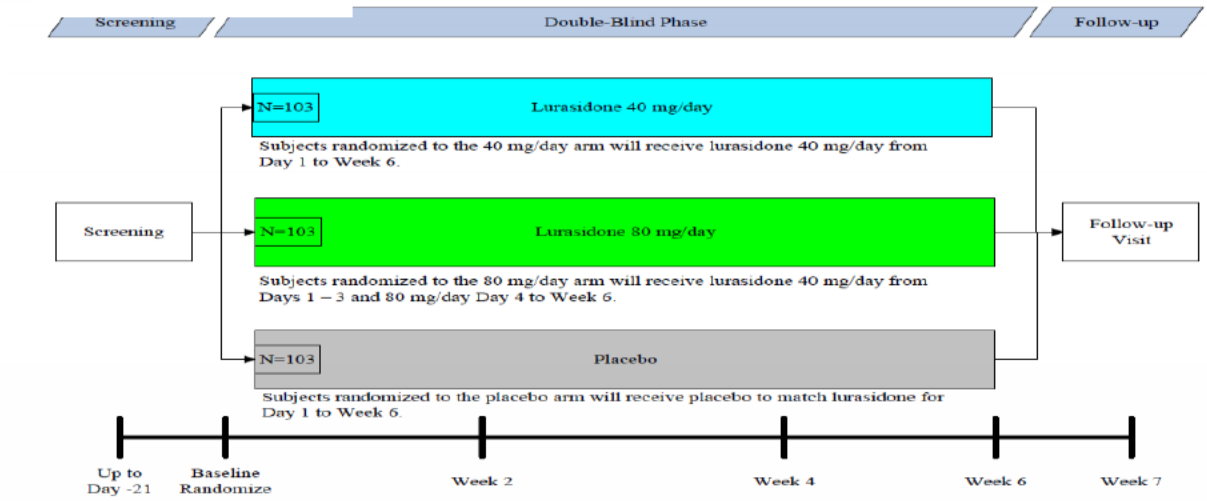
subjects (112 to placebo, 108 to lurasidone 40mg/day, and 106 to lurasidone 80mg/day). Dosages were based on the results from the pharmacokinetic study D1050300. (There is a run-in period for the 80mg group of 40mg from Day 1 to 3.)

The trial consisted of a screening/tapering period of up to 21 days, where some of the subjects were either inpatient or partial hospital or outpatient (or also in day or rehabilitation or school programs). Some were recently on concomitant antipsychotic medications that were tapered off (as were any psychotropic medications except for benzodiazepines) under medical supervision. (Inpatient stays had to be no longer than 14 days, unless they were stable and awaiting disposition only.)

Then the subjects entered a 6-week treatment period (where concomitant antipsychotics were prohibited), and a follow-up period of a week. Subjects were randomized to lurasidone 40mg or 80mg daily or placebo in a 1:1:1 ratio. Subjects were allowed to be hospitalized due to clinical instability during the study as warranted, but then usually discontinued from the study. Benzodiazepine or anticholinergic medications were permitted on an acute prn basis but not within 8 hours of scheduled assessments.

The statistical methods used for the primary and secondary endpoint efficacy analysis were as follows: all statistical tests were interpreted at a 2-sided significance level of 5% and all confidence intervals were presented at a 2-sided confidence level of 95%. The overall Type I error rate was controlled at a 5% level across all endpoints using a truncated Hochberg-based gatekeeping testing strategy. MMRM models were used for the main efficacy analyses, as well as supportive analyses with ANCOVA and LOCF with the ITT population, and sensitivity analyses based on pattern mixture model (PMM) using a placebo-based multiple imputation method.

Figure 1 D1050301 Study Schematic



6.1.2 Demographics

Adolescents (from all levels of care) aged 13 to 17 years with schizophrenia were included in the study based on PANSS total score ≥70 and CGI-S≥4 both at screening and baseline.

There were 110 subjects in the United States and Puerto Rico, and 217 subjects (66.3%) were overseas (Ukraine, Russia, Bulgaria, Romania, Poland, Spain, France, Hungary, Colombia, Mexico, Philippines, South Korea, and Malaysia.) 63.8% were male, 36.2% female. The mean age was 15.4 years. 67.5% were white. Mean baseline BMI was 22.48 kg/m_2. Distribution seemed grossly proportional across treatment arms.

Table 3 Study D1050301 Subject Demographics

Characteristic	Placebo (N=112)	Lurasidone 40 mg (N=110)	Lurasidone 80 mg (N=104)	Total (N=326)
Gender, n (%)	**112**	**110**	**104**	**326**
Male	71 (63.4)	67 (60.9)	70 (67.3)	208 (63.8)
Female	41 (36.6)	43 (39.1)	34 (32.7)	118 (36.2)
Age (years) *				
n	112	110	104	326
Mean (SD)	15.3 (1.37)	15.5 (1.33)	15.3 (1.35)	15.4 (1.35)
Median	16.0	16.0	15.0	16.0
Min, Max	13, 17	13, 17	13, 17	13, 17
Category, n (%)				
13-15 years old	55 (49.1)	50 (45.5)	55 (52.9)	160 (49.1)
16-17 years old	57 (50.9)	60 (54.5)	49 (47.1)	166 (50.9)
Race, n (%)	**112**	**110**	**104**	**326**
American Indian or Alaska Native	0	0	0	0
Asian	5 (4.5)	6 (5.5)	4 (3.8)	15 (4.6)
Black or African American	22 (19.6)	20 (18.2)	18 (17.3)	60 (18.4)
Native Hawaiian or Other Pacific Islander	0	0	0	0
White	74 (66.1)	73 (66.4)	73 (70.2)	220 (67.5)
Other	11 (9.8)	11 (10.0)	9 (8.7)	31 (9.5)
Ethnicity, n (%)	**112**	**110**	**104**	**326**
Hispanic or Latino	13 (11.6)	13 (11.8)	18 (17.3)	44 (13.5)
Not Hispanic or Latino	99 (88.4)	97 (88.2)	86 (82.7)	282 (86.5)
Country, n (%)	**112**	**110**	**104**	**326**
US	37 (33.0)	38 (34.5)	35 (33.7)	110 (33.7)
Non-US	75 (67.0)	72 (65.5)	69 (66.3)	216 (66.3)
Region, n (%)	**112**	**110**	**104**	**326**
North America	37 (33.0)	38 (34.5)	35 (33.7)	110 (33.7)
South America	9 (8.0)	9 (8.2)	8 (7.7)	26 (8.0)
Europe	61 (54.5)	57 (51.8)	57 (54.8)	175 (53.7)
Asia	5 (4.5)	6 (5.5)	4 (3.8)	15 (4.6)
Baseline BMI Percentile				
n	112	110	104	326
Mean (SD)	64.446 (30.1002)	63.070 (28.3891)	66.228 (27.8814)	64.550 (28.7707)
Median	76.238	67.401	75.568	73.817
Min, Max	3.58, 99.99	4.39, 99.19	0.19, 99.84	0.19, 99.99

Characteristic	Placebo (N=112)	Lurasidone 40 mg (N=110)	Lurasidone 80 mg (N=104)	Total (N=326)
Baseline BMI (kg/m^2)				
n	112	110	104	326
Mean (SD)	22.52 (3.606)	22.38 (3.262)	22.56 (3.497)	22.48 (3.448)
Median	22.43	21.99	22.26	22.33
Min, Max	15.9, 38.5	16.4, 31.1	15.0, 33.3	15.0, 38.5
Category, n (%)				
$< 25^{th}$ percentile	18 (16.1)	11 (10.0)	9 (8.7)	38 (11.7)
25^{th} to $< 50^{th}$ percentile	20 (17.9)	27 (24.5)	25 (24.0)	72 (22.1)
50^{th} to $\leq 85^{th}$ percentile	34 (30.4)	36 (32.7)	32 (30.8)	102 (31.3)
$> 85^{th}$ percentile	40 (35.7)	36 (32.7)	38 (36.5)	114 (35.0)
Baseline BMI Category, n (%)				
$< 3^{rd}$ percentile	0	0	1 (1.0)	1 (0.3)
3^{rd} to 85th percentile	72 (64.3)	74 (67.3)	65 (62.5)	211 (64.7)
$> 85^{th}$ to 97^{th} percentile	32 (28.6)	30 (27.3)	32 (30.8)	94 (28.8)
$> 97^{th}$ percentile	8 (7.1)	6 (5.5)	6 (5.8)	20 (6.1)
Baseline BMI Z-score				
n	112	110	104	326
Mean (SD)	0.54 (1.067)	0.48 (0.974)	0.57 (1.027)	0.53 (1.021)
Median	0.71	0.45	0.69	0.64
Min, Max	-1.8, 3.7	-1.7, 2.4	-2.9, 2.9	-2.9, 3.7
Baseline Weight (kg)				
n	112	110	104	326
Mean (SD)	64.0 (11.88)	63.5 (12.39)	63.9 (12.88)	63.8 (12.34)
Median	63.1	62.0	64.6	63.0
Min, Max	42, 102	37, 91	37, 94	37, 102
Baseline Height Percentile				
n	112	110	104	326
Mean (SD)	53.15 (27.044)	50.30 (29.353)	49.38 (28.253)	50.98 (28.184)
Median	55.47	48.12	51.45	52.45
Min, Max	0.1, 99.4	1.6, 99.0	3.6, 98.9	0.1, 99.4

Characteristic	Placebo (N=112)	Lurasidone 40 mg (N=110)	Lurasidone 80 mg (N=104)	Total (N=326)
Baseline Height (cm)				
n	112	110	104	326
Mean (SD)	168.40 (8.676)	167.95 (9.060)	167.72 (8.632)	168.03 (8.771)
Median	168.00	169.70	167.70	168.25
Min, Max	151.1, 186.0	146.0, 191.0	149.8, 186.0	146.0, 191.0
Baseline Height Z-score				
n	112	110	104	326
Mean (SD)	0.11 (0.935)	0.02 (0.969)	-0.01 (0.904)	0.04 (0.936)
Median	0.14	-0.05	0.04	0.06
Min, Max	-3.2, 2.5	-2.1, 2.3	-1.8, 2.3	-3.2, 2.5
Baseline Waist Circumference (cm)				
n	112	110	104	326
Mean (SD)	77.84 (10.949)	77.62 (11.395)	78.84 (10.659)	78.08 (10.990)
Median	77.00	77.00	78.00	77.75
Min, Max	52.0, 106.7	48.0, 109.5	58.0, 110.2	48.0, 110.2
Baseline PANSS Total Score (ITT)				
n	112	108	106	326
Mean (SD)	92.8 (11.08)	94.5 (10.97)	94.0 (11.12)	93.8 (11.04)
Median	92.0	93.0	92.5	92.5
Min, Max	70, 119	73, 119	73, 118	70, 119
Baseline CGI-Severity of Illness (ITT)				
n	112	108	106	326
Mean (SD)	4.8 (0.61)	4.9 (0.62)	4.8 (0.66)	4.8 (0.63)
Median	5.0	5.0	5.0	5.0
Min, Max	4, 7	4, 7	4, 6	4, 7

Abbreviations: BMI – Body Mass Index; CGI = Clinical Global Impression; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation; US = United States.
[a] Age is calculated at screening.
Note: Percentages are calculated with the number of subjects in each characteristic as denominator.
Note: Age and gender specific z-scores and percentiles are obtained by using WHO Growth Charts (2007).
Source: Table 14.1.2.1, Table 14.1.2.3

6.1.3 Subject Disposition

There were 327 subjects randomized out of 380 screened. Then, 285 subjects (87.2%) completed the treatment phase (42 discontinuations). The efficacy and safety analysis (ITT population) included 326 subjects. Then, 271 entered the safety extension study D1050302. There were 49 subjects (15%) that had protocol deviations.

Table 4 Study D1050301 Subject Disposition

	Placebo (N=113) n (%)	Lurasidone 40 mg (N=108) n (%)	Lurasidone 80 mg (N=106) n (%)	Lurasidone All (N=214) n (%)	Total (N=327) n (%)
Subjects who were randomized	113 (100.0)	108 (100.0)	106 (100.0)	214 (100.0)	327 (100.0)
Subjects who were randomized, but not dosed	1 (0.9)	0	0	0	1 (0.3)
Subjects in the ITT population	112 (99.1)	108 (100.0)	106 (100.0)	214 (100.0)	326 (99.7)
Subjects in the PP population	93 (82.3)	94 (87.0)	91 (85.8)	185 (86.4)	278 (85.0)
Subjects in the Safety population [a]	112	110	104	214	326
Subjects in the ITT who completed the 6-Week DB Phase	93 (82.3)	96 (88.9)	96 (90.6)	192 (89.7)	285 (87.2)
Subjects in the ITT who completed the 6-Week DB Phase and entered into the open-label extension Study D1050302	90 (79.6)	90 (83.3)	91 (85.8)	181 (84.6)	271 (82.9)
Subjects who discontinued during the DB Phase Primary reason for discontinuation	20 (17.7)	12 (11.1)	10 (9.4)	22 (10.3)	42 (12.8)
Lack of efficacy	4 (3.5)	1 (0.9)	2 (1.9)	3 (1.4)	7 (2.1)
Adverse event	9 (8.0)	5 (4.6)	3 (2.8)	8 (3.7)	17 (5.2)
Lost to follow-up	1 (0.9)	0	0	0	1 (0.3)
Protocol violation	1 (0.9)	0	0	0	1 (0.3)
Withdrawal of consent	4 (3.5)	5 (4.6)	5 (4.7)	10 (4.7)	14 (4.3)
Other	1 (0.9)	1 (0.9)	0	1 (0.5)	2 (0.6)

Abbreviations: DB = double-blind; ITT = Intent-to-Treat; PP = Per Protocol.

Table 5 Protocol Deviations

Protocol Deviation Code Term	Placebo (N=113) n (%)	Lurasidone 40 mg (N=108) n (%)	Lurasidone 80 mg (N=106) n (%)	Lurasidone All (N=214) n (%)	Total (N=327) n (%)
Total Number of Subjects with Protocol Deviations	20 (17.7)	14 (13.0)	15 (14.2)	29 (13.6)	49 (15.0)
Receives the incorrect study treatment	0	0	1 (0.9)	1 (0.5)	1 (0.3)
No Baseline and post-Baseline PANSS total score	1 (0.9)	0	0	0	1 (0.3)
Do not have 14 days or more of continuous exposure	10 (8.8)	5 (4.6)	3 (2.8)	8 (3.7)	18 (5.5)
Unblinded during the double-blind phase	0	0	0	0	0
Non-compliance of study drug	6 (5.3)	5 (4.6)	5 (4.7)	10 (4.7)	16 (4.9)
Prohibited medication or prohibited dose	1 (0.9)	0	2 (1.9)	2 (0.9)	3 (0.9)
Violated inclusion/exclusion criteria	7 (6.2)	5 (4.6)	5 (4.7)	10 (4.7)	17 (5.2)
Tests positive for substance abuse	1 (0.9)	1 (0.9)	0	1 (0.5)	2 (0.6)

Abbreviations: PANSS = Positive and Negative Symptoms Score.
Note: Subjects may have more than one protocol deviation.
Percentages are calculated with the number of subjects in each treatment group as denominator.

The distribution and types of protocol deviations were fairly consistent across treatment arms (18% placebo, 13% at 40mg, 14% at 80mg). Only one subject received the wrong treatment (one in the 80mg group). Rate of noncompliance with study drug violations

was about 5% overall. Protocol deviations were likely not a major factor influencing study results here.

Baseline Psychiatric History/Hospitalizations:
As per the ADHO.xpt dataset, a total of 102 subjects (31%) in the study underwent inpatient hospitalization either during the screening period and/or during the study period: 37 subjects (34%) in 40mg treatment arm, 29 subjects (28%) in the 80mg arm, and 36 subjects (32%) on placebo. Inpatient hospitalization status can reflect more severe and acute illness severity; the percentage of subjects with this status appeared roughly even across treatment arm groups and likely did not influence overall efficacy results in this study.

Mean baseline PANSS scores were also fairly even across treatment groups. The mean PANSS total score at Baseline was 94.0 ± 11.12 for the lurasidone 80 mg/day group, 94.5 ± 10.97 for the lurasidone 40 mg/day group, and 92.8 ± 11.08 for the placebo group.

Treatment Compliance:
Compliance with study drug was reportedly monitored closely at each visit, and the subjects were instructed to bring in any unused drug. Anyone missing at least two doses a week, or taking more than eight doses a week was reported to the Medical Monitor. Rates of noncompliance with study drug as per Table 6 were about 5% in each arm and were fairly even across treatment groups.

Concomitant Medications:
About 40% of trial subjects were on concomitant medication; 22% were on benzodiazepines which were the only other psychotropic drug permitted in the study aside from infrequent prn sleep medication only. The distribution was fairly similar across treatment groups (23% placebo, 25% at 40mg, 18% at 80mg). This usage likely did not influence the study results much.

Table 6 Concomitant Medications

ATC Level 3/ Preferred Name	Placebo (N=112) n (%)	Lurasidone			Total (N=326) n (%)
		40 mg (N=110) n (%)	80 mg (N=104) n (%)	All (N=214) n (%)	
Number of subjects					
With any Concomitant Medication	41 (36.6)	45 (40.9)	45 (43.3)	90 (42.1)	131 (40.2)
With any Concomitant Benzodiazepines	26 (23.2)	27 (24.5)	19 (18.3)	46 (21.5)	72 (22.1)
Adrenergics, Inhalants	2 (1.8)	6 (5.5)	4 (3.8)	10 (4.7)	12 (3.7)
Salbutamol	2 (1.8)	5 (4.5)	3 (2.9)	8 (3.7)	10 (3.1)
Anticholinergic Agents	2 (1.8)	5 (4.5)	3 (2.9)	8 (3.7)	10 (3.1)
Benzatropine Mesilate	0	3 (2.7)	0	3 (1.4)	3 (0.9)
Antiinflammatory And Antirheumatic Products, Non-Steroids	3 (2.7)	4 (3.6)	6 (5.8)	10 (4.7)	13 (4.0)
Ibuprofen	1 (0.9)	1 (0.9)	5 (4.8)	6 (2.8)	7 (2.1)
Anxiolytics	26 (23.2)	27 (24.5)	17 (16.3)	44 (20.6)	70 (21.5)
Alprazolam	2 (1.8)	4 (3.6)	1 (1.0)	5 (2.3)	7 (2.1)
Diazepam	5 (4.5)	1 (0.9)	1 (1.0)	2 (0.9)	7 (2.1)
Lorazepam	18 (16.1)	22 (20.0)	15 (14.4)	37 (17.3)	55 (16.9)
Beta Blocking Agents	2 (1.8)	3 (2.7)	3 (2.9)	6 (2.8)	8 (2.5)
Propranolol	2 (1.8)	2 (1.8)	3 (2.9)	5 (2.3)	7 (2.1)
Beta-Lactam Antibacterials, Penicillins	1 (0.9)	3 (2.7)	0	3 (1.4)	4 (1.2)
Amoxicillin	1 (0.9)	3 (2.7)	0	3 (1.4)	4 (1.2)
Hypnotics And Sedatives	5 (4.5)	8 (7.3)	3 (2.9)	11 (5.1)	16 (4.9)
Melatonin	1 (0.9)	3 (2.7)	0	3 (1.4)	4 (1.2)
Other Analgesics And Antipyretics	11 (9.8)	10 (9.1)	13 (12.5)	23 (10.7)	34 (10.4)
Paracetamol	7 (6.3)	8 (7.3)	11 (10.6)	19 (8.9)	26 (8.0)

Note: Percentages are calculated with the number of subjects in each treatment group as denominator.
Source: Table 14.1.7.2.2

As per my JMP analysis of the ADCM.xpt dataset, a total of 250 subjects (77% of N=326) were on antipsychotics at some point before and during the screening period up until Study Day 1. There were 81 subjects (74%) assigned to the 40mg arm, 87 (84%) to the 80mg arm, and 82 (73%) to placebo. 49 of these subjects ended up discontinuing the study early before Day 42 (12 (11%) on 40mg, 16 (15%) on 80mg, and 21 (19%) on placebo.) Overall, the distribution of subjects on prior recent antipsychotic treatment was fairly even across treatment arms (perhaps slightly higher in the 80mg arm) and likely did not lead to major bias in study results.

A total of 18 subjects (5.5%) eventually required addition of other antipsychotic medication during the study (11 (10%) on placebo, 3 (3%) on 40mg, and 4 (4%) on 80mg). All but three were discontinued early from the study. The three that remained were as follows: two on 80mg were started on another antipsychotic near the end of the study (Day 41 which was reported as SAE, and Day 42) but continued to Day 49 (end of trial), and one on placebo started another antipsychotic at Day 43 (and ended the study Day 43). As these subjects were basically discontinued from the trial (except three that were already at the end of the study), they did not affect overall efficacy results.

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint was the change from Baseline in the Positive and Negative Syndrome Scale (PANSS) Total Score at Week 6.

The LS mean change (± SE) from Baseline to Week 6 for the PANSS total score based on an MMRM model was -10.5 ± 1.59, -18.6 ± 1.59, and -18.3 ± 1.60 for the placebo, lurasidone 40 mg/day and 80 mg/day groups, respectively. There was a significant treatment difference favoring both the lurasidone 40 mg/day and 80 mg/day treatment groups (-8.0 ± 2.21, adjusted p = 0.0006 and -7.7 ± 2.22, adjusted p = 0.0008, respectively). These results were supported using an ANCOVA analysis, MMRM analysis using the PP population, as well PMM and REM sensitivity analyses. Therefore treatment with lurasidone significantly improved symptoms of schizophrenia, as measured by the PANSS Total Score, after 6 weeks of treatment as compared to placebo in this study.

However, the subgroup analyses showed some issues. The U.S. site subjects did not show statistically significant improvement in the PANSS total score in either drug arm versus placebo. Also, the other country regions when pooled without Ukraine or the U.S. did not show statistical significance. (This issue will be discussed further in Section 6.1.7).

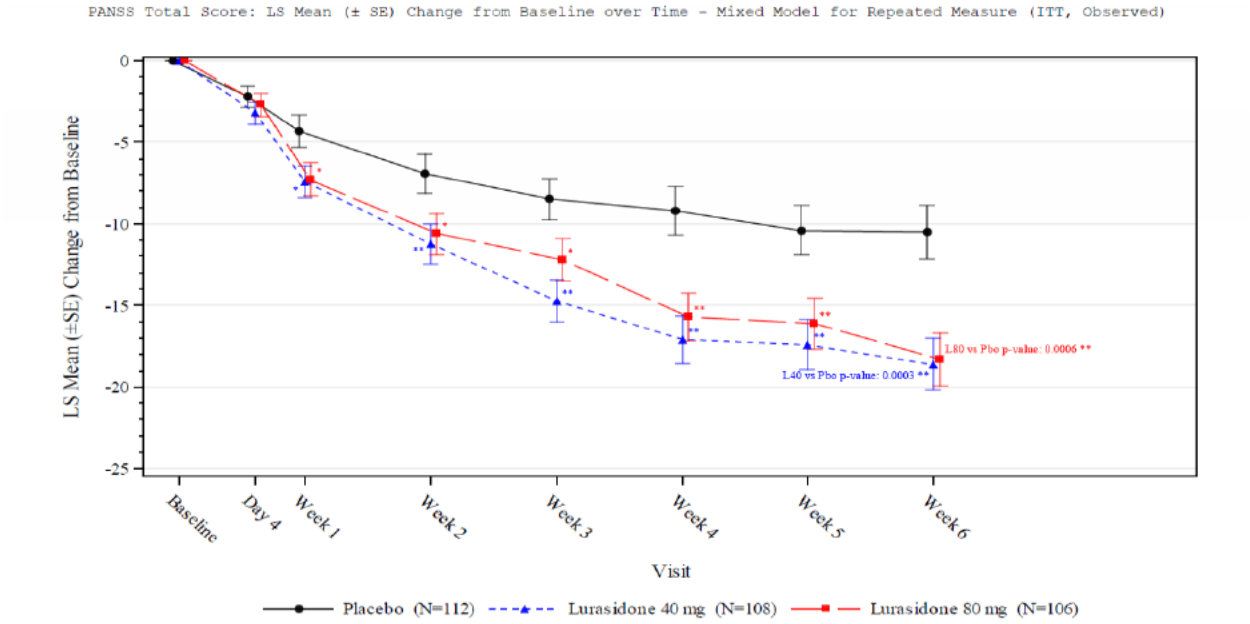
Table 7 Primary Endpoint: PANSS Total Score Change from Baseline

Change from Baseline in PANSS Total Score Over Time – Mixed Model for Repeated Measures (ITT Population)

PANSS Total Score	Placebo (N=112)	Lurasidone 40 mg (N=108)	Lurasidone 80 mg (N=106)
Week 5			
n	95	97	98
LS Mean (SE)	-10.4 (1.52)	-17.4 (1.52)	-16.1 (1.53)
Difference of LS Mean (SE) (vs. Placebo)		-7.0 (2.11)	-5.7 (2.11)
95% CI of Difference		(-11.2, -2.9)	(-9.9, -1.6)
p-value (vs. Placebo)		0.0010	0.0070
Week 6			
n	93	96	97
LS Mean (SE)	-10.5 (1.59)	-18.6 (1.59)	-18.3 (1.60)
Difference of LS Mean (SE) (vs. Placebo)		-8.0 (2.21)	-7.7 (2.22)
95% CI of Difference		(-12.4, -3.7)	(-12.1, -3.4)
p-value (vs. Placebo)		0.0003	0.0006

Abbreviations: CI = confidence interval; ITT = Intent-to-Treat; LS = Least Squares; PANSS = Positive and Negative Symptoms Scale; SE = standard error.
Note: LS Mean, LS mean difference, and the associated 95% CI and p-value for change from baseline are based on Mixed Model for Repeated Measures with fixed effects terms for treatment, visit (as a categorical variable), pooled country, age strata, PANSS total score at baseline, and treatment-by-visit interaction.
Note: Higher values of PANSS total score represent greater severity of illness.
Source: Table 14.2.1.1.1

Figure 2 PANSS Total Score Change from Baseline Graph

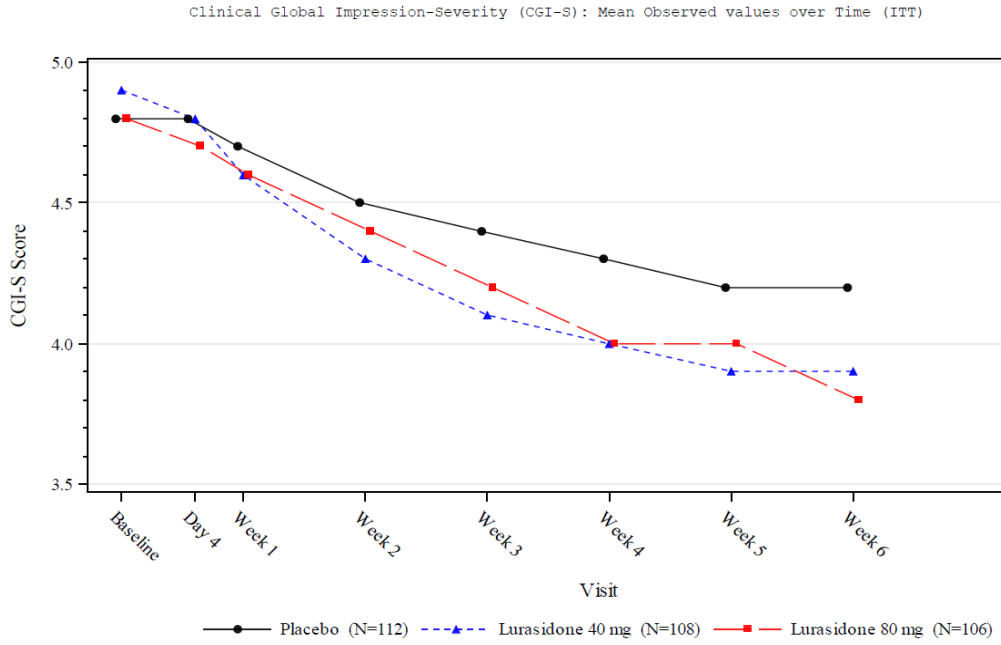


6.1.5 Analysis of Secondary Endpoints(s)

The key secondary endpoint was the change from Baseline in Clinical Global Impression Severity (CGI-S) scale at Week 6.

The LS mean change (± SE) from Baseline to Week 6 for the CGI-S score based on an MMRM model was -0.50 ± 0.094, -0.97 ± 0.093, and -0.92 ± 0.093 for the placebo, lurasidone 40 mg/day and 80 mg/day groups, respectively. There was a significant treatment difference favoring both the lurasidone 40 mg/day and 80 mg/day treatment groups (-0.47 ± 0.130, adjusted p = 0.0008 and -0.42 ± 0.130, adjusted p = 0.0015, respectively). These results were supported using an ANCOVA analysis, MMRM analysis using the PP population, as well PMM and REM sensitivity analyses. Therefore treatment with lurasidone significantly improved overall illness severity, as measured by the CGI-S score, after 6 weeks of treatment as compared to placebo in this study.

Figure 3 Key Secondary Endpoint: CGI-S Change from Baseline Graph



However, again, the U.S. population did not show statistical significance between drug and placebo on this measure.

6.1.6 Other Endpoints

- PANSS Subscale Scores
- Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)
- Clinician-Rated Children's Global Assessment Scale (CGAS)

Reviewer Comment:
Subscale scores are not felt to be as generalizable/significant as secondary endpoints, although in this study all the four subscales (Positive, Negative, General Psychopathology, Excitability) examined showed significant improvement from baseline by Week 6 in both treatment arms versus placebo. The PQ-LES-Q showed significant mean changes at Week 6 (6.1 for lurasidone 80mg and 5.6 for 40mg) compared to placebo (0.3). The CGAS also showed significant improvement from baseline by Week 6 in both treatment arms (11.0 for 80mg and 10.7 for 40mg) versus placebo (6.1). These secondary endpoints all seem to confirm some beneficial clinical effect of drug versus placebo at both dosages by the end of the study, although regional subgroup analyses for these secondary endpoints were not assessed.

6.1.7 Subpopulations

Age:

Table 8 PANSS Total Score Mean Change from Baseline by Age Group

Mean Change from Baseline (SD) to Week 6 (ITT, LOCF)

	Placebo (N=112)		Lurasidone 40mg (N=108)		Lurasidone 80mg (N=106)	
	N		N		N	
Ages 13-15	55	-11.4 (18.18)	49	-19.7 (14.60	54	-19.1 (15.67)
Ages 16-17	57	-8.1 (16.30)	59	-16.9 (16.30)	52	-16.7 (15.77)

Reviewer Comment: No major difference in placebo-adjusted efficacy is apparent between the age 13-15 year group and the age 16-17 year group for either dose group.

Race:

Table 9 PANSS Total Score by Race

PANSS Total Score: Subgroup Analysis by Race in Changes from Baseline to Week 6 (ITT LOCF)

PANSS Total Score	Placebo (N=112)	Lurasidone 40 mg (N=108)	Lurasidone 80 mg (N=106)
White			
n	74	72	74
Mean (SD) at Baseline	94.4 (10.32)	96.4 (11.38)	95.1 (11.34)
Mean (SD) at Week 6 LOCF	85.8 (15.69)	79.1 (18.35)	78.2 (17.15)
Change from Baseline			
Mean (SD)	-8.6 (14.43)	-17.3 (14.95)	-16.9 (14.00)
LS Mean (SE) (a)	-7.3 (2.17)	-15.3 (2.22)	-15.2 (2.18)
LS Mean Diff (95% CI) (vs. Placebo) (a)		-8.1 (-13.3, -2.9)	-8.0 (-13.2, -2.8)
Black or African American			
n	22	19	19
Mean (SD) at Baseline	88.4 (11.86)	87.0 (8.29)	86.8 (8.18)
Mean (SD) at Week 6 LOCF	73.3 (22.33)	72.1 (19.94)	67.7 (17.25)
Change from Baseline			
Mean (SD)	-15.0 (22.51)	-14.9 (18.32)	-19.1 (18.61)
LS Mean (SE) (a)	-10.8 (4.14)	-11.0 (4.38)	-15.0 (4.38)
LS Mean Diff (95% CI) (vs. Placebo) (a)		-0.2 (-10.1, 9.6)	-4.2 (-14.1, 5.7)

PANSS Total Score: Subgroup Analysis by Race in Changes from Baseline to Week 6 (ITT LOCF)

PANSS Total Score	Placebo (N=112)	Lurasidone 40 mg (N=108)	Lurasidone 80 mg (N=106)
Other			
n	11	11	9
Mean (SD) at Baseline	94.8 (13.14)	97.4 (7.09)	101.9 (7.57)
Mean (SD) at Week 6 LOCF	82.7 (26.71)	70.5 (14.56)	78.9 (26.50)
Change from Baseline			
Mean (SD)	-12.1 (21.92)	-26.9 (12.28)	-23.0 (22.26)
LS Mean (SE) (a)	-16.8 (6.78)	-31.7 (6.75)	-25.9 (6.99)
LS Mean Diff (95% CI) (vs. Placebo) (a)		-14.8 (-28.3, -1.4)	-9.0 (-23.3, 5.2)
p-value Treatment*Subgroup Interaction			0.4949

PANSS Total Score: Subgroup Analysis by Race in Changes from Baseline to Week 6 (ITT LOCF)

PANSS Total Score	Placebo (N=112)	Lurasidone 40 mg (N=108)	Lurasidone 80 mg (N=106)
Asian			
n	5	6	4
Mean (SD) at Baseline	84.6 (6.35)	89.5 (8.48)	89.3 (7.89)
Mean (SD) at Week 6 LOCF	88.2 (18.79)	67.0 (22.02)	71.0 (17.26)
Change from Baseline			
Mean (SD)	3.6 (13.43)	-22.5 (15.58)	-18.3 (18.39)

Reviewer Comment: The subgroup of black subjects (N=60) did not show significant efficacy at either dose versus placebo, as compared to all the other racial subgroups who did. Of note all the black subjects were in the U.S. sites (which also means 54.5% of U.S. subjects were black.) This might explain in part why the U.S. did not show statistical significance in efficacy (although the white U.S. subjects also did not show significance in efficacy per the Statistics reviewer.) It is unclear why this subgroup would show less treatment response than the other subgroups, although it may be again, connected to the U.S. sites overall not showing significant efficacy. There was a higher placebo response than the other subgroups, but also less robust improvements in the drug treatment arms than the other subgroups. It could also just be secondary to a low overall N/ lack of power for this subgroup analysis.

Ethnicity:

Table 10 PANSS Total Score by Ethnicity

PANSS Total Score: Subgroup Analysis by Ethnicity in Changes from Baseline to Week 6 (ITT LOCF)

PANSS Total Score	Placebo (N=112)	Lurasidone 40 mg (N=108)	Lurasidone 80 mg (N=106)
Hispanic or Latino			
n	13	12	19
Mean (SD) at Baseline	96.2 (10.81)	99.3 (7.98)	100.4 (11.79)
Mean (SD) at Week 6 LOCF	87.5 (24.95)	69.7 (15.20)	83.6 (20.75)
Change from Baseline			
Mean (SD)	-8.7 (21.59)	-29.7 (14.32)	-16.8 (18.81)
LS Mean (SE) (a)	-5.2 (5.52)	-26.6 (5.82)	-12.4 (4.32)
LS Mean Diff (95% CI) (vs. Placebo) (a)		-21.4 (-34.0, -8.7)	-7.3 (-18.9, 4.4)
Not Hispanic or Latino			
n	99	96	87
Mean (SD) at Baseline	92.4 (11.09)	93.9 (11.17)	92.6 (10.52)
Mean (SD) at Week 6 LOCF	82.6 (18.07)	77.2 (19.00)	74.5 (17.44)
Change from Baseline			
Mean (SD)	-9.8 (16.73)	-16.7 (15.15)	-18.1 (15.04)
LS Mean (SE) (a)	-9.2 (1.83)	-15.7 (1.88)	-17.4 (1.97)
LS Mean Diff (95% CI) (vs. Placebo) (a)		-6.5 (-11.0, -2.0)	-8.2 (-12.8, -3.5)
p-value Treatment*Subgroup Interaction			0.0339

Reviewer Comment: Although the p-value indicates some degree of significance in subgroup differences here (mainly probably due to an unusually robust response at the 40mg dose in Latinos of -29.7 versus non-Latinos at -16.7), the Statistical Reviewer notes that p-values cannot be used to interpret such significance accordingly. The 40mg difference is likely secondary to a disparity in sample size (N=12 Hispanic vs. N=96 non-Hispanic) leading to an artificially skewed value that likely did not affect overall results that much (and the same trend was not seen at the 80mg dose).

Gender:

Table 11 PANSS Total Score Mean Change from Baseline by Gender

PANSS Total Score Mean Change from Baseline (SD) to Week 6 (ITT, LOCF)

	Placebo (N=112)		Lurasidone 40mg (N=108)		Lurasidone 80mg (N=106)	
	N		N		N	
Male	71	-7.5 (16.70)	67	-18.1 (15.00)	70	-17.1 (15.42)
Female	41	-13.4 (17.76)	41	-18.2 (16.58)	36	-19.3 (16.32)

Reviewer Comment: No major differences in efficacy between gender groups are noted in this study (although there was a higher placebo response in females versus males).

Country:

Table 12 PANSS Total Score by U.S. versus Non-U.S.

PANSS Total Score: Subgroup Analysis by US vs. Rest of the World in Changes from Baseline to Week 6 (ITT LOCF)

PANSS Total Score	Placebo (N=112)	Lurasidone 40 mg (N=108)	Lurasidone 80 mg (N=106)
US			
n	37	36	37
Mean (SD) at Baseline	89.9 (11.64)	93.5 (11.84)	91.8 (12.00)
Mean (SD) at Week 6 LOCF	76.2 (22.15)	73.5 (18.84)	72.0 (23.40)
Change from Baseline			
Mean (SD)	-13.7 (20.18)	-20.0 (18.02)	-19.8 (20.76)
LS Mean (SE) (a)	-14.1 (2.67)	-19.8 (2.69)	-19.8 (2.66)
LS Mean Diff (95% CI) (vs. Placebo) (a)		-5.7 (-13.1, 1.7)	-5.7 (-13.0, 1.7)
Non-US			
n	75	72	69
Mean (SD) at Baseline	94.3 (10.56)	95.0 (10.56)	95.2 (10.51)
Mean (SD) at Week 6 LOCF	86.6 (16.20)	77.8 (18.60)	78.3 (14.61)
Change from Baseline			
Mean (SD)	-7.7 (15.37)	-17.2 (14.19)	-16.9 (12.21)
LS Mean (SE) (a)	-7.8 (1.86)	-17.3 (1.91)	-16.8 (1.94)
LS Mean Diff (95% CI) (vs. Placebo) (a)		-9.5 (-14.7, -4.3)	-9.0 (-14.2, -3.7)
p-value Treatment*Subgroup Interaction			0.6711

Reviewer Comment: Our Statistics Reviewer Kelly Yang, PhD, also did her own country subgroup analyses which confirm that the U.S. results do not appear statistically significant, although p-values for subgroup analyses are of limited significance and interpretability relative to the ITT population result. She noted that the Ukraine sites might be driving the efficacy results the most, as without the Ukraine sites, there is no possible statistical significance at the 80mg dose. (Excluding Ukraine, results remained significant only at 40mg (p=0.019), and at neither dose when excluding both the U.S. and Ukraine groups. Results were significant for both doses when only excluding the U.S. subgroup.) Of concern, Ukraine sites have been implicated several times in prior study fraud issues, and OSE site inspection there was unavailable due to travel restrictions there. (Per our Statistical Reviewer, none of the Ukraine sites showed unusual variation from each other.) Another issue is that the U.S. sites had a higher placebo response rate than elsewhere (and Ukraine had a smaller placebo response

rate). The U.S. subgroup did at least show numerical improvement over placebo on the PANSS total score for both doses, although to a lesser extent than the other sites.

Table 13 Statistical Reviewer Efficacy Data on PANSS Total Score by Country Region (P-Values not generalizable)

Overall Results

PANSS Total Score	**Placebo (N=112)**	**Lurasidone 40 mg (N=108)**	**Lurasidone 80 mg (N=106)**
Week 6			
n	93	96	97
LS Mean (SE)	-10.5 (1.59)	-18.6 (1.59)	-18.3 (1.60)
Difference of LS Mean (SE) (vs. Placebo)		**-8.0 (2.21)**	**-7.7 (2.22)**
95% CI of Difference		(-12.4, -3.7)	(-12.1, -3.4)
p-value (vs. Placebo)		0.0003	0.0006

Foreign (exclude USA)

PANSS Total Score	**Placebo (N=75)**	**Lurasidone 40 mg (N=71)**	**Lurasidone 80 mg (N=69)**
Week 6			
n	64	67	67
LS Mean (SE)	-8.2 (1.68)	-17.6 (1.68)	-16.8 (1.70)
Difference of LS Mean (SE) (vs. Placebo)		**-9.4 (2.36)**	**-8.6 (2.37)**
95% CI of Difference		(-14.1, -4.8)	(-13.3, -3.9)
p-value (vs. Placebo)		<0.0001	0.0004

USA only

PANSS Total Score	**Placebo (N=37)**	**Lurasidone 40 mg (N=35)**	**Lurasidone 80 mg (N=37)**
Week 6			
n	29	29	30
LS Mean (SE)	-16.0 (3.33)	-20.9 (3.32)	-21.9 (3.29)
Difference of LS Mean (SE) (vs. Placebo)		**-4.9 (4.69)**	**-5.9 (4.66)**
95% CI of Difference		(-14.2, 4.4)	(-15.2, 3.4)
p-value (vs. Placebo)		0.2997	0.2095

Overall (exclude UKR)

PANSS Total Score	Placebo (N=87)	Lurasidone 40 mg (N=82)	Lurasidone 80 mg (N=81)
Week 6			
n	70	73	72
LS Mean (SE)	-12.3 (1.97)	-18.8 (1.96)	-17.2 (1.99)
Difference of LS Mean (SE) (vs. Placebo)		**-6.5 (2.75)**	**-4.9 (2.76)**
95% CI of Difference		(-11.9, -1.1)	(-10.3, 0.6)
p-value (vs. Placebo)		0.0191	0.0785

UKR Only

PANSS Total Score	Placebo (N=25)	Lurasidone 40 mg (N=24)	Lurasidone 80 mg (N=25)
Week 6			
n	23	23	25
LS Mean (SE)	-5.0 (1.98)	-17.5 (2.00)	-21.3 (1.94)
Difference of LS Mean (SE) (vs. Placebo)		**-12.5 (2.81)**	**-16.3 (2.76)**
95% CI of Difference		(-18.1, -6.9)	(-21.8, -10.7)
p-value (vs. Placebo)		<0.0001	<0.0001

Weight (BMI):

Table 14 PANSS Total Score Mean Change from Baseline by BMI

PANSS Total Score Mean Change from Baseline (SD) to Week 6 (ITT, LOCF)

BMI Subgroup by Percentile	Placebo (N=112)		Lurasidone 40mg (N=108)		Lurasidone 80mg (N=106)	
	N		N		N	
<25th	18	-11.8 (21.37)	11	-17.6 (17.98)	9	-16.4 (14.24)
25th-85th	54	-8.6 (15.34)	61	-18.4 (14.30)	59	-16.5 (14.72)
>85th	40	-10.2 (18.00)	36	-17.8 (17.19)	38	-20.3 (17.49)

Reviewer Comment: Differences in BMI baseline (<25%, 25-85%, >85%) did not result in changes in efficacy trends in this study. Overall with these subgroup analyses, the p-value comparisons as per the statistics reviewer should only be considered exploratory and not generalizable due to the low sample sizes involved; the mean treatment differences should be used moreso for comparison. Also these subgroup analyses used LOCF values which are considered less accurate overall.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The Sponsor evaluated efficacy for lurasidone at both 40mg daily and 80mg daily versus placebo. Significant change in PANSS scores were noted at both dosages,

although not in the domestic sites. The 40mg dose is recommended given its similar efficacy to 80mg and lower AE potential in the adolescent population.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

(b) (4)

6.1.10 Additional Efficacy Issues/Analyses

N/A

7 Review of Safety

Safety Summary

Safety data in Study D1050301 was collected during the entire 6-week trial and follow-up period, as well as during a subsequent long-term open-label safety study D1050302. There were 201 subjects (137 on drug, 64 on placebo) reporting adverse events (AEs) during the treatment period. There were no deaths reported during this study. There were 15 serious adverse events (SAEs), with 6 occurring on lurasidone.
The AEs that occurred at ≥5% rate in my analysis and greater than twice that of placebo were: somnolence/sedation, nausea, vomiting, akathisia, EPS (non-akathisia), and rhinorrhea/rhinitis (80mg only).

These AEs are overall in keeping with expected side effects from prior lurasidone and atypical antipsychotic studies and current labeling.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data were derived from Study D1050301 during the randomized controlled trial portion only. An open-label long-term extension study D1050302 was also performed with 83% of subjects (271 subjects) from D1050301 as well as subjects from another pediatric autism study D1050325 (covered in Supplement 27).

7.1.2 Categorization of Adverse Events

AE terms verbatim terms were coded to preferred terms using MedDRA version 16.0. Although an audit of this coding process revealed no major inaccuracies, the granularity of MedDRA does allow splitting of some adverse event terms to an extent that may not

be clinically useful. Therefore, for purposes of this review, the following related AE preferred terms were subsumed under a common term for calculation of reporting rates in the following sections:

Somnolence: somnolence, sedation, hypersomnia
EPS (non-akathisia): hyperkinesia, muscle spasms, muscle rigidity, oculogyric crisis, dyskinesia, dystonia, Parkinsonism, tremor, cogwheel rigidity, extrapyramidal disorder, tardive dyskinesia, musculoskeletal stiffness, joint stiffness
Viral Infection: nasopharyngitis, influenza, viral infection, upper respiratory infection (URI)
Rhinitis/Rhinorrhea: rhinitis, allergic rhinitis, rhinorrhea, nasal congestion
Schizophrenia: schizophrenia, auditory hallucination
Abdominal Pain: abdominal pain, abdominal pain upper, abdominal discomfort, dyspepsia

Adverse events were also categorized as serious or non-serious. Serious adverse events (SAEs) were defined by one of the following criteria:

• results in death.
• life-threatening (at immediate risk of death at the time of the occurrence).
• requires inpatient hospitalization or prolongs inpatient hospitalization.
• results in persistent or significant disability or incapacity.
• congenital abnormality or birth defect.
• other important medical events, that is, events not meeting any of the above criteria but which may jeopardize the subject and may require medical or surgical intervention to prevent one of the above outcomes.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

There have only been two RCTs done (D1050301 and D1050325) in this population on lurasidone so far, for different indications/diagnoses, ages, and doses, so studies were not pooled by this reviewer.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

For the lurasidone Pediatric Written Request fulfillment, the Phase 3 trials being performed are:

- D1020301 (6-week study being reviewed in this supplement for schizophrenia, ages 13-17): 326 subjects who were dosed (40mg, 80mg, placebo)

- D1020325 (6-week study being reviewed in Supplement 27 for irritability in autism, ages 6-17): 149 subjects who were dosed (20mg, 60mg, placebo)
- D1020302 (6-month open-label extension safety study with subjects from both of the prior studies): 271 from D1020301 and 125 from D1020325 were screened to enter, with data from 305 total subjects available in the study (125 from D1020325, and 180 from D1020301, with data from 91 subjects from D1020301 still unavailable/in process as of March 1, 2016 cutoff date in original study report; some additional information on remaining subjects now available with 120-Day Update with October 27, 2016 cutoff date.)

Table 15 Exposure in Phase 3 Lurasidone Pediatric Trials D1050301, D1050325, and D1050302

Enumeration of Subjects by Exposure Duration in Phase 3 Lurasidone Pediatric Studies, through October 27, 2016

Indication	Age Range [a]	Any Exposure, n (%)	Exposure ≥ 26 Weeks, n (%)	Exposure ≥ 52 Weeks, n (%)
Schizophrenia	13-17	304 (100)	216 (71.1)	156 (51.3)
Autism	6-12	96 (100)	67 (69.8)	49 (51.0)
	13-17	41 (100)	29 (70.7)	19 (46.3)
Total	**6-17**	**441 (100)**	**312 (70.7)**	**224 (50.8)**

[a] age at screening in core study

A total of 546 pediatric patients in these studies (including Phase 1) received lurasidone for any duration as of the extension study data cut-off date of March 1, 2016 (441 in Phase 3). The mean days of lurasidone exposure was about 338 days.

Demographics across studies showed no major inconsistencies, although the overall rate of treatment duration was longer in the 6 to 12 year old group (402 days) compared to the 13 to 17 year group (315 days), which is attributed to all of those younger subjects (who were in D1050325 only) completing their study 13 months earlier than D1050301 (and some subjects in D1050301 not yet completing/being included in D1050302 data). Overall gender and race distributions seem roughly reflective of those in the general adolescent schizophrenia population (more males are typical in this age group).

Overall exposure to lurasidone in D1050301 was 23.3 subject-years. For D1050325 overall lurasidone exposure was 10.7 subject-years. As of the cut-off date of March 1, 2016, D1050302 overall lurasidone exposure was 282.5 subject-years. (As of the 120-Day Safety Update with cutoff date of Oct 27, 2016, it was 430.0 subject-years.)

Reviewer Comment: Duration of exposure seemed even across treatment groups in this study and likely was not a factor in any potential study bias.

7.2.2 Explorations for Dose Response

The fixed-dose design of Study D1050301 permitted an assessment of the dose-response relationship for safety findings.

7.2.3 Special Animal and/or In Vitro Testing

N/A

7.2.4 Routine Clinical Testing

In addition to AE assessments, safety measurements in Study D1050301 included the following: AE reporting, laboratory tests, vital signs, physical examination, height (as measured by stadiometer), electrocardiogram (ECG), body weight, body mass index (BMI) and waist circumference. Other safety assessments include: the Cogstate Computerized Cognitive Test Battery, Barnes Akathisia Rating Scale (BARS), the Abnormal Involuntary Movement Scale (AIMS), the Simpson-Angus Scale (SAS), the Columbia Suicide Severity Rating Scale (C-SSRS), Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU), Tanner staging, menstrual cyclicity (female subjects), and hormonal parameters. Overall labs, physical examination, and ECG assessments and urine tests were done only at screening, baseline (Day 1), and Week 6 (Day 43).

All safety analyses and summaries were based on the safety analysis population of 326 subjects. Safety reporting included all safety data reported during the 6-week double-blind period, as well as the post-treatment period, if the subject did not enter the extension study. There were no imputations of missing values for clinical laboratory test results, vital sign measurements, and ECG evaluations in the by-visit analyses. The same safety assessments were carried forward into the open-label extension study D1050302. (The C-SSRS was carried forward for subjects originally from D1050301 but not for subjects who were originally from the other pediatric trial D1050325, since the C-SSRS was not administered in that study. It was administered every two weeks for the first 8 weeks of D1050302, then every month thereafter until the end of the study at Week 104, and then also at Week 105 Follow-Up.)

Table 16 Schedule of Assessments for D1050301

Study Visit Number Study Visit Type	Visit 1[a] Screening	Visit 2 Baseline	Visit 3 Day 4	Visit 4 Week 1	Visit 5 Week 2	Visit 6 Week 3	Visit 7 Week 4	Visit 8 Week 5	EOS/ET Visit 9[b] Week 6	Visit 10 Follow-up[c]
Study Visit Day	-21 to -1	1	4±2	8±2	15±2	22±2	29±2	36±2	43±2	50±2
Study Visit Type	Inpatient or Out-patient	Inpatient Optional	Inpatient Optional	Inpatient Optional	Inpatient Optional	Inpatient Optional	Inpatient Optional	Inpatient Optional	Inpatient Optional	Out-patient
Obtain informed consent/assent	X									
Inclusion/exclusion criteria	X	X								
Randomize to treatment		X								
Interactive Voice/Web Response System (IXRS) subject registry/visit	X	X	X	X	X	X	X	X	X	X
Dispense study drug		X		X	X	X	X	X		
Study drug accountability/assess compliance				X	X	X	X	X	X	
Clinical and Laboratory Evaluations:										
Prior/concomitant medication review	X	X	X	X	X	X	X	X	X	X
Adverse event monitoring	X	X	X	X	X	X	X	X	X	X
Medical history	X									
Psychiatric history/mental status	X									
Schedule for Affective Disorders and Schizophrenia for School-age Children (K-SADS-PL)	X									
Physical examination	X	X							X	
Height as measured by stadiometer	X	X							X	
Tanner staging		X							X	

Study Visit Number Study Visit Type	Visit 1[a] Screening	Visit 2 Baseline	Visit 3 Day 4	Visit 4 Week 1	Visit 5 Week 2	Visit 6 Week 3	Visit 7 Week 4	Visit 8 Week 5	EOS/ET Visit 9[b] Week 6	Visit 10 Follow-up[c]
Study Visit Day	-21 to -1	1	4±2	8±2	15±2	22±2	29±2	36±2	43±2	50±2
Study Visit Type	Inpatient or Out-patient	Inpatient Optional	Inpatient Optional	Inpatient Optional	Inpatient Optional	Inpatient Optional	Inpatient Optional	Inpatient Optional	Inpatient Optional	Out-patient
Menstrual cyclicity (female subjects)[d]		X							X	
Vital sign[e]	X	X	X	X	X	X	X	X	X	X
Weight	X	X		X	X	X	X	X	X	X
Waist circumference measurement		X							X	
Electrocardiogram (ECG)	X	X							X	
Hematology, chemistry, and urinalysis	X	X							X	
Blood sample for lurasidone concentration[f]									X	
Rapid Plasma Reagin (RPR) test	X									
Serum prolactin[g]	X	X							X	
Glycosylated hemoglobin (HbA_{1c})	X	X							X	
Glucose and lipid panel	X	X[h]							X[h]	
Hormonal Parameters	X	X							X	
Serum insulin and C-reactive protein		X							X	
Serum human chorionic gonadotropin (β-hCG) (females only)	X									

Study Visit Number Study Visit Type	Visit 1[a] Screening	Visit 2 Baseline	Visit 3 Day 4	Visit 4 Week 1	Visit 5 Week 2	Visit 6 Week 3	Visit 7 Week 4	Visit 8 Week 5	EOS/ET Visit 9[b] Week 6	Visit 10 Follow-up[c]
Study Visit Day	-21 to -1	1	4±2	8±2	15±2	22±2	29±2	36±2	43±2	50±2
Study Visit Type	Inpatient or Out-patient	Inpatient Optional	Inpatient Optional	Inpatient Optional	Inpatient Optional	Inpatient Optional	Inpatient Optional	Inpatient Optional	Inpatient Optional	Out-patient
Urine drug screen	X	X							X	
Urine β-hCG[i] (females only)		X				X			X	X
Barnes Akathisia Rating Scale (BARS)		X	X	X	X	X	X	X	X	X
Abnormal Involuntary Movement Scale (AIMS)		X	X	X	X	X	X	X	X	X
Simpson-Angus Scale (SAS)		X	X	X	X	X	X	X	X	X
Positive and Negative Syndrome Scale (PANSS)	X	X	X	X	X	X	X	X	X	
Cogstate Computerized Cognitive Test Battery	X	X							X	
Clinical Global Impression – Severity Scale (CGI-S)	X	X	X	X	X	X	X	X	X	
Children's Global Assessment Scale (CGAS)		X							X	
Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)		X							X	
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X	X	X	X	X	X	X	X	X
Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU)		X				X			X	

[a] Screening period may have occurred over more than 1 day.
[b] If a subject discontinued from the study, all Visit 9 procedures were to be performed at the discontinuation visit, and if possible within 48 hours of the last dose of study drug. Subjects continuing in the extension study (D1050302) received extension phase medication at Visit 9. The extension study (D1050302) began at the end of Week 6 (Visit 9).
[c] Visit for subjects who did not entering the D1050302 study only.
[d] See Section 11.1.2 of the Protocol for description.
[e] Vital sign measurements included orthostatic changes in blood pressure and heart rate.
[f] Time and date of the 3 previous doses of study drug, time and date of in-clinic dose of study drug when applicable, and the time of the blood sampling were to be recorded.
[g] Prolactin levels were blinded, except at screening and Baseline visits. Investigators were to be notified if prolactin concentrations were more than 200 ng/mL.
[h] Subjects were to fast for lipids and glucose laboratory tests only. These visits were scheduled in the morning, and blood work was done first.
[i] Any positive urine β-hCG test was to be confirmed by serum β-hCG
Abbreviations: EOS = End of Study; ET = Early Termination

Table 17 Assessments Carried Forward to D1050302

Study Visit Number Study Visit Week (±3 days)
Children's Global Assessment Scale (CGAS)
Clinical Global Impression – Severity (CGI-S)
Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)
Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU)
Columbia Suicide Severity Rating Scale (C-SSRS)
Positive and Negative Syndrome Scale (PANSS)
CogState Computerized Cognitive Test Battery

Study Visit Number **Study Visit Week (±3 days)**
Obtain informed consent/assent
Inclusion/exclusion criteria
Interactive Voice/Web Response System (IXRS) subject registry/visit
Dispense study medication
Study drug accountability/assess compliance
Clinical and Laboratory Evaluations: ALL SUBJECTS
Prior/concomitant medication review
Adverse event (AE) monitoring
Physical examination
Height as measured by stadiometer
Tanner staging
Menstrual cyclicity (female subjects)
Vital signs
Weight
Waist circumference measurement
Electrocardiogram (ECG)
Hematology, chemistry, and urinalysis
Hormonal Parameters
Serum prolactin
Glycosylated hemoglobin (HbA_{1c})
Glucose and lipid panel
Serum insulin and C-reactive protein
Urine drug screen
Urine β-hCG
Simpson-Angus Scale (SAS)
Barnes Akathisia Rating Scale (BARS)
Abnormal Involuntary Movement Scale (AIMS)
Clinical Evaluations: **SUBJECTS from D1050301 ONLY**

7.2.5 Metabolic, Clearance, and Interaction Workup

N/A

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The above assessments are expected to be adequate to detect potential adverse effects seen with similar drugs in this class, for example, metabolic changes, orthostatic hypotension, neutropenia, and tardive dyskinesia.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in this study, or in the open-label extension study D1050302 as of the October 27, 2016 cutoff date.

7.3.2 Nonfatal Serious Adverse Events

SAEs occurred more frequently in the placebo group (8%) than the drug treatment groups (3.6% at 40mg, and 1.9% at 80mg), and were mostly psychiatric AEs (likely primary illness-related). A total of six subjects on lurasidone experienced SAEs and nine on placebo for a total of 15 SAEs in the study. Four were on 40mg, two on 80mg.

Table 18 Serious Adverse Events (SAEs) by Treatment Arm

	Placebo (N=112) n (%)	Lurasidone 40mg (N=110) n (%)	Lurasidone 80mg (N=104) n (%)
Total Subjects with Serious AEs	9 (8.0)	4 (3.6)	2 (1.9)
Total SAEs (Events)	9	4	2
Event Rate per Subject-Year Exposure	0.787	0.342	0.172
Gastrointestinal/Diarrhea	0	1 (0.9)	0
Total Psychiatric SAEs	9 (8.0)	3 (2.7)	2 (1.9)
Homicidal Ideation	0	1 (0.9)	0
Psychotic Disorder	1 (0.9)	0	0
Schizophrenia	7 (6.3)	2 (1.8)	2 (1.9)
Suicidal Ideation	1 (0.9)	0	0

Table 19 List of SAE Cases

Subject ID	Demographics	Event	Treatment Group
301352003	15yo Colombian F	Exacerbation of schizophrenia. Also taking lorazepam. Occurred Day 41 after starting study drug. Had been inpatient for 1 month during earlier part of trial (discharged 16 days before event) and restarted partial hospital 5 days before event. Study drug was stopped 1 day prior to event, and subject was rehospitalized and risperidone was started.	Lurasidone 80mg

301352006	16yo Colombian M	Worsening of schizophrenia. Occurred Day 15 after starting study drug, which was discontinued that day. Subject withdrew from study the next day (had been hospitalized during trial). Was also on lorazepam and diphenhydramine. After leaving study, was switched to risperidone (eventually discharged 16 days later).	Lurasidone 80mg
301012003	15yo WF (US)	Exacerbation of schizophrenia. Occurred Day 6. Study drug was discontinued that day. Subject had been hospitalized during trial and had also been taking aripiprazole, paroxetine, lorazepam, and melatonin.	Lurasidone 40mg
301038002	15yo BM (US)	Homicidal Ideation. Occurred Day 30 of study and drug was discontinued that day. Was noted to be increasingly defiant/agitated and having mood swings since 8 days prior, and had urinated into an AC unit 3 days prior. HI occurred after teacher confronted subject on behavior and writing lyrics about killing people, and he threatened to “cut her feet off and shove them up her ass.” Father also worried by behavior. Was hospitalized the next day and withdrew from study the day after, started on risperidone. Utox negative. Had also been on lorazepam, zolpidem.	Lurasidone 40mg

301250002	16yo WF (Bulgaria)	Worsening of schizophrenia. Occurred Day 8 of study. Discontinued drug that day and withdrew from study the next day and was hospitalized and put back on olanzapine (had been on it until 4 days before study started) and haloperidol. (Also day of AE received one IM shot of Thorazine/Haldol, indicating agitation.) Had also been on diazepam and zolpidem.	Lurasidone 40mg
301682004	13yo WM (Russia)	Diarrhea/Hospitalization. Occurred Day 19 of study. Several days prior had also been symptomatic with frequent diarrhea, fever, loss of appetite. Was hospitalized on Day 19 due to symptoms which resolved 3 days later. Subject was discharged and remained in study and on drug. Felt to be likely due to food poisoning/infection, not drug-related.	Lurasidone 40mg
301004001	16yo WM (US)	Worsening of schizophrenia, Day 14, withdrew from study.	Placebo
301030004	14yo BM (US)	Worsening of schizophrenia, Day 26, withdrew from study.	Placebo
301030010	17yo BM (US)	Worsening of schizophrenia, Day 8, withdrew from study.	Placebo
301035004	16yo WM (US)	Suicidal Ideation, Day 19. Wanted to stop eating and drinking in order to no longer live. Was hospitalized afterwards for 1 day.	Placebo
301350003	17yo Colombian M	Worsening of psychosis, Day 4. Withdrew from study.	Placebo
301352002	14yo Colombian M	Worsening of schizophrenia, Day 16. Withdrew from study.	Placebo
301352004	15yo Colombian F	Exacerbation of schizophrenia, Day 22. Withdrew from study.	Placebo
301679001	14yo WM (Russia)	Exacerbation of schizophrenia, Day 20. Withdrew from study.	Placebo
301751001	15yo Asian F (Korea)	Aggravation of schizophrenia, Day 3. Withdrew consent for study 4 days later.	Placebo

Most of the cases appear to be related to lack of treatment efficacy, particularly with the cases on placebo as might be anticipated. The one medical SAE (diarrhea) seemed unrelated to the drug. No major causality or trends can be noted from these cases.

From the March cutoff for the interim report, a total of 33 subjects (10.8%) had SAEs (37 events) that occurred in the open-label extension study D1050302 (20 of whom were originally from this study). Psychiatric SAEs: 25 total, 8 with SI (7 from this study), 6 with aggression, 4 with agitation, 4 with schizophrenia (all from this study), 3 with akathisia, 3 with anxiety. Non-psychiatric SAEs: 7 fractures, 1 nerve injury, 1 seizure, 1 influenza.

As of the October 27, 2016 update, a total of 39 subjects (9.8%) had SAEs (52 events), now 26 originally from this study. Psychiatric SAEs: 30 subjects total with 35 events (24 subjects from D1050301 with 29 events) with 1 additional suicidal behavior case reported since March. Non-psychiatric SAEs: 1 appendicitis, 5 fractures, 1 nerve injury, 1 soft tissue injury, 1 Type I DM, 1 concussion, 1 intentional OD (unclear if it is the same case adjudicated as a suicide behavior event), 1 akathisia, 1 ataxia, 1 seizure. It's unclear why a few non-psychiatric SAEs are missing compared to previous March report (influenza, 2 fractures).

Table 20 Psychiatric SAEs from D1050302 as of October 27, 2016 Update

SAE	From D1050301 (N=271)	From D1050325 (N=125)	Total D1050302 (N=396)
Schizophrenia/Paranoid Type	10 (3.7%)	0	10 (2.5%)
Psychotic Disorder	5 (1.8%)	0	5 (1.3%)
Suicidal Ideation	7 (2.6%)	1 (0.8%)	8 (2.0%)
Suicide Attempt	1 (0.4%)	1 (0.8%)	2 (0.5%)
Suicidal Behavior	1 (0.4%)	0	1 (0.3%)
Aggression/Violence-Related Symptom	1 (0.4%)	4 (3.2%)	5 (1.3%)
Agitation	1 (0.4%)	0	1 (0.3%)
Confusional State	1 (0.4%)	0	1 (0.3%)
Depression/Depressive Symptom	2 (0.7%)	0	2 (0.5%)
TOTAL	29	6	35

7.3.3 Dropouts and/or Discontinuations

A total of 17 subjects discontinued the study due to AEs. The discontinuation rates due to AEs were highest in the placebo arm (8% or 9 subjects), and also higher in the 40mg arm (5.5% or 6 subjects) than the 80mg arm (1.9% or 2 subjects). The most common AE leading to dropouts were psychiatric events (14 total, including irritability which is miscoded in the table above under the 'general disorders' SOC.) There were 7

psychiatric dropout events on placebo, 6 on 40mg, and 1 on 80mg. One hypothesis for these results then may be that discontinuation rates reflect worsening illness course without drug versus placebo, and possibly higher efficacy at the 80mg dose than 40mg.

The three non-psychiatric events leading to dropout were hypersensitivity reaction (on 80mg), elevated CPK (on placebo), and akathisia (on placebo).

No subjects had elevated liver enzymes that met criteria for potential drug-induced liver injury (DILI) such as Hy's Law; all subjects with any elevation of AST or ALT had total bilirubin that was less than or equal to 2x the ULN. No other discontinuations due to vital signs, or ECGs/ QTC prolongation were noted.

For the extension safety study D1050302's interim data, there were 36 subjects who dropped out due to AEs out of 305 total (12%), including 20 out of 180 total (11%) enrolled from Study D1050301. Types of AEs leading to discontinuation in these subjects in the long-term study included: schizophrenia/psychotic exacerbation, suicidal ideation/attempt, depression, bilirubinuria, proteinuria, akathisia, agitation. These AEs are in keeping with AEs and findings from D1050301. (Per the 120-Day Safety Update through Oct. 27, 2016, there were 44 dropouts due to AEs out of 396 total (11%), including 26 dropouts due to AEs from subjects out of 271 total (9.6%) originally enrolled from D1050301.)

Table 21 AEs Leading to Discontinuation by Treatment Arm

Incidence of Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of Study drug (Safety Population)

System Organ Class (SOC)/ Preferred Term	Placebo (N=112) n (%)	Lurasidone 40 mg (N=110) n (%)	Lurasidone 80 mg (N=104) n (%)	Lurasidone All (N=214) n (%)
Total No. Subjects with TEAEs	9 (8.0)	6 (5.5)	2 (1.9)	8 (3.7)
General Disorders And Administration Site Conditions	0	1 (0.9)	0	1 (0.5)
Irritability	0	1 (0.9)	0	1 (0.5)
Immune System Disorders	0	0	1 (1.0)	1 (0.5)
Hypersensitivity	0	0	1 (1.0)	1 (0.5)
Investigations	1 (0.9)	0	0	0
Blood Creatine Phosphokinase Increased	1 (0.9)	0	0	0
Nervous System Disorders	1 (0.9)	0	0	0
Akathisia	1 (0.9)	0	0	0
Psychiatric Disorders	7 (6.3)	5 (4.5)	1 (1.0)	6 (2.8)
Anxiety	0	1 (0.9)	0	1 (0.5)
Homicidal Ideation	0	1 (0.9)	0	1 (0.5)
Psychotic Disorder	1 (0.9)	0	0	0
Schizophrenia	6 (5.4)	2 (1.8)	1 (1.0)	3 (1.4)
Suicidal Ideation	0	1 (0.9)	0	1 (0.5)

Abbreviations: SOC = System Organ Class; TEAE = treatment-emergent adverse event
Note: Percentage is calculated by using the number of subjects in each treatment group as denominator.
Note: Incidence is based on the number of subjects experiencing at least 1 TEAE, not the number of events.
Source: Table 14.3.2.1.

7.3.4 Significant Adverse Events

SIB Events (by AE Report):
There were 2 subjects on placebo (1.8%), 1 subject on lurasidone 40mg/day (0.9%), 0 on 80mg/day.

Table 22 SIB Events by AE Report

Subject ID	Event	Dose
301035004	Suicidal Ideation	Placebo
301501003	Intentional Self-injury (scratching)	Placebo
301087003	Suicidal Ideation	Lurasidone 40mg

C-SSRS:

Table 23 C-SSRS Findings in D1050301

Subjects with Events Detected by C-SSRS	Placebo (N=112) n (%)	Lurasidone 40mg (N=110) n (%)	Lurasidone 80mg (N=104) n (%)
Baseline SIB Reported*	5 (4.5)	3 (2.7)	4 (3.8)
Post-Baseline Emergent/Worsening Suicidal Ideation (SI)	3 (2.7)	5 (4.6)	0
Post-Baseline Emergent Serious SI (SI Score 4+)	0	0	0
Post-Baseline Emergent Suicidal Behavior	1 (1.0)**	0	1 (1.0)
Post-Baseline Emergent SIB Total	3 (2.7)	5 (4.6)	1 (1.0)
Post-Baseline Any SIB Total	6 (5.4)	6 (5.5)	1 (1.0)

*All were Ideation Events with Scores < 4, No Behavior Events
**Self-injurious behavior without suicidal intent (included in Post-Baseline Any SIB Total)

There were no significant differences between drug and placebo groups on the C-SSRS overall during this study. There was a slight uptick in reported SI in the 40mg group compared to baseline (3 new subjects, 6 total at the end) during the study, while the 80mg group with SI decreased by 3 subjects (4 subjects to 1 subject). Placebo stayed the same throughout with 5 subjects. Only one subject on placebo reported self-injurious behavior during the study (which was reported as an AE).

Reviewer Comment: No drug association with SIB events are evident from this study, and overall low N's make it difficult to detect significant associations. There were no suicide attempts or completed suicides during D1050301.

Of note, in the long-term extension study D1050302 thus far, there were seven subjects with SI and one suicide attempt noted in the interim data for SAEs (8 SIB events out of 180 subjects total or 4.4% who enrolled from D1050301, 10 total SIB events in the combined trial of 305 subjects or 3.3%). Per the October 27, 2016 update, in D1050302 there was at least one additional suicidal behavior SAE (possibly also one called "intentional overdose" that may or may not be the same case) noted out of now 271 subjects originally from D1050301 (9 SIB events or 3.3%, 11 total SIB events now in D1050302 or 2.8%). No major SIB conclusions can be noted from D1050302, an open-label trial, although comparison to background SIB rates for adolescents with schizophrenia may be considered in future post-marketing analyses as needed.

7.3.5 Submission Specific Primary Safety Concerns

N/A

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most common AEs were in the nervous system, gastrointestinal, and psychiatric disorder SOCs in all treatment groups.

The most common AEs (per MAED and JMP analysis of the ADAE.xpt dataset) with an incidence ≥ 5% and greater than twice that of placebo were: somnolence/sedation, nausea, vomiting, akathisia, EPS (non-akathisia, 40mg only), and rhinitis/rhinorrhea (80mg only).

Table 24 Most Common AEs in Study D1050301 (≥ 5% in any drug arm and greater than placebo)

AE	Lurasidone 40mg N=110	Lurasidone 80mg N=104	Placebo N=112
Somnolence/Sedation/Hypersomnia	17 (15.5%)	14 (13.5%)	8 (7.1%)
Nausea	14 (12.7%)	15 (14.4%)	3 (2.7%)
Vomiting	9 (8.2%)	6 (5.8%)	2 (1.8%)
Akathisia	10 (9.1%)	9 (8.7%)	2 (1.8%)
EPS (non-akathisia)	8 (7.3%)	7 (6.7%)	4 (3.6%)
Anxiety	10 (9.1%)	3 (2.9%)	9 (8%)
Agitation	4 (3.6%)	6 (5.8%)	5 (4.5%)

Nasopharyngitis/Influenza/Viral Infection/URI	12 (11%)	9 (8.7%)	7 (6.3%)
Rhinitis/Allergic Rhinitis/Rhinorrhea/Nasal Congestion	1 (0.9%)	8 (7.7%)	2 (1.8%)

*Colored boxes are greater than 5%

Table 25 Common AEs in Study D1050301 (≥2% in any drug arm and greater than placebo, not already included in ≥5% table)

AE	Lurasidone 40mg N=110	Lurasidone 80mg N=104	Placebo N=112
Dry Mouth	2 (1.8%)	3 (2.9%)	0
Diarrhea	3 (2.7%)	5 (4.8%)	1 (0.9%)
Dizziness	5 (4.6%)	5 (4.8%)	1 (0.9%)
Hyperhidrosis	1 (0.9%)	3 (2.9%)	2 (1.8%)
Oropharyngeal Pain	1 (0.9%)	3 (2.9%)	0
Weight Increase	1 (0.9%)	3 (2.9%)	3 (2.7%)
Tachycardia	0	3 (2.9%)	0

*Colored boxes are greater than 2%

7.4.2 Laboratory Findings

Hematology:
The hematology parameters that were assessed in this study include: leukocytes, eosinophils (absolute count and percentage), basophils (absolute count and percentage), neutrophils (absolute count and percentage), lymphocytes (absolute count and percentage), monocytes (absolute count and percentage), platelet count, hemoglobin, hematocrit, erythrocytes, erythrocyte distribution width, erythrocyte mean corpuscular volume, erythrocyte mean corpuscular hemoglobin concentration, erythrocyte and mean corpuscular hemoglobin.

At Endpoint, small fluctuations in hematology parameters were observed, with the majority of subjects remaining within the normal range for all parameters. There were no notable differences between the lurasidone treatment groups and placebo in the mean change from Baseline for any hematology parameter.

Table 26 Select Markedly Abnormal Hematology Parameters

Incidence of Select Potential Markedly Abnormal Post-Baseline Hematology Laboratory Values (Safety Population)

Parameter (unit)	Unit	Placebo n (%)	Lurasidone		
			40 mg n (%)	80 mg n (%)	All n (%)
Hemoglobin (g/dL)	n	102	99	100	199
	Females: ≤ 9.5 Males: ≤ 11.5	0	2 (2.0)	0	2 (1.0)
	≥ 17.2	0	2 (2.0)	1 (1.0)	3 (1.5)
Hematocrit (%)	n	100	97	98	195
	≤ 30	0	1 (1.0)	0	1 (0.5)
	≥ 50	5 (5.0)	6 (6.2)	6 (6.1)	12 (6.2)
Leukocytes (× 10^3/μL)	n	102	99	100	199
	≤ 2.8	0	1 (1.0)	1 (1.0)	2 (1.0)
Erythrocytes (× 10^6/μL)	n	102	99	100	199
	≥ 6.0	0	4 (4.0)	3 (3.0)	7 (3.5)
Platelets (× 10^3/μL)	n	102	98	100	198
	≥ 500	0	0	1 (1.0)	1 (0.5)

Note: Definition of markedly abnormal criteria is provided in SAP Table 3.
Note: Percentages are based on the number of subjects per time interval.
Source: Table 14.3.4.5.1.

Reviewer Comment:
As noted by the Sponsor, mean changes from baseline were minimal overall for hematologic lab parameters, and there were no major differences between drug and placebo for any changes. Of note, in the AE analysis, in the 80mg arm there were higher than placebo rates of both viral/respiratory infections and rhinitis/rhinorrhea events. But per the Sponsor-submitted hematology analyses, there were no signs of unusual leukopenia or leukocytosis, hemolytic anemia, neutropenia, eosinophilia, thrombocytosis or thrombocytopenia, lymphocytosis or lymphopenia, or any significant drug-dependent differences.

Shift tables only showed a handful of events that also did not correlate to any specific clinical findings or trends, and did not appear to show significant differences between drug and placebo. This data seems to indicate no major acute hematologic effects of drug versus placebo in this 6-week study.

Liver:
Reviewer Comment:
Liver function test (LFT) mean changes from baseline were unremarkable, and showed no significant differences between drug and placebo. Shift changes also showed no unusual trends or significant differences between drug and placebo. Of the outlier subjects on lurasidone, only one (301251011) showed a clear rise on 40mg from baseline AST of 15 to 68 by Week 6. The other two subjects with elevated post-baseline LFTs were already elevated at baseline (one on 40mg went from ALT 67 baseline to ALT 62 Week 6, the other 301030017 on 80mg went from ALT 180 baseline to 362 Day

4 then 73 Day 7 and 34 endpoint, and AST 154 baseline to 191 Day 4 to 69 endpoint.) One subject on 80mg with bilirubin greater than twice ULN at Week 6 (2.0) already had a higher bilirubin at baseline (2.3). Except for a couple outliers, this data seems to indicate no general acute liver function effects of drug versus placebo in this 6-week study. No patients met criteria for Hy's Law in this study.

Renal:
Reviewer Comment:
There were no major mean changes from baseline for BUN or creatinine or differences between lurasidone and placebo (BUN: -0.2 on placebo, -0.8 on 40mg, +0.2 on 80mg; Creatinine: +0.02 on placebo, -0.06 at 40mg, +0.03 at 80mg). For shift tables, although there were about the same (1.5%) in the drug arms who shifted from normal to high BUN compared to placebo (1%), for creatinine the shift rates from normal to high were 7.2% on drug (same at both dosages) versus 2.9% on placebo. Still, none of the subjects developed creatinine at twice the ULN in the study, and only one subject (on lurasidone 40mg) had mildly elevated creatinine reported as an AE at Day 18. This data seems to indicate no major acute renal function effects of drug versus placebo in this 6-week study.

Other Electrolytes:
No significant mean changes or shifts were noted in the other chemistry laboratory results (sodium, potassium, chloride, bicarbonate, et al).

Prolactin:
Reviewer Comment:
Prolactin levels showed a slightly significant mean increase in the 80mg group (+4.03) over placebo (-0.78), and not in the 40mg group (+0.93). Similarly, shift tables show a higher rate of subjects with normal to high prolactin changes on the higher dose of drug (7% at 40mg, 18% at 80mg) versus placebo (7%). Overall, there may be a mild dose-dependent effect of increased prolactin levels on lurasidone versus placebo in this 6-week study. This issue is already covered in current labeling

Table 27 Prolactin and Triglyceride Abnormal Value Outliers

Incidence of Select Potential Markedly Abnormal Post-Baseline Clinical Chemistry Laboratory Values

Parameter (unit)	Unit	Placebo n (%)	Lurasidone		
			40 mg n (%)	80 mg n (%)	All n (%)
Prolactin (ng/mL)	n	103	102	99	201
	≥ 1 x ULN	10 (9.7)	16 (15.7)	23 (23.2)	39 (19.4)
	≥ 2 x ULN	3 (2.9)	5 (4.9)	5 (5.1)	10 (5.0)
	≥ 3 x ULN	2 (1.9)	3 (2.9)	1 (1.0)	4 (2.0)
Triglycerides (mg/dL) - fasting	n	95	90	92	182
	Female: ≥ 170 Male: ≥ 200	8 (8.4%)	9 (10.0)	11 (12.0)	20 (11.0)

Abbreviations: ULN = upper limit of normal
Note: Definition of markedly abnormal criteria is provided in SAP Table 3.
Note: Percentages are based on the number of subjects per time interval.
Source: Table 14.3.4.5.1 and Table 14.3.4.5.3.

Table 28 Prolactin Mean Parameters (Including Gender Subgroups)

	Statistics	Placebo (N=112)	Lurasidone 40 mg (N=110)	Lurasidone 80 mg (N=104)	Lurasidone All (N=214)
Prolactin (ng/mL) - Overall					
Endpoint	n	103	102	99	201
	Baseline Mean (SD)	13.40 (16.166)	15.75 (22.292)	11.01 (13.408)	13.41 (18.566)
	Mean (SD)	-0.78 (22.202)	0.93 (24.098)	4.03 (14.951)	2.46 (20.129)
	Median	0.10	0.75	1.20	1.10
	Min, Max	-78.6, 138.4	-109.4, 174.5	-85.9, 35.8	-109.4, 174.5
	p-value (vs. Placebo)		0.1952	0.0173	0.0378
Prolactin (ng/mL) - Females					
Endpoint	n	39	42	33	75
	Baseline Mean (SD)	16.12 (17.446)	21.59 (30.809)	11.90 (8.702)	17.32 (24.127)
	Mean (SD)	-2.27 (22.769)	2.37 (35.349)	7.94 (14.351)	4.82 (28.091)
	Median	0.70	0.60	4.40	2.60
	Min, Max	-78.6, 66.7	-109.4, 174.5	-33.2, 35.8	-109.4, 174.5
	p-value (vs. Placebo)		0.1845	0.0318	0.0490
Prolactin (ng/mL) - Males					
Endpoint	n	64	60	66	126
	Baseline Mean (SD)	11.74 (15.237)	11.67 (12.241)	10.56 (15.270)	11.09 (13.867)
	Mean (SD)	0.12 (21.981)	-0.08 (11.101)	2.07 (14.965)	1.05 (13.258)
	Median	-0.00	0.75	1.00	1.00
	Min, Max	-72.5, 138.4	-28.9, 38.7	-85.9, 34.6	-85.9, 38.7
	p-value (vs. Placebo)		0.3521	0.1175	0.1794

Abbreviations: Max = maximum; Min = minimum; SD = standard deviation
Note: Baseline: the last value prior to the first dose of study drug.
Note: Endpoint: the last post-baseline assessment during double-blind treatment period.
Note: P-values from stratified Mantel-Haenszel raw mean score test per Rank ANCOVA. Rank was stratified by age group at Screening.
Source: Table 14.3.4.2.1.

Table 29 Prolactin Shift Analysis (from Baseline to Endpoint)

		Placebo N=112 (Endpoint N=103)			Lurasidone 40mg N=110 (Endpoint N=102)			Lurasidone 80mg N=104 (Endpoint N=99)		
Baseline	Endpoint	Low	Normal	High	Low	Normal	High	Low	Normal	High
Low		1 (1.0)	7 (6.8)	0	0	5 (4.9)	1 (1.0	0	2 (2.0)	0
Normal		1 (1.0)	73 (70.9)	7 (6.8)	1 (1.0)	68 (66.7)	7 (6.9)	5 (5.1)	63 (63.6)	18 (18.2)
High		1 (1.0)	10 (9.7)	3 (2.9)	0	12 (11.8)	8 (7.8)	1 (1.0)	5 (5.1)	5 (5.1)

Metabolic Chemistry:
Reviewer Comment:
Some mean change increases were noted for fasting glucose (higher in the 80mg group) compared to placebo, although they were not considered statistically significant. Fasting cholesterol was slightly higher than baseline in the 80mg group (which was considered statistically significant) and decreased in the 40mg and placebo groups. (A similar trend was seen in fasting LDL cholesterol, without statistical significance.) Fasting triglycerides also showed an increase in the 80mg group compared to placebo

and 40mg (although again, not considered statistically significant.) Shift tables indicate similar trends. Overall, there do appear to be some trends towards increased fasting glucose and lipid changes in the 80mg group, but not in the 40mg group compared to placebo (which may point to a dose-dependent effect), and these results only reflect a 6-week trial.

Table 30 Subjects with Abnormal Post-Baseline Metabolic Chemistry Lab Values

Lab	Placebo (N=112)	Lurasidone 40mg (N=110)	Lurasidone 80mg (N=104)
Glucose, Fasting >125	0	0	1 (1%)
Cholesterol, Fasting >239	3 (3%)	1 (1%)	3 (3%)
Triglycerides, Fasting >170 female, >200 male	8 (8%)	9 (10%)	11 (12%)
LDL cholesterol Fasting >160	2 (2%)	1 (1%)	2 (2%)

Table 31 Metabolic Chemistry Mean Change from Baseline Values

Change from Baseline to Endpoint in Metabolic-Related Clinical Laboratory Parameters (Safety Population)

			Lurasidone		
	Statistics	Placebo (N=112)	40 mg (N=110)	80 mg (N=104)	All (N=214)
Glucose (Overall) (mg/dL)					
Endpoint	n	103	98	100	198
	Baseline Mean (SD)	91.1 (12.56)	89.3 (10.78)	89.6 (9.27)	89.5 (10.02)
	Mean Change (SD)	-0.3 (14.14)	-0.3 (11.08)	0.8 (11.56)	0.3 (11.31)
	Median Change	0.0	0.0	1.0	1.0
	Min, Max Change	-54, 49	-46, 26	-62, 36	-62, 36
	p-value (vs. Placebo)		0.4421	0.7239	0.8354
Glucose (Fasting) (mg/dL)					
Endpoint	n	95	90	92	182
	Baseline Mean (SD)	91.4 (12.46)	88.7 (8.99)	88.9 (8.71)	88.8 (8.82)
	Mean Change (SD)	-1.3 (12.88)	0.1 (9.41)	1.8 (9.86)	0.9 (9.65)
	Median Change	-1.0	0.0	1.0	1.0
	Min, Max Change	-54, 30	-30, 22	-32, 36	-32, 36
	p-value (vs. Placebo)		0.7711	0.3302	0.6837
Cholesterol (Overall) (mg/dL)					
Endpoint	n	103	97	100	197
	Baseline Mean (SD)	161.5 (37.62)	161.8 (32.28)	157.3 (29.01)	159.5 (30.67)
	Mean Change (SD)	-8.2 (23.91)	-5.2 (24.93)	1.0 (29.34)	-2.1 (27.36)
	Median Change	-7.0	-4.0	-2.0	-3.0
	Min, Max Change	-96, 59	-83, 58	-60, 125	-83, 125
	p-value (vs. Placebo)		0.3909	0.0482	0.1062

	Statistics	Placebo (N=112)	Lurasidone		
			40 mg (N=110)	80 mg (N=104)	All (N=214)
Cholesterol (Fasting) (mg/dL)					
Endpoint	n	95	89	92	181
	Baseline Mean (SD)	163.5 (38.68)	160.1 (31.01)	156.5 (27.36)	158.2 (29.19)
	Mean Change (SD)	-9.6 (24.77)	-4.4 (22.78)	1.6 (29.62)	-1.4 (26.57)
	Median Change	-7.0	-3.0	-2.0	-2.0
	Min, Max Change	-96, 59	-74, 58	-54, 125	-74, 125
	p-value (vs. Placebo)		0.2112	0.0230	0.0452
HDL Cholesterol (Overall) (mg/dL)					
Endpoint	n	103	96	99	195
	Baseline Mean (SD)	52.3 (14.82)	51.2 (14.59)	53.1 (12.76)	52.2 (13.69)
	Mean Change (SD)	-2.4 (9.70)	-0.4 (10.72)	-1.2 (9.57)	-0.8 (10.13)
	Median Change	-1.0	-1.0	-2.0	-1.0
	Min, Max Change	-33, 18	-21, 56	-21, 38	-21, 56
	p-value (vs. Placebo)		0.5303	0.8761	0.6305
HDL Cholesterol (Fasting) (mg/dL)					
Endpoint	n	95	88	91	179
	Baseline Mean (SD)	52.5 (15.04)	51.8 (14.96)	53.2 (12.82)	52.5 (13.89)
	Mean Change (SD)	-3.1 (9.77)	-1.0 (8.92)	-1.2 (9.87)	-1.1 (9.39)
	Median Change	-2.0	-0.5	-2.0	-2.0
	Min, Max Change	-33, 18	-21, 23	-21, 38	-21, 38
	p-value (vs. Placebo)		0.2593	0.4221	0.2418
LDL Cholesterol (Overall) (mg/dL)					
Endpoint	n	103	96	99	195
	Baseline Mean (SD)	91.1 (30.49)	91.4 (27.72)	85.2 (25.68)	88.2 (26.82)
	Mean Change (SD)	-5.1 (19.45)	-4.4 (19.92)	0.6 (24.89)	-1.9 (22.66)
	Median Change	-4.0	-3.5	0.0	-2.0
	Min, Max Change	-72, 52	-68, 47	-55, 121	-68, 121
	p-value (vs. Placebo)		0.9438	0.3411	0.6433

	Statistics	Placebo (N=112)	Lurasidone 40 mg (N=110)	Lurasidone 80 mg (N=104)	Lurasidone All (N=214)
LDL Cholesterol (Fasting) (mg/dL)					
Endpoint	n	95	88	91	179
	Baseline Mean (SD)	92.4 (31.18)	90.4 (25.94)	84.3 (24.21)	87.3 (25.19)
	Mean Change (SD)	-5.6 (20.15)	-4.0 (19.06)	1.3 (25.01)	-1.3 (22.38)
	Median Change	-4.0	-3.0	0.0	-2.0
	Min, Max Change	-72, 52	-68, 44	-49, 121	-68, 121
	p-value (vs. Placebo)		0.7776	0.2794	0.4806
Triglycerides (Overall) (mg/dL)					
Endpoint	n	103	97	100	197
	Baseline Mean (SD)	92.8 (45.64)	100.3 (60.17)	97.3 (68.07)	98.8 (64.16)
	Mean Change (SD)	0.8 (51.15)	-6.1 (62.35)	8.7 (55.62)	1.4 (59.34)
	Median Change	-2.0	-2.0	7.0	2.0
	Min, Max Change	-128, 209	-335, 221	-299, 161	-335, 221
	p-value (vs. Placebo)		0.7408	0.1052	0.4454
Triglycerides (Fasting) (mg/dL)					
	n	95	89	92	181
	Baseline Mean (SD)	95.1 (46.36)	93.4 (52.83)	97.4 (69.97)	95.5 (62.00)
	Mean Change (SD)	0.1 (51.64)	-0.6 (50.11)	8.5 (56.10)	4.0 (53.28)
	Median Change	-3.0	-2.0	7.0	2.0
	Min, Max Change	-128, 209	-172, 221	-299, 161	-299, 221
	p-value (vs. Placebo)		0.6991	0.1425	0.4963
Hemoglobin AIC (%)					
	n	104	101	99	200
	Baseline Mean (SD)	5.14 (0.340)	5.19 (0.358)	5.13 (0.328)	5.16 (0.344)
	Mean Change (SD)	0.01 (0.211)	0.00 (0.238)	0.01 (0.217)	0.01 (0.228)
	Median Change	0.00	0.00	0.0	0.00
	Min, Max Change	-0.5, 0.7	-0.8, 1.1	-0.6, 0.7	-0.8, 1.1
	p-value (vs. Placebo)		0.8513	0.8413	0.8586

Creatine Kinase:

Reviewer Comment:

No acute trends in CK are evident in drug versus placebo according to these lab results in this 6-week study. One subject on placebo discontinued the study due to a reported AE of elevated CPK (also had elevated LFTs) on Day 6 (both were already elevated at baseline). No NMS events were noted during this trial.

Table 32 Creatine Kinase Markedly Abnormal Value Outliers

	Placebo	40mg	80mg	All Drug
Creatine Kinase (U/L)				
Any Post-Baseline DB Visit	103	97	100	197
>=450	7 (6.8)	4 (4.1)	1 (1.0)	5 (2.5)

Urinalysis:
The urinalysis parameters included pH, specific gravity, color, appearance, ketones, urobilinogen, bilirubin, erythrocytes, leukocytes, nitrite, protein, and glucose. There were no clinically meaningful mean changes from Baseline to Endpoint for any urinalysis parameter (Table 14.3.4.4.1).

At Endpoint, 1+ urine protein was detected in 10 (9.9%) subjects receiving lurasidone 40 mg/day and 8 (8.2%) subjects receiving lurasidone 80 mg/day compared to 4 (3.8%) subjects receiving placebo. At Baseline, however, the incidence of 1+ urine protein was 10.7% in the placebo group, 9.6% in the lurasidone 80 mg/day group, and 3.6% in the lurasidone 40 mg/day group. At Endpoint, the incidence of 2+ urine protein was 2.0% in the lurasidone 40 mg/day group and 2.9% in the placebo group. Only 1 (1.0%) subject, in the placebo group, had 3+ urine protein.

Reviewer Comment:
No major acute urine parameter changes between drug and placebo are apparent in this 6-week study.

Hormone Parameters:
Reviewer Comment: Thyroid hormones, FSH, LH, estradiol, and testosterone were measured, but showed no significant trends in drug versus placebo in the study. Gender analysis also did not show any clear trends.

7.4.3 Vital Signs

Reviewer Comment:
Blood pressure and pulse parameters between drug versus placebo don't show major differences at the endpoint, except a heart rate mean decrease in lurasidone 40mg (-2.8) that is slightly larger than the other arms (-0.3 placebo, -0.2 80mg). There is also a higher number of subjects with orthostatic systolic BP decrease in lurasidone 80mg (5.8%) compared to the other arms (2.7% placebo, 1.8% 40mg) although not for the other orthostatic parameters at 80mg (diastolic BP, HR), so this finding is likely not significant.

In terms of any clinical significance, only two subjects on drug seemed to have associated AEs that correlated with marked orthostatic changes: 301502001 was on lurasidone 80mg and had a 10mmHg diastolic orthostatic BP decrease at Day 4, and was noted to have AEs of confusion and dizziness at Day 2 (while on 40mg) and then again at Day 8 after going up to 80mg (also palpitations and weakness at Day 26/27); 301020002 was on lurasidone 40mg and had persistent orthostatic tachycardia >20 beats/min from Day 1 (reported as AE), and also had reported AEs of dizziness, erectile dysfunction, and lightheadedness. (Two other subjects with marked orthostatic findings and associated AEs of tachycardia were both on placebo. Of note, no one with markedly abnormal systolic orthostatic issues had associated AEs.)

As per Table 34, many more subjects had markedly abnormal orthostatic values, but the rest did not have associated AEs. Overall, there don't appear to be acute changes in vital signs between drug and placebo in this 6-week study.

Table 33 Vital Signs Mean Change from Baseline

Changes in Select Vital Signs from Baseline to Endpoint (Safety Population)

			Lurasidone		
	Statistics	Placebo (N=112)	40 mg (N=110)	80 mg (N=104)	All (N=214)
Heart Rate (beats/min), Supine					
Endpoint	n	112	109	104	213
	Baseline Mean (SD)	73.3 (9.55)	73.7 (10.54)	73.2 (8.66)	73.5 (9.65)
	Mean Change (SD)	-0.3 (8.16)	-2.8 (9.37)	-0.2 (9.40)	-1.5 (9.45)
	Median Change	0.0	-2.0	0.0	-1.0
	Min, Max Change	-18, 20	-33, 24	-26, 26	-33, 26
Systolic Blood Pressure (mmHg), Supine					
Endpoint	n	112	109	104	213
	Baseline Mean (SD)	115.7 (8.12)	114.1 (9.23)	114.8 (7.51)	114.5 (8.42)
	Mean Change (SD)	0.4 (7.62)	0.9 (6.62)	-0.5 (7.23)	0.2 (6.94)
	Median Change	1.0	0.0	0.0	0.0
	Min, Max Change	-21, 22	-14, 30	-20, 21	-20, 30
Diastolic Blood Pressure (mmHg), Supine					
Endpoint	n	112	109	104	213
	Baseline Mean (SD)	70.5 (6.67)	71.1 (7.62)	71.4 (7.67)	71.3 (7.63)
	Mean Change (SD)	0.7 (7.89)	-0.5 (6.66)	-1.6 (8.10	-1.0 (7.40)
	Median Change	0.0	0.0	-2.0	-1.0
	Min, Max Change	-17, 40	-19, 17	-24, 29	-24, 29
Respiration Rate (breaths/min)					
Endpoint	n	112	109	104	213
	Baseline Mean (SD)	17.9 (2.41)	17.4 (2.27)	17.4 (1.90)	17.4 (2.09)
	Mean Change (SD)	-0.3 (1.87)	0.1 (1.78)	0.2 (1.69)	0.2 (1.73)
	Median Change	0.0	0.0	0.0	0.0
	Min, Max Change	-6, 6	-7, 6	-4, 8	-7, 8

	Statistics	Placebo (N=112)	Lurasidone		
			40 mg (N=110)	80 mg (N=104)	All (N=214)
Temperature (°C)					
Endpoint	n	112	109	104	213
	Baseline Mean (SD)	36.60 (0.324)	36.60 (0.344)	36.57 (0.316)	36.58 (0.330)
	Mean Change (SD)	0.00 (0.330)	0.03 (0.310)	0.01 (0.351)	0.02 (0.330)
	Median Change	0.0	0.0	0.0	0.0
	Min, Max Change	-0.9, 0.8	-1.0, 1.0	-0.9, 1.5	-1.0, 1.5

Abbreviations: SD = standard deviation
Note: Baseline: the last value prior to the first dose of study drug is used.
Note: Endpoint: the last post-baseline assessment during double-blind treatment period.
Source: Table 14.3.5.1.

Table 34 Markedly Abnormal Vital Signs Incidence

Number and Percentage of Subjects with Potential Markedly Abnormal Post-Baseline Vital Signs (MAPVS) (Safety Population)

Parameter	Placebo (N=112) n (%)	Lurasidone		
		40 mg (N=110) n (%)	80 mg (N=104) n (%)	All (N=214) n (%)
Systolic Blood Pressure (mmHg), Supine				
Any Post-Baseline DB Visit	112	109	104	213
Potentially Markedly Low	1 (0.9)	0	4 (3.8)	4 (1.9)
Potentially Markedly High	4 (3.6)	2 (1.8)	2 (1.9)	4 (1.9)
Systolic Blood Pressure (mmHg), Standing				
Any Post-Baseline DB Visit	112	109	104	213
Potentially Markedly Low	1 (0.9)	0	1 (1.0)	1 (0.5)
Potentially Markedly High	2 (1.8)	3 (2.8)	2 (1.9)	5 (2.3)
Orthostatic Systolic Blood Pressure (mmHg)				
Any Post-Baseline DB Visit	112	109	104	213
≥ 20 decrease from supine to standing position	3 (2.7)	1 (0.9)	6 (5.8)	7 (3.3)
Diastolic Blood Pressure (mmHg), Supine				
Any Post-Baseline DB Visit	112	109	104	213
Potentially Markedly Low	0	1 (0.9)	1 (1.0)	2 (0.9)
Potentially Markedly High	3 (2.7)	2 (1.8)	1 (1.0)	3 (1.4)

Parameter	Placebo (N=112) n (%)	Lurasidone 40 mg (N=110) n (%)	Lurasidone 80 mg (N=104) n (%)	Lurasidone All (N=214) n (%)
Diastolic Blood Pressure (mmHg), Standing				
Any Post-Baseline DB Visit	112	109	104	213
Potentially Markedly Low	0	1 (0.9)	0	1 (0.5)
Potentially Markedly High	3 (2.7)	3 (2.8)	2 (1.9)	5 (2.3)
Orthostatic Diastolic Blood Pressure (mmHg)				
Any Post-Baseline DB Visit	112	109	104	213
≥ 10 decrease from supine to standing position	13 (11.6)	9 (8.3)	9 (8.7)	18 (8.5)
Heart Rate (beats/min), Supine				
Any Post-Baseline DB Visit	112	109	104	213
Potentially Markedly Low	1 (0.9)	2 (1.8)	0	2 (0.9)
Potentially Markedly High	0	0	0	0
Heart Rate (beats/min), Standing				
Any Post-Baseline DB Visit	112	109	104	213
Potentially Markedly Low	0	0	0	0
Potentially Markedly High	2 (1.8)	2 (1.8)	1 (1.0)	3 (1.4)
Orthostatic Heart Rate (beats/min)				
Any Post-Baseline DB Visit	112	109	104	213
≥ 20 increase from supine to standing position	33 (29.5)	28 (25.7)	20 (19.2)	48 (22.5)
Temperature (°C)				
Any Post-Baseline DB Visit	112	109	104	213
Potentially Markedly High	1 (0.9)	0	0	0

Abbreviations: DB = double-blind; MAPVS = markedly abnormal post-Baseline vital signs
Note: Definition of markedly abnormal criteria is provided in Table 14.3.5.2.0. For each post-baseline value, age at the visit is used to decide age-related marked abnormality.
Percentages are based on the number of subjects per time interval.
Source: Table 14.3.5.2.1.

Table 35 Markedly Abnormal Vital Signs Parameter Criteria

Vital Sign Parameter (unit)	Markedly Abnormal Low	Markedly Abnormal High
Systolic BP (mmHg) Supine or Standing	Value ≤90 and ≥20 decrease from baseline	Value ≥135 and ≥20 increase from baseline
Diastolic BP (mmHg) Supine or Standing	Value ≤50 and ≥15 decrease from baseline	Value ≥90 and ≥15 increase from baseline
HR (beats/min) Supine or Standing	Value ≤50 and ≥15 decrease from baseline	Value ≥120 and ≥15 increase from baseline
Systolic BP (mmHg) Orthostatic Criteria	≥20 decrease from supine to standing position	NA
Diastolic BP (mmHg) Orthostatic Criteria	≥10 decrease from supine to standing position	NA

HR (beats/min) Orthostatic Criteria	NA	≥20 increase from supine to standing position
Temperature (Degrees Celsius)	NA	Value ≥38.3 and ≥0.8 increase from baseline

Weight:

Reviewer Comment:

Weight (LS mean change) showed a small dose-dependent increase from Baseline to Week 6, with +0.12 at lurasidone 40mg and +0.44 at 80mg. BMI showed a similar trend with +0.04 at 40mg and +0.16 at 80mg. Weight gain is a known issue with atypical antipsychotics and is already reflected in current Latuda labeling.

Figure 4 Body Weight LS Mean Change from Baseline in D1050301

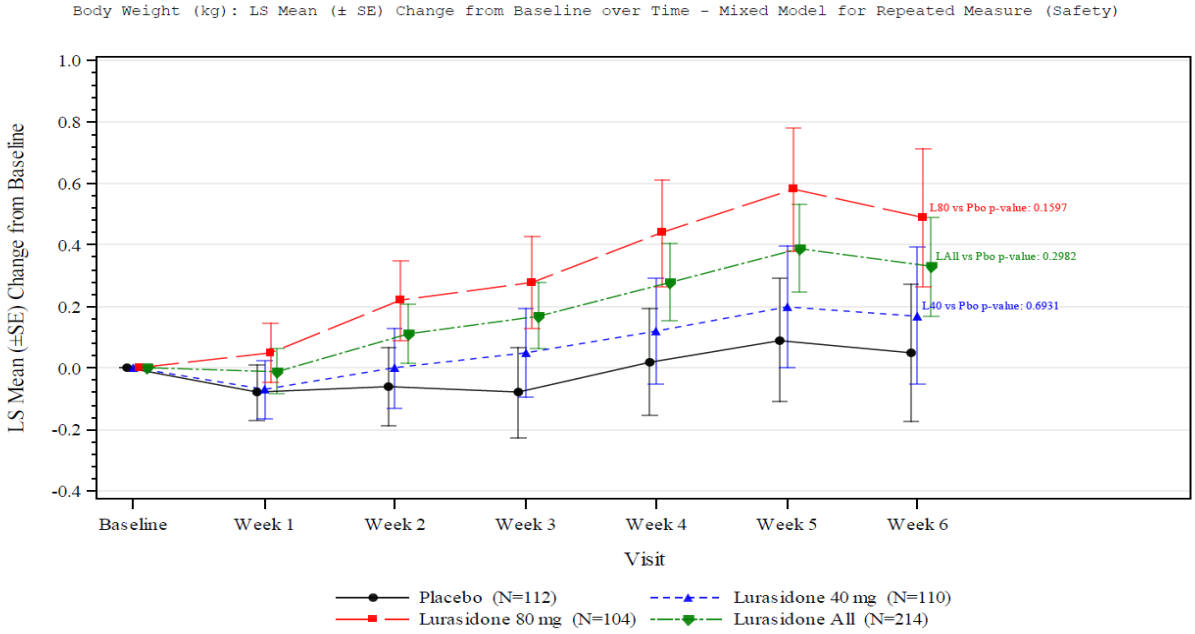


Table 36 Weight LS Mean Change from Baseline in D1050301

Change from Baseline in Body Weight – Mixed Model for Repeated Measures (Safety Population)

Weight (kg)	Placebo (N=112) [a]	Lurasidone		
		40 mg (N=110) [a]	80 mg (N=104) [a]	All (N=214) [b]
Week 1				
n	110	106	104	210
LS Mean (SE)	-0.08 (0.092)	-0.07 (0.094)	0.05 (0.096)	-0.01 (0.073)
Difference of LS Mean (SE) (vs. Placebo)		0.01 (0.120)	0.13 (0.121)	0.07 (0.104)
95% CI of Difference		(-0.23, 0.25)	(-0.10, 0.37)	(-0.13, 0.28)
p-value (vs. Placebo)		0.9349	0.2689	0.4895
Week 2				
n	102	106	104	210
LS Mean (SE)	-0.06 (0.128)	-0.00 (0.129)	0.22 (0.131)	0.11 (0.096)
Difference of LS Mean (SE) (vs. Placebo)		0.06 (0.173)	0.28 (0.175)	0.17 (0.150)
95% CI of Difference		(-0.29, 0.40)	(-0.07, 0.62)	(-0.13, 0.46)
p-value (vs. Placebo)		0.7485	0.1122	0.2681
Week 3				
n	99	102	102	204
LS Mean (SE)	-0.08 (0.147)	0.05 (0.147)	0.28 (0.149)	0.17 (0.109)
Difference of LS Mean (SE) (vs. Placebo)		0.13 (0.201)	0.36 (0.202)	0.25 (0.175)
95% CI of Difference		(-0.26, 0.53)	(-0.04, 0.76)	(-0.10, 0.59)
p-value (vs. Placebo)		0.5089	0.0751	0.1580
Week 4				
n	96	99	99	198
LS Mean (SE)	0.02 (0.174)	0.12 (0.173)	0.44 (0.175)	0.28 (0.126)
Difference of LS Mean (SE) (vs. Placebo)		0.10 (0.239)	0.42 (0.240)	0.26 (0.208)
95% CI of Difference		(-0.37, 0.57)	(-0.05, 0.89)	(-0.15, 0.67)
p-value (vs. Placebo)		0.6871	0.0825	0.2157

Weight (kg)	Placebo (N=112) [a]	Lurasidone		
		40 mg (N=110) [a]	80 mg (N=104) [a]	All (N=214) [b]
Week 5				
n	95	97	98	195
LS Mean (SE)	0.09 (0.200)	0.20 (0.199)	0.58 (0.201)	0.39 (0.144)
Difference of LS Mean (SE) (vs. Placebo)		0.11 (0.277)	0.49 (0.278)	0.30 (0.240)
95% CI of Difference		(-0.43, 0.66)	(-0.06, 1.04)	(-0.17, 0.77)
p-value (vs. Placebo)		0.6857	0.0780	0.2100
Week 6				
n	93	96	97	193
LS Mean (SE)	0.05 (0.225)	0.17 (0.223)	0.49 (0.225)	0.33 (0.161)
Difference of LS Mean (SE) (vs. Placebo)		0.12 (0.312)	0.44 (0.313)	0.28 (0.271)
95% CI of Difference		(-0.49, 0.74)	(-0.17, 1.06)	(-0.25, 0.82)
p-value (vs. Placebo)		0.6931	0.1597	0.2982

Abbreviations: CI = confidence interval; LS = least squared; SE = standard error
[a] LS Mean, LS mean difference, and the associated 95% CI and p-value for change from baseline are based on Mixed Model for Repeated Measures (MMRM) with fixed effects terms for treatment, visit (as a categorical variable), pooled country, age group, baseline weight, and treatment-by-visit interaction.
[b] Outputs are based on a same MMRM.
Source: Table 14.3.6.1.1.

Figure 5 BMI LS Mean Change from Baseline in D1050301

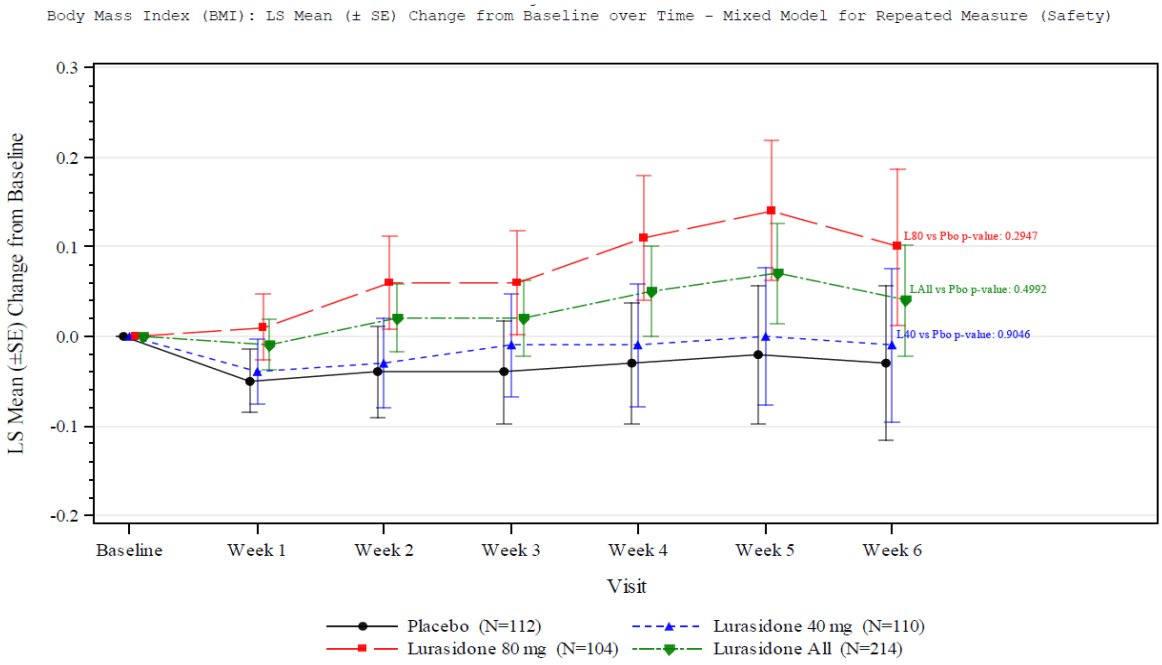


Table 37 BMI Mean Change from Baseline in D1050301

	Placebo (N=112)		Lurasidone 40mg (N=108)		Lurasidone 80mg (N=106)	
	N		N		N	
Baseline Mean (SD)	112	22.52 (3.606)	110	22.38 (3.262)	104	22.56 (3.497)
Mean Change from Baseline at Endpoint (SD)	106	+0.03 (0.969)	105	+0.03 (0.782)	100	+0.16 (0.693)

7.4.4 Electrocardiograms (ECGs)

Reviewer Comment:
*QTcF intervals showed **no** subjects reaching greater than 460 msec. Mean QTcF interval change from baseline was slightly higher in the drug arms versus placebo (+2.4 on 40mg, +2.3 on 80mg, -0.5 on placebo). This mean increase did not appear dose-dependent or clinically risky due to its small magnitude; there were also wider SD ranges (around 14-16) within each treatment arm, indicating substantial overlap in distribution curves for changes from baseline. Incidence of subjects with major QTcF changes from baseline (greater than 30 and 60msec) was rare and comparable between drug (3%) and placebo (2%), and again, none of them exceeded overall values of 460 msec. No QTc-related AEs were reported. Overall, no clinically risky QTcF prolongation is apparent between drug at either dose and placebo according to this study.*

Table 38 Abnormal ECG Parameter Outliers (HR, PR, QRS)

Number and Percentage of Subjects with Abnormal Electrocardiogram Values (Safety Population)

ECG Parameter (unit)	Visit	Placebo (N=112) n (%)	Lurasidone 40 mg (N=110) n (%)	Lurasidone 80 mg (N=104) n (%)	Lurasidone All (N=214) n (%)
Heart Rate (bpm) Abnormally High	Baseline	2 (1.8)	0	4 (3.8)	4 (1.9)
	Week 6	2 (2.2)	0	0	0
	Endpoint	2 (1.9)	0	0	0
PR Interval (msec) Abnormally High	Baseline	4 (3.6)	6 (5.5)	4 (4.8)	11 (5.2)
	Week 6	1 (1.1)	5 (5.3)	4 (4.1)	9 (4.7)
	Endpoint	1 (1.0)	6 (5.8)	4 (4.0)	10 (4.9)
QRS Interval (msec) Abnormally High	Baseline	0	1 (0.9)	0	1 (0.5)
	Week 6	0	1 (1.0)	0	1 (0.5)
	Endpoint	0	1 (1.0)	0	1 (0.5)

Abbreviations: ECG = electrocardiogram.
Note: Definition of abnormal criteria is provided by age group in Table 14.3.7.3.0. Age at the study visit is used.
Note: Percentages are based on the number of subjects per time interval.
Source: Table 14.3.7.3.1.

Table 39 Markedly Abnormal ECG Parameter Criteria

ECG Parameter Cutoffs	Age Group	Abnormally Low	Abnormally High
HR (bpm)	12-15	<50	>105
	16+	<50	>100
PR Interval (msec)	12-15	--	>180
	16+	--	>200
QRS Interval (msec)	12-15	--	>110
	16+	--	>120

Table 40 ECG Parameter Mean Change from Baseline

Change from Baseline to Endpoint in Electrocardiogram Parameters (Safety Population)

			Lurasidone		
	Statistics	Placebo (N=112)	40 mg (N=110)	80 mg (N=104)	All (N=214)
Heart Rate (beats/min)					
Endpoint	n	107	105	100	205
	Baseline Mean (SD)	70.7 (12.38)	72.0 (11.68)	73.8 (14.95)	72.9 (13.37)
	Mean Change (SD)	-0.7 (9.82)	-2.9 (9.84)	-2.1 (13.08)	-2.5 (11.51)
	Median Change	0.0	-2.0	0.5	-1.0
	Min, Max Change	-22, 22	-33, 22	-42, 29	-42, 29
RR Interval (msec)					
Endpoint	n	107	105	100	205
	Baseline Mean (SD)	871.5 (139.01)	855.9 (144.71)	844.2 (157.51)	850.2 (150.83)
	Mean Change (SD)	12.9 (121.79)	35.9 (124.50)	13.5 (135.43)	25.0 (130.11)
	Median Change	12.0	23.0	-4.5	16.0
	Min, Max Change	-261, 350	-269, 498	-256, 398	-269, 498
PR Interval (msec)					
Endpoint	n	105	104	100	204
	Baseline Mean (SD)	146.4 (18.58)	151.4 (26.27)	149.3 (18.02)	150.4 (22.57)
	Mean Change (SD)	0.8 (12.91)	1.0 (13.99)	-0.3 (13.54)	0.3 (13.75)
	Median Change	0	0	1.0	1.0
	Min, Max Change	-59, 42	-42, 34	-45, 35	-45, 35
QRS Interval (msec)					
Endpoint	n	106	105	100	205
	Baseline Mean (SD)	91.9 (8.39)	91.8 (8.96)	91.2 (9.19)	91.5 (9.05)
	Mean Change (SD)	1.7 (6.54)	0.8 (6.73)	-0.2 (7.26)	0.3 (6.99)
	Median Change	1.0	0	0	0
	Min, Max Change	-11, 39	-18, 16	-30, 15	-30, 16
QT Interval (msec)					
Endpoint	n	106	104	100	204
	Baseline Mean (SD)	374.7 (22.05)	372.0 (24.84)	367.7 (30.63)	369.9 (27.85)
	Mean Change (SD)	1.8 (21.43)	7.6 (22.27)	4.5 (23.86)	6.1 (23.06)
	Median Change	3.0	6.0	0	5.0
	Min, Max Change	-43, 56	-55, 76	-59, 91	-59, 91

	Statistics	Placebo (N=112)	Lurasidone		
			40 mg (N=110)	80 mg (N=104)	All (N=214)
QTcB – Bazett's Correction Formula (msec)					
Endpoint	n	106	104	100	204
	Baseline Mean (SD)	404.6 (22.72)	404.3 (22.38)	403.0 (20.95)	403.7 (21.65)
	Mean Change (SD)	-1.6 (20.37)	-0.4 (17.33)	0.9 (18.15)	0.2 (17.70)
	Median Change	-0.5	-2.5	0.5	-1.0
	Min, Max Change	-52, 48	-48, 67	-50, 48	-50, 67
QTcF – Fridericia's Correction Formula (msec)					
Endpoint	n	106	104	100	204
	Baseline Mean (SD)	394.1 (16.64)	393.0 (17.54)	390.5 (17.69)	391.8 (17.62)
	Mean Change (SD)	-0.5 (16.47)	2.4 (14.15)	2.3 (13.80)	2.3 (13.94)
	Median Change	-2.0	0	1.0	0.5
	Min, Max Change	-36, 43	-25, 46	-36, 42	-36, 46

Abbreviations: SD = standard deviation
Note: Baseline: the last value prior to the first dose of study drug is used.
Note: Endpoint: the last post-baseline assessment during double-blind treatment period.
Source: Table 14.3.7.1.

Table 41 Abnormal QTc Outliers

Number and Percentage of Subjects with Prolonged Electrocardiogram QTc Results (Safety Population)

ECG Parameter (unit)	Visit	Placebo (N=112) n (%)	Lurasidone		
			40 mg (N=110) n (%)	80 mg (N=104) n (%)	All (N=214) n (%)
QTcB (msec)	Baseline	112	109	104	213
	QTc > 460 msec	0	1 (0.9)	0	1 (0.5)
	Week 6	93	96	97	193
	QTc > 460 msec	1 (1.1)	1 (1.0)	0	1 (0.5)
	≥ 30 msec increase from Baseline	7 (7.5)	3 (3.1)	2 (2.1)	5 (2.6)
	≥ 60 msec increase from Baseline	0	1 (1.0)	0	1 (0.5)
	Endpoint	106	105	100	205
	QTc > 460 msec	1 (0.9)	1 (1.0)	0	1 (0.5)
	≥ 30 msec increase from Baseline	7 (6.6)	3 (2.9)	2 (2.0)	5 (2.4)
	≥ 60 msec increase from Baseline	0	1 (1.0)	0	1 (0.5)
QTcF (msec)	Baseline	112	109	104	213
	QTc > 460 msec	0	0	0	0
	Week 6	93	96	97	193
	QTc > 460 msec	0	0	0	0
	≥ 30 msec increase from Baseline	2 (2.2)	3 (3.1)	3 (3.1)	6 (3.1)
	≥ 60 msec increase from Baseline	0	0	0	0
	Endpoint	106	105	100	205
	QTc > 460 msec	0	0	0	0
	≥ 30 msec increase from Baseline	2 (1.9)	3 (2.9)	3 (3.0)	6 (2.9)
	≥ 60 msec increase from Baseline	0	0	0	0

Abbreviations: ECG = electrocardiogram; QTcB = Bazett's Correction Formula; QTcF = Fridericia's Correction Formula.
Note: Percentages are based on the number of subjects per time interval.
Source: Errata Table 14.3.7.5.

7.4.5 Special Safety Studies/Clinical Trials

N/A

7.4.6 Immunogenicity

Reviewer Comment:
There was a slightly higher incidence of hypersensitivity AEs on drug versus placebo, possibly in a dose-dependent fashion given the higher rate at 80mg versus 40mg, but not with any clear degree of statistical significance in part due to low N's and a low number of events. It is unclear if the higher incidence of rhinitis/rhinorrhea AEs in the 80mg group versus placebo is also a sign pointing to increased hypersensitivity issues on lurasidone. Current lurasidone labeling already contains a warning for hypersensitivity reactions with this drug.

Table 42 Hypersensitivity AEs per Sponsor

	Placebo N=112	40mg N=110	80mg N=103	All Drug N=214
Total No. Subjects with Hypersensitivity TEAEs	1 (0.9)	2 (1.8)	4 (3.8)	6 (2.8)
Dermatitis Contact	0	0	1 (1.0)	1 (0.5)
Hypersensitivity	0	0	1 (1.0)	1 (0.5)
Pruritus	0	0	1 (1.0)	1 (0.5)
Urticaria	0	0	1 (1.0)	1 (0.5)
Glossodynia	0	1 (0.9)	0	1 (0.5)
Lip Swelling	0	1 (0.9)	0	1 (0.5)
Rash	1 (0.9)	0	0	0

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Overall, the most common AEs (>5%) were not clearly dose-dependent, except for rhinitis/rhinorrhea, at the higher 80mg dose versus the lower 40mg dose versus placebo. However, mean prolactin, fasting glucose, fasting lipids, and weight values seemed to show dose-dependent trends.

7.5.2 Time Dependency for Adverse Events

N/A

7.5.3 Drug-Demographic Interactions

Due to low overall number of subjects in this study and no pooled data available, demographic subgroup analyses by AE via odds ratios et al are likely not to be statistically interpretable.

7.5.4 Drug-Disease Interactions

N/A

7.5.5 Drug-Drug Interactions

Benzodiazepines were the only concomitant psychotropic medication permitted in the trial. Prior discussion noted that it was not likely to have affected overall results given its reasonably even distribution between treatment arms. Other drug-drug interactions did not appear in this study, and subgroup analyses are not applicable/relevant due to low N's in this study.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

N/A

7.6.2 Human Reproduction and Pregnancy Data

Lurasidone's effects during pregnancy have not been studied. The current labeling has been updated to PLLR standards to reflect this information. No pregnancies occurred during this trial.

7.6.3 Pediatrics and Assessment of Effects on Growth

As this study was a short-term trial of 6 weeks, growth effects could not be fully assessed. For the long-term extension trial D1050302, preliminary results show some gradual BMI increases over one year, not that different from expected WHO growth curve results as per the Z-scores.

Table 43 BMI and BMI Z-Score Change from Baseline by Age Group

Change from Baseline in BMI and BMI Z-Scores by Age Group

Timepoint	N	BMI (kg/m^2) Mean (SD)	Expected BMI (kg/m^2) Mean (SD)[a]	BMI Z-score Mean (SD)[a]
Age group: 13-15 years old				
DB Baseline	110	22.16 (3.997)	NA	0.67 (1.116)
Change from DB Baseline at Week 28	79	0.72 (2.020)	0.49 (0.126) [b]	-0.02 (0.544)
Change from DB Baseline at Week 52	45	0.88 (2.863)	0.81 (0.216) [c]	-0.13 (0.681)
Change from DB Baseline at Endpoint	108	0.91 (2.220)	0.66 (0.381) [d]	0.00 (0.610)
Age group: ≥ 16 years old				
DB Baseline	113	23.04 (3.187)	NA	0.51 (0.970)
Change from DB Baseline at Week 28	79	0.67 (1.500)	0.31 (0.128)	0.09 (0.413)
Change from DB Baseline at Week 52	43	0.75 (2.224)	0.50 (0.207)	0.02 (0.559)
Change from DB Baseline at Endpoint	110	0.66 (2.030)	0.39 (0.270)	0.06 (0.539)

Abbreviations: DB=double blind; NA = not applicable
[a] Expected weight and age-and-gender adjusted z-score is based on WHO growth reference
[b] n=78
[c] n=44
[d] n=107
Source: Study D1050302 Table 14.3.6.3.2.00

For height, overall mean increases also seemed similar to expected rates on the WHO growth chart.

For the 13-15 age group, the average (mean ± SD) DB Baseline height was 163.72 ± 9.115 cm and the average DB Baseline Z-score was 0.07 ± 1.053. The increase in height (mean ± SD) from DB Baseline to Week 52 was 3.86 ± 3.728 cm and from DB Baseline to Endpoint was 3.02 ± 3.526 cm, as compared to expected values of 3.60 ± 2.179 cm and 3.07 ± 2.543 cm, respectively, based on the WHO growth chart. At Week 52 and Endpoint, there were minor mean changes from DB Baseline in height Z-scores of 0.03 ± 0.413 and 0.00 ± 0.353, respectively.

For the ≥ 16 age group, the average (mean ± SD) DB Baseline height was 170.12 ± 8.031 cm and the average DB Baseline Z-score was -0.11 ± 0.810. The increase in height (mean ± SD) from DB Baseline to Week 52 was 1.17 ± 1.558 cm and from DB Baseline to Endpoint was 0.96 ± 1.338 cm, as compared to expected values of 0.80 ± 0.677 cm and 0.70 ± 0.666 cm, respectively, based on the WHO growth chart. At Week 52 and Endpoint, there were minor mean changes from DB Baseline in height Z-scores of 0.05 ± 0.224 and 0.04 ± 0.194, respectively.

Reviewer Comment: Overall no unusual growth trends are evident from these initial long-term safety study results so far.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

N/A

7.7 Additional Submissions / Safety Issues

Barnes Akathisia Rating Scale:
There were slight increases in the overall mean BARS total score in both treatment groups (+0.08 for 40mg, +0.12 for 80mg) compared to placebo (+0.02), but not in the statistically significant range. Overall scores did not change much from baseline in any group and were low.

Simpson-Angus Rating Scale:
There were no significant differences in the treatment groups versus placebo for the SAS mean score, and no real change from baseline (which was near zero) in any group by the end of the study.

AIMS:
There were slightly higher changes from baseline in the treatment groups (+0.05 for 40mg, +0.11 for 80mg) versus placebo (-0.02) for the AIMS, but not to any statistically significant degree. The overall changes from baseline were almost negligible in any of the groups, and scores were near zero.

Cogstate Computerized Cognitive Test Battery:
This scale measured working memory and task processing speed, and an increase in score indicated better cognitive processing speed. No significant differences between drug (-0.04 for 40mg, +0.18 for 80mg) and placebo (-0.01) groups were evident with this test, and there were no significant changes from baseline.

UKU Side Effect Rating Scale:
This scale measures specific categories of side effects such as psychic, neurological, autonomic, and other. No significant differences between treatment groups and placebo were evident in this assessment even in subcategories. (For the total UKU score mean change from baseline, 40mg was -1.5, 80mg was -1.0, and placebo was -1.0).

Tanner Staging:
No significant trends were noted in drug versus placebo groups.

Reviewer Comment:
Overall there were no major acute differences between drug and placebo detected by these additional safety screenings, and detected issues were none to minimal.

8 Postmarket Experience

As reported by the Sponsor in their Summary of Clinical Safety (p. 124), the cumulative overall patient exposure to lurasidone from product launch (October 2010) through the cutoff date for this sNDA of October 31, 2015 in the US was estimated at (b) (4) patients, or (b) (4) patient-years (b) (4) For the summary update period (November 2013 to October 2015), the exposure was estimated at (b) (4) patients with (b) (4) patient-years. Worldwide exposure through October 2015 was estimated at (b) (4) patients (b) (4) patients for 2014 to 2015) with (b) (4) **patient-years** of exposure. (After the Annual Report Update covering October 2015 to October 2016, the patient exposure numbers for that period were (b) (4) unique patients with approximately (b) (4) patient-years exposure.)

Table 44 Worldwide Exposure for Lurasidone Since Marketing Approval to October 2015

Cumulative and Interval Exposure From Marketing Experience

Country	Number of Patients Exposed		Patient Years of Treatment	
	Interval	Cumulative	Interval	Cumulative
US	(b) (4)			
Canada				
Europe				
Denmark				
Finland				
The Netherlands				
Norway				
Switzerland				
United Kingdom				
Germany				
Total				

As of April 27, 2016, a total of 15,477 adverse drug reaction (ADR) events with 10,494 reports were entered into the Sponsor pharmacovigilance database since marketing approval in October 2010. The most common ADR groupings were psychiatric SOC (4050), nervous system SOC (3097), general disorders SOC (1799), and gastrointestinal disorders SOC (1382). The most common ADRs reported were drug ineffective (538), nausea (488), akathisia (437), off-label use (433), somnolence (415), weight increased (359), insomnia (308), suicidal ideation (282), anxiety (278), and bipolar disorder (264). Out of 10,494 ADR reports, 1126 were serious. The most common serious ADRs were suicidal ideation (89), seizure (40), death (30), neuroleptic malignant syndrome (26), psychotic disorder (26), suicide attempt (22), aggression (17),

and completed suicide (17). 1652 reports of EPS events (89 serious) were received. 508 reports of hypersensitivity events (95 serious) were received.

For children and adolescent off-label cases with a wide range of psychiatric diagnoses, 162 ADRs were reported (456 events), with 32 serious (45 events). Four events of suicidal ideation and one suicide attempt were reported.

There were 103 death reports: 64 male, 31 female, 8 unknown, median age 50 years. 29 were completed suicides, one was a gunshot wound from police after the patient slit own wrists and stabbed parents. 22 were unknown cause, 12 were sudden death, 33 were due to underlying medical illness or other comorbidity (6 due to MI, 2 due to pneumonia, 2 due to multiorgan failure, 2 in MVAs, 2 due to NMS, others single cases due to infection, fall, congenital anemia, rhabdomyolysis, heat-related dehydration, diabetes, clogged dialysis port, lung CA, newborn after in utero exposure, Alzheimer's, non-suicidal drug OD, stroke, liver cirrhosis, gastric hemorrhage, choking, etc.)

UPDATE FROM Oct 28, 2016 Annual Report:
For the reporting period between October 28, 2015 through October 27, 2016, a total of 1811 ADR cases generated 4768 reports. 312 ADR cases (421 reports with 293 domestic, 128 foreign) were submitted as 15-day Alert reports, with 300 initial and 121 follow-up.

The most frequently reported adverse experiences received for Latuda during the reporting period, occurring at a frequency >30 were: Nausea (134), Akathisia (126), Weight increased (126), Drug ineffective (112), Somnolence (100), Anxiety (100), Restlessness (87), Insomnia (86), Depression (83), Suicidal ideation (83), Tardive dyskinesia (75), Vomiting (67), Fatigue (64), Agitation (63), Tremor (60), Feeling abnormal (54), Dizziness (53), Dyskinesia (51), Mania (51), Bipolar disorder (51), Headache (48), Malaise (46), Hyperhidrosis (35), Aggression (36), Irritability (35), Extrapyramidal disorder (34), Dyspnoea (32).

The most frequently reported **serious** adverse experiences for the same period occurring at a frequency >2 events (% out of 4768 reports) were: Suicidal ideation (83/1.74%), Seizure (22/0.46%), Suicide attempt (19/0.40%), Completed suicide (13/0.27%), Syncope (12/0.25%), Death (10/0.21%, as PT not as a fatal outcome), Swollen tongue (10/0.21%), Psychotic disorder and Weight increased (9/0.19% each), Blood glucose increased, Hyponatraemia, and Myocardial infarction (8/0.17% each), Aggression, Depression, Dyspnoea and Weightdecreased (7/0.15% each), Cerebrovascular accident, Fall, Mania and Neuroleptic malignant syndrome (6/0.13%) each), Akathisia, Coma, Hypersensitivity, Loss of consciousness, Neutropenia, Oculogyric crisis, Seizure like phenomena and Suicidal behaviour (5/0.10% each), Abnormal behaviour, Acute kidney injury, Altered state of consciousness, Bipolar disorder, Blister, Blood creatine phosphokinase increased, Confusional state, Drug abuse, Electrocardiogram QT prolonged, Fatigue, Hallucination, auditory, Insomnia,

Renal impairment, Schizophrenia, Serotonin syndrome, Urticaria (4/0.08%) each), Agitation, Blood creatinine increased, Cardiac disorder, Dizziness, Drug ineffective, Dyskinesia, Hallucination, Hyperhidrosis, Intentional self-injury, Lip swelling, Palpitations, Pancreatitis, Pharyngeal oedema, Pneumonia, Rash, Restlessness, Somnolence, Throat tightness, Tremor (3/0.06% each).

There were 28 death reports during this time period:

- Female unknown age with bipolar disorder (U.S.), no other info available.
- Male unknown age with bipolar depression (U.S.), started lurasidone in Feb 2015, titrated to 80mg, reported restlessness, also benztropine, lamotrigine, sertraline subsequently added, later committed suicide in (b) (6).
- 47yo Caucasian male with schizophrenia (U.S.), started lurasidone in Mar 2015, titrated to 120mg, also on clonazepam and ziprasidone, committed suicide at unknown date (reported (b) (6)).
- 45yo male with schizophrenia and depression (U.S.), h/o unspecified liver disorder, started lurasidone in Jun 2015, titrated to 120mg, noted to have possible increased tardive dyskinesia symptoms, found unresponsive in bed in late (b) (6) and died that day. Autopsy noted presence of 4 drugs (unknown).
- 71yo male (U.S.), no other info available.
- Female unknown age with schizophrenia (U.S.), committed suicide, no other info available.
- 56yo male (U.S.) with anxiety, GERD, tardive dyskinesia, chronic pain, rheumatoid arthritis, h/o tobacco, alcohol, narcotic use, and unknown other history, was on lurasidone 80mg, also on benztropine and gabapentin, passed away from sudden respiratory arrest in late (b) (6), no other info available.
- 25yo female with depression and anxiety (U.S.), started lurasidone off-label in Mar 2015, dose reported as “0.05mg” from a sample pack but this dose does not exist. Sudden death in (b) (6) of unknown cause (possible overdose-suicide suspected?)
- 40yo female with bipolar disorder (Australia), h/o renal failure from lithium, was on lurasidone 40mg (reportedly for 6 days only per spouse), also on lamotrigine and carbamazepine, died of myocardial infarction in (b) (6)
- 53yo Caucasian female with schizoaffective disorder (U.S.), with cardiovascular disease, DM2, HTN, started on lurasidone 20mg, also had been on alprazolam, hydrocodone, lisinopril, simvastatin, prasugrel, died the next day of myocardial infarction in (b) (6).
- Male unknown age (U.S.), had reported suicidal thoughts on lurasidone and felt it wasn’t working, was also on lamotrigine and aripiprazole (timing unclear), then committed suicide in (b) (6)
- 61yo female (U.S.) who was on lurasidone 40mg, also on atorvastatin, had sudden cardiac death in (b) (6)

- 39yo female with bipolar disorder (U.S.), on lurasidone 40mg for a month, also on quetiapine, gabapentin, mirtazapine, topiramate, past heroin addiction, who committed suicide via overdose (with 19 empty pill bottles beside her) in (b) (6)
- 41yo female with bipolar disorder (U.S.), died of acute sepsis/ thrombosis/ multiorgan failure/ hyperglycemia (with emergent leg amputations beforehand) and had undiagnosed DM, had been on lurasidone for unknown period, also on quetiapine.
- 60-something Caucasian male (U.S.), on lurasidone, died of leukemia in (b) (6)
- 50yo male with bipolar depression (U.S.), on lurasidone 60mg and clonazepam who had reportedly stopped his medications at times, had been hospitalized for suicidal ideation and was discharged, then committed suicide in (b) (6)
- Male unknown age (U.S.), who had recently been discontinued from lurasidone, committed suicide three days after.
- Female unknown age (U.S.) who had been on lurasidone, committed suicide.
- Male of unknown age (U.S.), who had been on lurasidone after a hospitalization, committed suicide by driving into a wall at high speed.
- Female of unknown age (U.K.), h/o insulin-dependent DM, cardiomyopathy, obesity, had been on lurasidone for several months, died of likely myocardial infarction.
- 55yo African-American male with major depression and anxiety (U.S.), using lurasidone 80mg off-label and cross-titrating off quetiapine, using lorazepam prn, als on duloxetine, trazodone, multiple medical medications for asthma, HTN, DM2, hyperlipidemia, had started lurasidone in (b) (6) but died one month later due to unknown cause.
- 36yo male with schizoaffective disorder (U.S.), started lurasidone in late Apr 2016, was hospitalized at some point after and remained on lurasidone 60mg, also on clonazepam, committed suicide by hanging in (b) (6).
- 54yo male (U.S.), had started lurasidone Dec 2015, reportedly “very ill, not stable” and died (b) (6) of unknown cause.
- Male of unknown age with unspecified psychiatric disorder, had been on lurasidone 60mg for some time, but committed suicide by hanging in (b) (6). Reportedly had legal issues/possible long-term imprisonment pending.
- 69yo male with bipolar depression (U.S.), had been on lurasidone 40mg started Mar 2016, also on buspirone, clonazepam, and duloxetine, some marked EPS symptoms (muscle rigidity) noted along with paranoia, so lurasidone stopped in early (b) (6), but patient then committed suicide two days after.
- 50yo female with bipolar depression (U.S.), had been on lurasidone 40mg since (b) (6) (also on trazodone) but died 40 days after in (b) (6) of methamphetamine toxicity (had reportedly been abusing) and pulmonary thromboembolism.

- 33yo male (U.S.) who had been on Latuda for one month but committed suicide in late (b) (6).
- 54yo male (U.S.) with chronic pain who had been on Latuda 120mg and nortriptyline and gabapentin and suddenly died (b) (6) years ago. Reportedly had a high lurasidone blood level on autopsy.

No clear trends can be noted from these postmarketing reports, although they seem consistent with other medications in this drug class and for the psychiatric and medical issues found in this treatment population (such as risk of suicidality, and risk of metabolic syndrome exacerbation/already elevated cardiovascular disease background risk found in patients with psychiatric illness.)

No deaths were reported in the lurasidone **pediatric** clinical development program during this time period.

Overall, the post-marketing data shows no unexpected AE findings or trends; existing issues are covered by current lurasidone labeling, and pediatric safety data will be updated with this supplement.

9 Appendices

9.1 Literature Review/References

The Sponsor conducted a literature search covering the period from October 28, 2015 (their last PADER) to October 1, 2016. The following search criteria were utilized in multiple databases including Biosis Previews, Derwent Drug File, EMBASE, Medline, PsycINFO, International Pharmaceutical Abstracts, and Current Contents: (No restrictions were placed on language.)
1. Search date: 18 October 2016
2. Start and end dates of the search: 28 October 2015 – 01 October 2016
3. Search terms: lurasidone OR lurasidona OR lurasidon OR lurasidoni OR latuda OR sm13496 OR smp13496 OR sm ADJ '13496' OR smp ADJ '13496' OR sm ADJ '13' ADJ '496' OR smp ADJ '13' ADJ '496' OR mk3756 OR mk ADJ '3756' OR RN=(367514-87-2 OR 367514-88-3 OR 367414-87-2)
4. Level of Review: The level of review (e.g., entire text versus abstract only) was initially abstract text. Specific articles that may have contained additional safety data for lurasidone HCl were reviewed as entire text.

95 articles were reviewed. No new adverse safety findings associated with lurasidone were noted in the literature during this time period.

9.2 Labeling Recommendations

- Indication for the use of lurasidone in adolescents with schizophrenia at the 40mg and 80mg dose.
- Safety data for adolescents such as common AE tables, generally in keeping with adult study AEs and expected parameter effects (increases in prolactin, fasting lipids and glucose, weight, hypersensitivity reactions.)

9.3 Advisory Committee Meeting

N/A

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEAN S KIM
01/27/2017

JASMINE C GATTI
01/27/2017