CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	200603 S-027
Priority or Standard	Priority
Submit Date(s)	August 1, 2016
Received Date(s)	August 1, 2016
PDUFA Goal Date	February 1, 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	(b) (4) po daily
Indication(s)	(b) (4)
Intended Population(s)	(b) (4)

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

(b) (4)

. Their completed study did not show statistically significant separation between drug and placebo in terms of overall efficacy on their primary endpoint.

1.2 Risk Benefit Assessment

(b) (4)

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 and at the 5-hydroxytryptamine (5-HT) receptors 5-HT_{2A} and 5-HT_7. Lurasidone is currently approved for the treatment of schizophrenia and 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 Irritability in Autism in Children and Adolescents

- Risperidone (Risperdal) ages 5 to 16 years
- Aripiprazole (Abilify) ages 6 to 17 years

2.3 Availability of Proposed Active Ingredient in the United States

Lurasidone has been available in the US 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 requirements (PMR) 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. We requested the two trials as per the above PMRs as well as:

- D1050302: an additional pediatric long-term safety study of at least 6 months duration.
- D1050325: an additional study for a pediatric waiver for autistic disorder which is being reviewed in this supplement: a clinical trial for the treatment of irritability associated with autistic disorder in children ages 6 to 17 years, since other

atypical antipsychotics (aripiprazole and risperidone) currently had that indication, and lurasidone might also be used off-label for that indication.

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

The Sponsor agreed to this WR. The protocol for study D1050325 was submitted to NDA 200603 and was amended twice afterwards, last in April 2014, with minor criteria changes.

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 from the Phase 3 autism efficacy study: Case Report Forms (CRFs), Narrative Summaries (NSs), and adverse event data listings (ae.xpt files). The 6 patients audited were:

325006001
325018003
325029003
325036005
325037008
325052002

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 D1050325 was conducted in accordance with Good Clinical Practice standards. An Office of Scientific Investigations (OSI) inspection was waived due to no overtly

unusual safety or efficacy signals from clinical study sites that were not restricted from FDA inspection visits.

3.3 Financial Disclosures

Clinical Investigator Financial Disclosure
Review Template

Application Number: NDA 200603, Supplement 27

Submission Date(s): 7/30/16

Applicant: Sunovion

Product: Latuda (lurasidone)

Reviewer: Jean Kim MD, MA

Date of Review: 8/30/16

Covered Clinical Study (Name and/or Number): D1050325

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from applicant)
Total number of investigators identified: 47 principal, 211 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 ☐

There were two investigators who disclosed amounts of $306,612.50 and $106,277.50 from 2011-2015 respectively. However, one was a sub-investigator whose site only enrolled (b) (6) in the study, and the other was an investigator whose site enrolled only (b) (6) 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 irritability in autism.

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' (ID-14283, ID-14326, ID-11614, ID-20219, and ID-20220) 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.

102 subjects were 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

Study D1050325 is entitled: "A 6-Week, Randomized, Parallel, Double-Blind, Placebo-Controlled, Fixed-Dose, Multicenter Study to Evaluate the Efficacy and Safety of Lurasidone in Children and Adolescent Subjects with Irritability Associated with Autistic Disorder." Children from ages 6 to 12 years were studied, and adolescents from ages 13 to 17 years.

The studies done by the Sponsor (b) (4) are:

Table 1 Lurasidone Studies for Pediatric Irritability in Autism

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: D1050325	6-week randomized double-blind placebo-controlled efficacy and safety study in pediatric subjects with autism at 20 to 60mg lurasidone.
Phase 3: D1050302	6-month open-label extension safety study for completers of D1050301 (adolescent schizophrenia, see Supplement 26) and D1050325 on lurasidone.

5.2 Review Strategy

The efficacy review of this supplement is solely based on the results of Study D1050325.

The safety review of this supplement is based on serious adverse events (SAEs) and other adverse events (AEs) from Study D1050325 and D1050302 and an evaluation of supportive safety findings from safety assessment data (laboratory tests, vital signs, ECGs) from Study D1050325.

Table 2 Sponsor Updates for this sNDA

Date	eCTD #	Content
7/30/16	143	Original sNDA Submission for Supplement 27
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 D1050325 did not use the site in question. (D1050300 or 302 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 providing 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 efficacy study for this supplement, Section 5.1).

6 Review of Efficacy

Efficacy Summary

The efficacy of lurasidone at 20 to 60mg daily for the treatment of irritability in autism in children and adolescents was evaluated in one clinical trial, D1050325. Two different doses (20mg and 60mg) were compared to placebo using the primary endpoint of change in baseline to Week 6 on the Aberrant Behavior Checklist (ABC) irritability subscale score. Both doses did not show significant difference than placebo for the primary endpoint.

6.1 Indication

Treatment of irritability in autism in children and adolescents.

6.1.1 Methods

(b) (4) Per the division director, a single efficacy trial was deemed sufficient to fulfill this PREA requirement for lurasidone, since this drug is an already approved drug, and two other medications in the class (risperidone and aripiprazole) already received approval for this indication using two trials each, establishing the safety-efficacy feasibility of that indication; subsequent drugs in the class (b) (4) required one trial (b) (4)

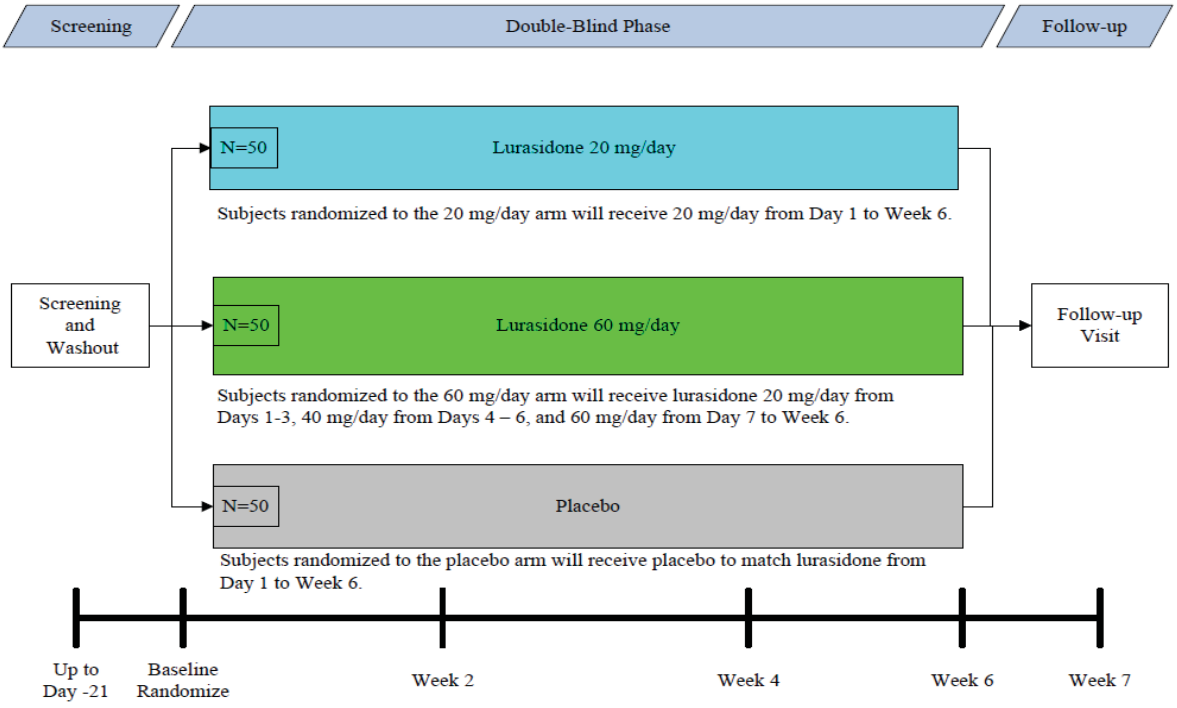
D1050325 was a 6-week randomized, double-blind, placebo-controlled, parallel group trial. This study was conducted at 40 domestic centers with 149 randomized total subjects (49 to placebo, 49 to lurasidone 20mg/day, and 51 to lurasidone 60mg/day). Dosages were based on the results from the pharmacokinetic study D1050300. (There was a run-in period for the 60mg group of 20mg from Day 1 to 3, and 40mg from Day 4 to 6.)

The trial consisted of a screening/tapering period of up to 21 days. Subjects had to be discontinued from any other psychotropic medications at least 3 days prior to randomization (fluoxetine and MAOIs at least 21 days prior, clozapine at least 120 days prior, depot neuroleptics at least one dose cycle prior). Subjects had to have been deemed stable from a behavioral therapy standpoint for at least 4 weeks before screening and during the study.

Then the subjects entered a 6-week treatment period, and a follow-up period of one week. Subjects were randomized to lurasidone 20mg daily, 60mg daily, and placebo in a 1:1:1 ratio.

The statistical methods used were as follows: Unless otherwise specified, all statistical tests were interpreted at a 2-sided significance level of 5% and all confidence intervals (CIs) were presented at a 2-sided confidence level of 95%. The overall type I error rate for testing lurasidone 20 mg/day versus placebo and lurasidone 60 mg/day versus placebo was controlled at the 5% level across the primary endpoint using the Hochberg step-up procedure. (Multiplicity adjustment was not done for secondary endpoints.) Efficacy analyses were performed on the ITT population for change from baseline in ABC irritability subscale score at Week 6 using a likelihood-based MMRM model. Additional analyses that were planned included: PP population analysis and a repeated measures model (adding a fixed effect test of the interaction of pooled center and treatment, and for age groups). Several other supportive (dispensing errors factor) and sensitivity analyses (PM, REM) were performed and mentioned in the study report; they all corroborated the primary analyses.

Figure 1 D1050325 Study Design



6.1.2 Demographics

There were significantly more males in this study (82% male versus 18% female) in this study, likely reflecting overall demography for autism. More children (ages 6 to 12 years) were enrolled (72%) versus adolescents aged 13 to 17 years (28%) in the study. The majority were white (77%), with a mild imbalance in the placebo arm (86% versus 73% in the drug arms). Hispanic ethnicity was also slightly higher in the lurasidone 20mg arm (22%) versus 14% in the other arms. Other demographics were fairly balanced across treatment arms.

Table 3 Demographics in D1020325

Demographics (Safety Population)

Characteristic	Placebo (N=49)	Lurasidone			Total (N=149)
		20 mg (N=49)	60 mg (N=51)	All (N=100)	
Gender, n (%)	49	49	51	100	149
Male	40 (81.6)	39 (79.6)	43 (84.3)	82 (82.0)	122 (81.9)
Female	9 (18.4)	10 (20.4)	8 (15.7)	18 (18.0)	27 (18.1)
Age (years)[a]; n	49	49	51	100	149
Mean (SD)	11.0 (3.01)	10.6 (3.26)	10.5 (3.11)	10.6 (3.17)	10.7 (3.12)
Median	11.0	10.0	10.0	10.0	10.0
Min, Max	6, 17	6, 17	6, 17	6, 17	6, 17
Category, n (%)					
6-12	35 (71.4)	36 (73.5)	36 (70.6)	72 (72.0)	107 (71.8)
13-17	14 (28.6)	13 (26.5)	15 (29.4)	28 (28.0)	42 (28.2)
Category, n (%)					
6-9	16 (32.7)	19 (38.8)	21 (41.2)	40 (40.0)	56 (37.6)
10-12	19 (38.8)	17 (34.7)	15 (29.4)	32 (32.0)	51 (34.2)
13-15	8 (16.3)	9 (18.4)	11 (21.6)	20 (20.0)	28 (18.8)
16-17	6 (12.2)	4 (8.2)	4 (7.8)	8 (8.0)	14 (9.4)
Race, n (%)	49	49	51	100	149
American Indian or Alaska Native	0	1 (2.0)	1 (2.0)	2 (2.0)	2 (1.3)
Asian	1 (2.0)	0	1 (2.0)	1 (1.0)	2 (1.3)
Black or African American	5 (10.2)	10 (20.4)	9 (17.6)	19 (19.0)	24 (16.1)
White	42 (85.7)	35 (71.4)	38 (74.5)	73 (73.0)	115 (77.2)
Other	1 (2.0)	3 (6.1)	2 (3.9)	5 (5.0)	6 (4.0)
Ethnicity, n (%)	49	49	51	100	149
Hispanic or Latino	7 (14.3)	11 (22.4)	7 (13.7)	18 (18.0)	25 (16.8)
Not Hispanic or Latino	42 (85.7)	38 (77.6)	44 (86.3)	82 (82.0)	124 (83.2)
Baseline Weight (kg); n	49	49	51	100	149
Mean (SD)	42.9 (14.46)	42.1 (17.72)	43.9 (17.20)	43.0 (17.39)	43.0 (16.43)
Median	40.6	39.5	42.9	40.9	40.6
Min, Max	20, 83	19, 90	19, 95	19, 95	19, 95
Category, n (%)					
< 5th percentile	1 (2.0)	1 (2.0)	0	1 (1.0)	2 (1.3)
5th to 95th percentile	46 (93.9)	44 (89.8)	46 (90.2)	90 (90.0)	136 (91.3)
> 95th percentile	2 (4.1)	4 (8.2)	5 (9.8)	9 (9.0)	11 (7.4)

Characteristic	Placebo (N=49)	Lurasidone			Total (N=149)
		20 mg (N=49)	60 mg (N=51)	All (N=100)	
Baseline Weight Z-score (n)	49	49	51	100	149
Mean (SD)	0.29 (0.873)	0.25 (1.005)	0.57 (0.946)	0.41 (0.984)	0.37 (0.948)
Baseline Height (cm); n	49	49	51	100	149
Mean (SD)	147.26 (16.856)	145.69 (19.876)	148.04 (18.627)	146.89 (19.188)	147.01 (18.397)
Median	149.00	143.00	149.10	148.30	148.60
Min, Max	111.8, 183.0	110.5, 190.5	111.8, 188.0	110.5, 190.5	110.5, 190.5
Category, n (%)					
< 5th percentile	2 (4.1)	3 (6.1)	1 (2.0)	4 (4.0)	6 (4.0)
5th to 95th percentile	46 (93.9)	41 (83.7)	41 (80.4)	82 (82.0)	128 (85.9)
> 95th percentile	1 (2.0)	5 (10.2)	9 (17.6)	14 (14.0)	15 (10.1)
Baseline Height Z-score (n)	49	49	51	100	149
Mean (SD)	0.03 (0.877)	0.11 (1.156)	0.51 (1.130)	0.31 (1.154)	0.22 (1.077)
Baseline BMI (kg/m^2); n	49	49	51	100	149
Mean (SD)	19.23 (3.186)	18.85 (3.525)	19.16 (3.291)	19.01 (3.394)	19.08 (3.318)
Median	18.76	18.16	18.70	18.56	18.67
Min, Max	14.4, 26.8	13.4, 28.7	13.2, 26.8	13.2, 28.7	13.2, 28.7
Category, n (%)					
< 5th percentile	0	2 (4.1)	2 (3.9)	4 (4.0)	4 (2.7)
5th to 95th percentile	48 (98.0)	45 (91.8)	47 (92.2)	92 (92.0)	140 (94.0)
> 95th percentile	1 (2.0)	2 (4.1)	2 (3.9)	4 (4.0)	5 (3.4)
Baseline BMI Z-score (n)	49	49	51	100	149
Mean (SD)	0.37 (0.974)	0.28 (0.950)	0.43 (0.989)	0.35 (0.968)	0.36 (0.967)
Baseline Waist Circumference (cm); n	48	48	51	99	147
Mean (SD)	69.00 (11.703)	68.12 (11.972)	67.94 (11.388)	68.03 (11.615)	68.34 (11.613)
Median	67.30	66.00	65.00	66.00	66.50
Min, Max	45.0, 104.0	50.8, 100.0	52.0, 94.5	50.8, 100.0	45.0, 104.0

Abbreviations: BMI = body mass index; Max = maximum; Min = minimum; SD = standard deviation.
[a] Age is calculated at screening.
Note: Percentages are calculated with the number of subjects in each characteristic as denominator.
Source: Table 14.1.2.3.

6.1.3 Subject Disposition

Out of 239 screened subjects for D1050325, 150 were randomized, with 149 subjects dosed in the study. 128 (85%) completed the 6-week double-blind phase, with a higher numbers of dropouts in the placebo arm (24%) than the drug arms (12% on 20mg and 8% on 60mg).

Table 4 Subject Disposition in D1050325

Subject Disposition (All Subjects)

	Placebo (N=50) n (%)	Lurasidone			Total (N=150) n (%)
		20 mg (N=49) n (%)	60 mg (N=51) n (%)	All (N=100) n (%)	
Screened Subjects					239
Screening Failures [a]					89 (37.2)
Subjects who were randomized [a]	50 (20.9)	49 (20.5)	51 (21.3)	100 (41.8)	150 (62.8)
Subjects who were randomized, but not dosed	1 (2.0)	0	0	0	1 (0.7)
Subjects in the ITT who completed the 6-Week DB Phase	38 (76.0)	43 (87.8)	47 (92.2)	90 (90.0)	128 (85.3)
Subjects in the ITT who completed the 6-Week DB Phase and entered into the open-label extension Study D1050302	37 (74.0)	42 (85.7)	46 (90.2)	88 (88.0)	125 (83.3)
Subjects who discontinued during the DB Phase Primary reason for discontinuation	12 (24.0)	6 (12.2)	4 (7.8)	10 (10.0)	22 (14.7)
Lack of Efficacy	1 (2.0)	1 (2.0)	1 (2.0)	2 (2.0)	3 (2.0)
Adverse Event	4 (8.0)	2 (4.1)	2 (3.9)	4 (4.0)	8 (5.3)
Lost To Follow-Up	1 (2.0)	2 (4.1)	0	2 (2.0)	3 (2.0)
Withdrawal of Consent	6 (12.0)	1 (2.0)	0	1 (1.0)	7 (4.7)
Other	0	0	1 (2.0)	1 (1.0)	1 (0.7)

[a] For screening failures and subjects randomized, percentages are based on the number of subjects screened. All other percentages are based on the number of randomized subjects.
Source: Table 14.1.1.3 and Table 14.1.1.4.

Table 5 Analysis Populations in D1050325

Analysis Populations (All Randomized Subjects)

	Placebo (N=50) n (%)	Lurasidone			Total (N=150) n (%)
		20 mg (N=49) n (%)	60 mg (N=51) n (%)	All (N=100) n (%)	
Subjects in the ITT population	49 (98.0)	48 (98.0)	51 (100.0)	99 (99.0)	148 (98.7)
Subjects in the PP population	43 (86.0)	38 (77.6)	28 (54.9)	66 (66.0)	109 (72.7)
Subjects in the Safety population	49 (98.0)	49 (100.0)	51 (100.0)	100 (100.0)	149 (99.3)

Abbreviations: ITT = intent to treat; PP = per protocol.
Note: Percentages are calculated with the number of subjects in each treatment group as denominator.
Source: Table 14.1.1.3.

Dropouts/discontinuations due to Adverse Events (AEs) will be discussed in 7.3.3.

Protocol Deviations:

Table 6 Protocol Deviations in D1050325

Protocol Deviations (All Randomized Subjects)

Item	Placebo (N=50) n (%)	Lurasidone 20 mg (N=49) n (%)	Lurasidone 60 mg (N=51) n (%)	Lurasidone All (N=100) n (%)	Total (N=150) n (%)
Total Number of Subjects With Deviation	7 (14.0)	11 (22.4)	23 (45.1)	34 (34.0)	41 (27.3)
Receives the incorrect study treatment	0	0	17 (33.3)	17 (17.0)	17 (11.3)
No baseline and post-baseline ABC-I score	1 (2.0)	1 (2.0)	0	1 (1.0)	2 (1.3)
Do not have 14 days or more of continuous exposure	6 (12.0)	6 (12.2)	2 (3.9)	8 (8.0)	14 (9.3)
Unblinded during the double-blind phase	0	1 (2.0)	0	1 (1.0)	1 (0.7)
Non-compliance of study drug	2 (4.0)	3 (6.1)	4 (7.8)	7 (7.0)	9 (6.0)
Prohibited medication or prohibited dose	2 (4.0)	0	2 (3.9)	2 (2.0)	4 (2.7)
Violated inclusion /exclusion criteria	0	4 (8.2)	3 (5.9)	7 (7.0)	7 (4.7)
Tests positive for substance abuse	0	0	0	0	0

Abbreviations: ABC-I = Aberrant Behavior Checklist irritability subscale.
Notes: Subjects may have more than one protocol deviation. Percentages are calculated with the number of subjects in each treatment group as denominator.
Source: Table 14.1.1.7.

A high number of subjects (17, or 33%) in the 60mg arm received the incorrect study treatment due to a dispensing error, and not in the other treatment arms. The error was due to an IXRS coding error at the final resupply visit (Week 5) affecting those 17 subjects who were accidentally given 40mg instead of 60mg for the rest of the study. A separate analysis was done by the Sponsor attempting to account for this discrepancy and did not find that the overall negative efficacy results changed and no major differences were noted between Week 5 and Week 6 after the error occurred. (This exploratory analysis was done by adding analysis groups for lurasidone 60mg without dispense error and with dispense error and measuring ABC irritability score and CGI-S score with both MMRM and ANCOVA methods for the ITT population for both the entire study, and also looking at the change from Week 5 to Week 6.) Slightly higher inclusion/exclusion criteria violations occurred on drug (7 subjects) versus placebo (0).

Overall the rates of protocol deviations were markedly higher on drug (34%) than placebo (14%) mainly due to the dispensing error.

Baseline Psychiatric History/Hospitalizations:
Mean baseline ABC irritability subscale scores were similar across treatment groups (29.1 on placebo, 28.3 on lurasidone 20mg, 27.1 on 60mg) so there was no significant bias effect in that regard.

For past psychiatric history, the proportion of subjects with comorbid psychiatric disorders permitted in this study was similar between drug (60% overall) and placebo (55% overall) groups:

- Attention Deficit/Hyperactivity Disorder (DSM-IV-TR code 314.01) - 38.0% for the

combined lurasidone group and 40.8% for the placebo group;
- Oppositional Defiant Disorder (DSM-IV-TR code 313.81) - 16.0% for the combined lurasidone group and 18.4% for the placebo group;
- Attention Deficit/Hyperactivity Disorder (DSM-IV-TR code 314.00) - 8.0% for the combined lurasidone group and 6.1% for the placebo group
- Insomnia (DSM-IV-TR code 780.52) - 7.0% for the combined lurasidone group and 4.1% for the placebo group

The average age of initial onset of autism diagnosis was was 4.78 ± 3.513 years for the combined lurasidone group and 5.05 ± 3.765 years for the placebo group. The average duration of autistic disorders from onset to Screening was 6.27 ± 3.954 years for the combined lurasidone group and 6.50 ± 3.942 years for the placebo group.

Overall, baseline illness factors were generally comparable between treatment groups and likely did not bias study results.

Treatment Compliance:
No major differences were noted between treatment arms in terms of overall treatment compliance (7% drug noncompliance on lurasidone versus 4% placebo).

Concomitant Medications:
No major differences in usage of prohibited concomitant medications was noted between treatment arms, and it was rare (only four subjects total). For general concomitant medications, 53% of placebo subjects, 65% of 20mg, and 59% of 60mg were on one or more concomitant medications (no subjects on benzodiazepines, 5 on diphenhydramine, 25 on melatonin).

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint was the change from Baseline to Week 6 in the Aberrant Behavior Checklist (ABC) irritability subscale.

The LS mean change from Baseline to Week 6 for the ABC irritability scale score based on an MMRM model was -7.5 for placebo, -8.8 for lurasidone 20mg, and -9.4 for lurasidone 60mg. The overall degree of treatment difference from placebo of -1.3 for 20mg and -1.9 for 60mg was **not** statistically significant, with p-values at 0.546 for 20mg and 0.359 for 60mg. (This was after multiplicity adjustment via Hochberg step-up procedure.) These results were confirmed with multiple analyses (ANCOVA, exploratory/sensitivity analyses) discussed earlier.

Table 7 Primary Endpoint: ABC Irritability Subscale Mean Change from Baseline

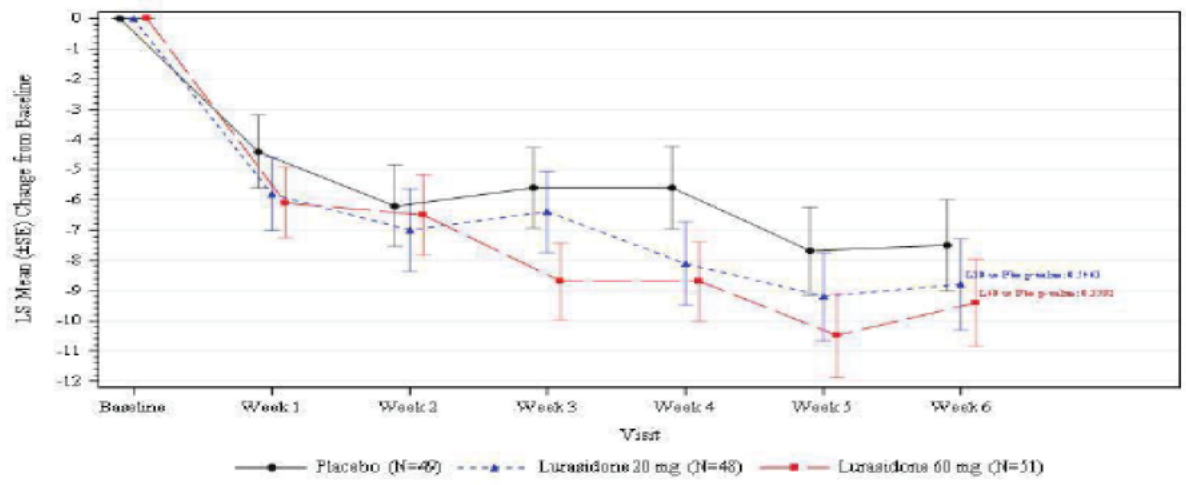
Change from Baseline in the Aberrant Behavior Checklist (ABC) Irritability Subscale Score – Mixed Model for Repeated Measures (Intent-to-Treat Population) (Continued)

ABC Irritability Subscale Score	Placebo (N=49)	Lurasidone 20 mg (N=48)	Lurasidone 60 mg (N=51)
Change from Baseline to Week 6			
n	38	43	47
LS Mean (SE)	-7.5 (1.52)	-8.8 (1.50)	-9.4 (1.43)
Difference of LS Mean (SE) (vs. Placebo)		-1.3 (2.15)	-1.9 (2.09)
95% CI of Difference		(-5.6, 3.0)	(-6.1, 2.2)
p-value (vs. Placebo)		0.5463	0.3592

Abbreviations: ABC = Aberrant Behavior Checklist; CI = confidence intervals; LS = least squares; SE = standard errors.
Notes: 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 center, ABC irritability score at baseline, and treatment-by-visit interaction.
Note: Higher values of ABC subscale scores represent greater severity of illness.
Source: Table 14.2.1.1.1.

Figure 2 ABC Irritability Subscale Mean Change from Baseline

Change from Baseline (LS Mean ± SE) in the Aberrant Behavior Checklist (ABC) Irritability Subscale Score - Mixed Model for Repeated Measures (Intent-to-Treat Population)



Source: Figure 14.2.2.1.

6.1.5 Analysis of Secondary Endpoints(s)

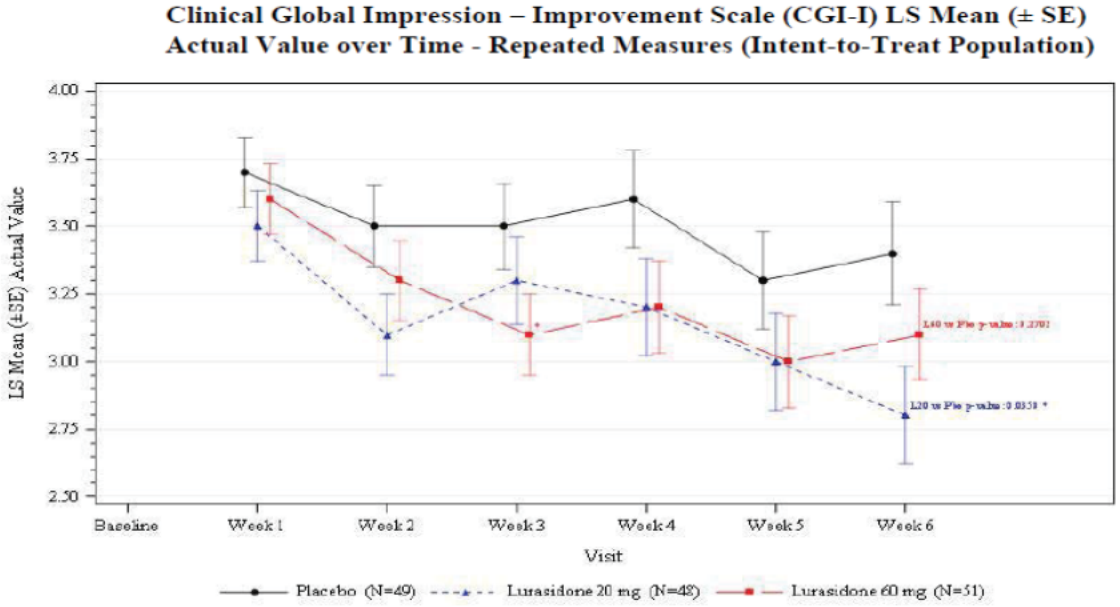
The following secondary endpoints were measured and analyzed in Study D1050325:

- Change from Baseline in Clinical Global Impression severity (CGI-S) scale as compared to placebo
- Clinical Global Impression Improvement (CGI-I) scale

- Change from Baseline in other Aberrant Behavior Checklist (ABC) subscale scores (hyperactivity, stereotypy, inappropriate speech, and lethargy/social withdrawal)
- Change from Baseline in Children's Yale-Brown Obsessive Compulsive Scales (CY-BOCS) modified for pervasive developmental disorders (PDDs)
- Change from Baseline in the Caregiver Strain Questionnaire (CGSQ)
- Proportion of subjects who have CGI-I score of 1 (very much improved) or 2 (much improved) at Week 6
- Proportion of subjects who have at least 25% reduction from Baseline to Week 6 in the ABC irritability subscale score.

CGI-I:

Figure 3 CGI-I Mean Change from Baseline



Note: * p<=0.05.
Source: Figure 14.3.1.1.

Table 8 Secondary Endpoint: CGI-I Mean Change from Baseline

	Placebo	Lurasidone 20mg	Lurasidone 60mg
Week 6			
n	38	43	47
LS Mean (SE)	3.4 (0.19)	2.8 (0.18)	3.1 (0.17)
Difference of LS Mean (SE) (vs. Placebo)		-0.6 (0.26)	-0.3 (0.26)
95% CI of Difference		(-1.1, -0.0)	(-0.8, 0.2)
p-value (vs. Placebo)		0.0350	0.2702

Abbreviations: CGI-I = Clinical Global Impression – Improvement; CI = confidence intervals; LS = least squares; SE = standard errors.
Notes: LS mean, LS Mean difference and associated 95% CI, and p-value for CGI-I value are based on Mixed Model for Repeated Measures with fixed effects terms for treatment, visit (as a categorical variable), pooled center, and treatment-by-visit interaction.
Note: Smaller values of CGI-I scores represent greater improvement.
Source: Table 14.2.2.1.1.

CGI-I did not show significant improvement at Week 6 between placebo and lurasidone at 60mg, and some small significant improvement at 20mg. All of the other scales such as the other ABC subscale scores, CGI-S, CY-BOCS, and CGSQ showed no significant changes between placebo and drug arms. (Sponsor study report includes tables of actual numbers under Tables 14.2.2.1.1).

An additional treatment by pooled center interaction analysis done by the Sponsor showed no significant anomalies.

6.1.6 Other Endpoints

N/A

6.1.7 Subpopulations

Subgroup analyses by age, gender, race, ethnicity, and BMI/weight were performed by the Sponsor (full tables are in the study report under Tables 14.2.1.7). None showed statistically significant treatment subgroup differences. Results are of limited interpretability due to low N's in many of the subgroups and wide SD ranges.

Table 9 LS Mean Diff (95% CI) ABC Irritability Change in Baseline at Week 6 Difference from Placebo (N=49)

Subgroup Type	Subgroup	Total N (All Arms, N=148)	Placebo N (N=49)	Lurasidone 20mg (N=48)	20mg N	Lurasidone 60mg (N=51)	60mg N
Age	Age 6-12	107	35	-1.6 (-6.2, 3.1)	36	-1.3 (-5.9, 3.4)	36
	Age 13-17	41	14	-2.9 (-10.7, 4.9)	12	-5.8 (-13.1, 1.5)	15
Gender	Male	121	40	-1.6 (-6.1, 2.8)	38	-2.7 (-7.0, 1.7)	43
	Female	27	9	-2.5 (-11.6, 6.5)	10	-2.4 (-11.9, 7.1)	8
Race	White	114	42	-1.3 (-5.9, 3.2)	34	-1.4 (-5.8, 2.9)	38
	Black	24	5	-2.2 (-13.0, 8.6)	10	-4.3 (-15.3, 6.6)	9
	Asian	2	1	n/a		1	1
	Other	8	1	2.0	4	-1.3	3
Ethnicity	Hispanic/Latino	25	7	-2.3 (-12.1, 7.6)	11	1.3 (-9.3, 11.8)	7
	Non-	123	42	-1.5 (-5.9,	37	-3.2 (-7.5,	44

	Hispanic/Latino			3.0)		1.0)	
BMI	<25th percentile	25	8	-0.6 (-9.8, 8.6)	10	-9.8 (-19.8, 0.2)	7
	25th to 85th percentile	81	24	-0.5 (-5.9, 4.9)	28	-1.6 (-7.0, 3.7)	29
	>85th percentile	42	17	-4.6 (-12.4, 3.2)	10	-0.8 (-7.8, 6.2)	15

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The Sponsor evaluated efficacy for lurasidone at both 20mg daily and 60mg daily versus placebo. However, neither dose showed significant efficacy for irritability in autism based on the primary endpoint (ABC irritability score).

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

This is a short-term 6-week trial and is the only one performed for this clinical indication for lurasidone, so persistence of efficacy/tolerance is not relevant.

6.1.10 Additional Efficacy Issues/Analyses

N/A

7 Review of Safety

Safety Summary

Safety data in Study D1050325 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 no deaths reported during either study. For D1050325, there were 5 serious adverse events (SAEs) all occurring on lurasidone (but only one was psychiatric and the other medical SAEs did not appear drug-related.)

The AEs that occurred at ≥5% rate (per MAED and JMP analysis of the ADAE.xpt dataset) and greater than twice that of placebo for both dosages were: vomiting, somnolence/sedation, nasopharyngitis/URI, abdominal discomfort/gastritis, fatigue/lethargy, weight increase, and akathisia. For 60mg only, constipation, nausea, allergic rhinitis/rhinorrhea.

These AEs are overall in keeping with expected side effects from prior lurasidone and atypical antipsychotic studies and current labeling. Of note, there appeared to be markedly higher than usual rates for vomiting in this study, particularly in children ages 6 to 12.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data were derived from Study D1050325 during the randomized controlled trial portion only. An open-label long-term extension study D1050302 was also performed with 84% of subjects (125 subjects) screened for participation out of those who were originally enrolled in D1050325, as well as 83% of subjects (271 subjects, 180 of whom are included in the interim analysis) screened out of those who were originally enrolled in D1050301 (covered in Supplement 26). 396 total subjects from both studies entered D1050302.

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

Somnolence: somnolence, sedation
Fatigue: fatigue, lethargy
Viral Infection: nasopharyngitis, influenza, viral infection, upper respiratory infection (URI)
Rhinitis/Rhinorrhea: rhinitis, rhinitis allergic, rhinorrhea, nasal congestion, sinus congestion
Abdominal Pain: abdominal pain (including upper), abdominal discomfort, gastritis
EPS (non-akathisia): muscle twitching, oculogyric crisis, Parkinsonism, dystonia
Akathisia: akathisia, psychomotor hyperactivity

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

Table 10 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

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, some additional information available with 120-Day Update with October 27, 2016 cutoff date.)

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 (but a total of 441 from 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) for this study, 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 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: For Study D1050325, duration of exposure seemed fairly even across treatment groups (slightly higher in the 60mg group at 5.6) and likely was not a factor in any potential study bias. Demographics of the study population roughly reflect those of the general pediatric autism population (majority males versus females, American racial demographics.)

7.2.2 Explorations for Dose Response

The fixed-dose design of Study D1050325 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 D1050325 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: Barnes Akathisia Rating Scale (BARS), Abnormal Involuntary Movement Scale (AIMS), and Simpson-Angus Scale (SAS), Tanner staging, and menstrual cyclicity (females). Overall labs, physical examination, and ECG assessments and urine tests were done only at screening, baseline (Day 1), and Week 6 (Day 43). The same safety assessments were carried forward into the open-label extension study D1050302.

All safety analyses and summaries were based on the safety analysis population of 149 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.

Table 11 Schedule of Assessments for D1050325

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 -3	1	4±1	8±1	15±2	22±2	29±2	36±2	43±2	50±2
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 medication		X		X	X	X	X	X		
Study drug accountability/assess compliance			X	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									
Autism Diagnostic Interview, Revised (ADI-R)	X									
Mini International Neuropsychiatric Interview for children and adolescents (MINI-Kid)	X									
Physical examination	X	X							X	
Height as measured by stadiometer	X	X							X	
Tanner staging		X							X	
Menstrual cyclicity (female subjects)	X								X	
Vital sign[d]	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	
Hematology, chemistry, and urinalysis	X								X	
Blood sample for lurasidone concentration[e]									X	
Serum prolactin[f]	X								X	
Glycosylated hemoglobin (HbA_{1c})	X								X	
Glucose and lipid panel	X[g]								X[g]	
Serum insulin and C-reactive protein	X								X	
Serum human chorionic gonadotropin (β-hCG)[h]	X									
Urine drug screen	X								X	
Urine β-hCG[h,i]						X			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 -3**	**1**	**4±1**	**8±1**	**15±2**	**22±2**	**29±2**	**36±2**	**43±2**	**50±2**
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
Children's Yale-Brown Obsessive Compulsive Scales (CY-BOCS) compulsion scale only		X				X			X	
Aberrant Behavior Checklist (ABC)	X	X		X	X	X	X	X	X	
Clinical Global Impression – Severity Scale (CGI-S)	X	X		X	X	X	X	X	X	
Clinical Global Impression – Improvement Scale (CGI-I)				X	X	X	X	X	X	
Caregiver Strain Questionnaire (CGSQ)		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 medication. 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 enter the D1050302 study only.
[d] Vital sign measurements included orthostatic changes in blood pressure and heart rate.
[e] Time and date of the 3 previous doses of study medication, time and date of dose of study medication, and the time of the blood sampling were to be recorded.
[f] Prolactin levels were blinded, except at screening visit. Investigators were to be notified if prolactin concentrations were more than 200 ng/mL.
[g] Subjects were to fast for lipids and glucose laboratory tests only.
[h] Females subjects ≥ 11 years of age only.
[i] Any positive urine β-hCG test was to be confirmed by serum β-hCG.

Table 12 Assessments Carried Forward to D1050302

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 D1050325 ONLY
Aberrant Behavior Checklist (ABC)
Clinical Global Impression – Severity (CGI-S)
Children's Yale-Brown Obsessive Compulsive Scales (CY-BOCS) modified for pervasive developmental disorders (PDDs)
Caregiver Strain Questionnaire (CGSQ)

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 in 5 subjects (5%) on lurasidone (3 on 20mg and 2 on 60mg), and none on placebo. Only one SAE was psychiatric, and that subject discontinued their medication (20mg) at Day 12. The others were medical events that did not appear related to the study drug (accidental fractures, appendicitis).

Table 13 SAEs in Study D1050325

Subject ID	Demographics	Event	Treatment Group
325012007	6yo Native American M	Broken left arm after accidental fall (missed step off of curb). Occurred Day 9.	Lurasidone 20mg
325020004	6yo WM	Worsening Irritability (Occurred Day 13 and was hospitalized. Drug was withdrawn that day. Had also been taking Benadryl several times	Lurasidone 20mg

		for insomnia before event. Pt subsequently started clonidine, guanfacine, olanzapine afterwards while in hospital and was discharged 1 week later.)	
325051003	10yo WF	Left wrist fracture (Occurred Day 9 after accidental fall while playing and slipping on ice patch.)	Lurasidone 20mg
325036011	9yo WM	Acute appendicitis (Occurred Day 9, had appendectomy aftewards). Restarted study drug after hospital stay (had to stop for 4 days).	Lurasidone 60mg
325055011	7yo BM	Right thumb fracture after accidental injury (Occurred Day 31.)	Lurasidone 60mg

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 (13 of whom were originally from this study D1050325). Psychiatric SAEs: 25 total, 8 with SI (1 from this study), 6 with aggression, 4 with agitation, 4 with schizophrenia, 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, for D1050302 a total of 39 subjects (9.8%) had SAEs (52 events). Psychiatric SAEs: 30 subjects total with 35 events (6 subjects from D1050325 with 6 events) with 1 additional suicidal behavior case reported since March (from D1050301 originally). 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 report (influenza, 2 fractures).

Table 14 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

There were 4 subjects (4%) who were on lurasidone (2 on 20mg, 1 on 40mg, 1 on 60mg) and 4 subjects (8%) on placebo who stopped treatment due to AEs. (They were noted as nausea, vomiting, suicidal ideation, irritability for lurasidone, and decreased appetite, disturbance in attention, psychomotor hyperactivity, affect lability on placebo.)

No discontinuations due to acute lab toxicity, vital signs, or ECGs/QTC prolongation were noted.

Per the 120-Day Safety Update through Oct. 27, 2016, for the extension safety study D1050302, there were 44 dropouts due to AEs out of 396 total (11%), including 18 dropouts due to AEs out of 125 total (14%) originally enrolled from D1050325.

Reviewer Comment: Overall, no clear association between lurasidone and study dropouts/discontinuations versus placebo was evident during this trial.

7.3.4 Significant Adverse Events

Suicidal Ideation or Behavior Events:

Table 15 SIB AEs in Study D1050325

Subject ID	Event	Dose
325023001	Intentional self-injury, 11yo WM, occurred Day 8 (withdrew from study treatment, but reportedly due to severe decreased appetite, not due to SA event although they occurred the same day).	Placebo
325043002	Suicidal ideation, 8yo WM, remained in study.	Placebo
325052002	Suicidal ideation, 10yo WM, occurred Day 25, drug was subsequently withdrawn. Event resolved that day and subject was not	Lurasidone 60mg

	hospitalized. Was on no other medications.	

Reviewer Comment: No association between lurasidone and SIB events was evident from this study, and overall low N's make it difficult to detect any significant associations. There was no C-SSRS or other suicidality scale administered during this study or for its subjects subsequently enrolled in the extension study D1050302. (Due to communication issues with autism, these scales would be difficult to use consistently in this population.) None were reported as SAEs as none led to hospitalizations. In the extension study D1050302, only 2 SIB events (one suicidal ideation, one suicide attempt) were reported as SAEs among subjects originally from D1050325.

7.3.5 Submission Specific Primary Safety Concerns

N/A

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 16 Most Common AEs ≥5% in Any Drug Arm (n (%))

AE	Lurasidone 60mg (includes 40mg N=7) N=51	Lurasidone 20mg N=49	Placebo N=49
Vomiting	14 (27%)	4 (8%)	2 (4%)
Somnolence/Sedation	10 (20%)	6 (12%)	3 (6%)
Nasopharyngitis/URI/ Viral Infection/Influenza	5 (10%)	7 (14%)	2 (4%)
Abdominal Pain/Discomfort/Gastritis	5 (10%)	4 (8%)	2 (4%)
Cough	2 (4%)	3 (7%)	3 (6%)
Diarrhea	1 (2%)	4 (8%)	4 (8%)
Fatigue/Lethargy	4 (8%)	3 (6%)	1 (2%)
Weight Increase	4 (8%)	1 (2%)	1 (2%)
Headache	3 (6%)	2 (4%)	3 (6%)
Constipation	3 (6%)	1 (2%)	1 (2%)
Akathisia/PM Hyperactivity	5 (10%)	5 (10%)	1 (2%)
Nausea	3 (6%)	2 (4%)	0
Insomnia/Initial/Middle	3 (6%)	2 (4%)	5 (10%)

Allergic Rhinitis/Rhinorrhea/Nasal or Sinus Congestion	2 (4%)	4 (8%)	0

Reviewer Comment: There were 103 subjects with AEs (327 events) reported in the Sponsor's ADAE.xpt dataset. Overall, the common AEs are in keeping with expected AEs for lurasidone in prior studies, and are generally included in current labelling for lurasidone.

There do not appear to be any unusual new AE trends for this child and adolescent autism population, although there may be some higher rates in this study than other trials with adolescents/adults for vomiting and somnolence events. This elevated rate was seen particularly at the higher dosage of 60mg, and possibly higher for gastrointestinal SOC events overall. (It is inconclusive though because the dosages are different between studies, and the overall N's are lower which might inflate rates. Also some adolescents are still included in this trial. Baseline rates of pre-existing gastrointestinal disorders were relatively high in this population, with 29% placebo, 24.5% 20mg, 18% 60mg; there were also high rates of pre-existing immune system and allergic disorders, with 57% placebo, 71% 20mg, 73% 60mg.)

Of note, in the long-term extension study D1050302, there also seemed to be a much higher rate of vomiting (21%) amongst subjects originally from D1050325 than D1050301 (5.5%) or other lurasidone trials (4 to 8% in adult RCTs). It is unclear if this is partially due to some sort of age or diagnosis-related lurasidone sensitivity in this population. (D1050325 included children under age 13 and D1050301 did not.) 13 of out the 20 (65%) subjects with vomiting (13 out of 18 on drug or 72%) in D1050325 were ages 6 to 12. D1050302 ages are unavailable.

Table 17 Subjects from D1050325 with Vomiting AE by Age Group

Treatment Arm	Age Group	n	Crude Rate*	Total in Arm by Age
Lurasidone 20 mg	Screening age 13-17 years old	1	2%	13
N=49	Screening age 6-12 years old	3	6%	36
Lurasidone 40-60 mg	Screening age 13-17 years old	4	8%	15
N=51	Screening age 6-12 years old	10	20%	36
Placebo	Screening age 13-17 years old	2	4%	14
N=49	Screening age 6-12 years old	0	0%	35

*Crude Rate = Vomiting Events n/Treatment Arm Total N

The AEs that occurred at ≥5% rate (per MAED and JMP analysis of the ADAE.xpt dataset) and greater than twice that of placebo for both dosages were: vomiting, somnolence/sedation, nasopharyngitis/URI, abdominal discomfort/gastritis, fatigue/lethargy, akathisia. For 60mg only: nausea, constipation, weight increase. For 20mg only: allergic rhinitis/rhinorrhea.

Of note, due to relatively low N's in this study, numerous AEs could be included with only 1 subject or more leading to ≥2% rate (and several were already subsumed into a larger category to avoid splitting as I did in the 5% table), so I did not list those here.

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.

Reviewer Comment: No clinically meaningful changes from baseline were noted by Week 6 for any hematology parameters in this study. The only drug arm subjects with markedly abnormal values were one subject with hematocrit ≥50% in the lurasidone 60mg group, two subjects each on 20mg and 60mg (four total on drug) with eosinophils ≥10% (and also 3 subjects on placebo), and one subject on 20mg with neutrophils ≤15%. These outliers do not indicate any clear drug-related trends.

Liver:
For liver lab values, there were no clear trends evident in this study and mean changes from baseline were very minimal for all the values, with no clear dose-dependent trends. There were 3 AEs reported in the lurasidone 20mg group related to LFTs (one subject 325044001 with elevated ALT (of 64 U/L at screening) and GGT (44 U/L at screening) and one 325055005 with decreased ALT.) (Subject 325044001 withdrew consent for the study 18 days after study enrollment and also refused repeat labwork except for a negative urinalysis and toxicology screen.) 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 subjects on drug met criteria for markedly abnormal LFT values in this study.

Table 18 Liver Function Mean Changes from Baseline in D1050325

Mean Change from Baseline at Endpoint	N	Placebo N=49	N	Lurasidone 20mg N=49	N	Lurasidone 60mg N=44
AST	41	+0.8 (4.40)	43	-0.3 (4.79)	42	+0.1 (6.01)
ALT	41	+2.0 (10.02)	43	+0.2 (8.81)	42	+3.5 (12.79)
Alk Phos	43	-4.7	43	-6.7 (30.72)	43	+5.3 (47.18)

		(35.42)				
GGT	43	-0.3 (5.08)	43	+0.2 (2.32)	43	+1.3 (3.65)
Bilirubin	43	+0.03 (0.183)	43	+0.03 (0.181)	43	-0.01 (0.302)

Reviewer Comment: No significant effects on liver function were noted in this study.

Renal:

Table 19 Renal Function Mean Changes from Baseline in D1050325

Mean Change from Baseline at Endpoint	N	Placebo N=49	N	Lurasidone 20mg N=49	N	Lurasidone 60mg N=44
BUN	43	+0.7 (2.89)	43	-0.4 (3.01)	43	+0.7 (3.34)
Creatinine	43	+0.01 (0.15)	43	+0.01 (0.05)	43	+0.06 (0.11)

Reviewer Comment: No major trends for renal findings were noted in this study, and no related AEs were reported. No subjects met criteria for markedly abnormal renal values in this study.

Prolactin:
A small increase in prolactin was evident by Week 6 from baseline in this study for the lurasidone 60mg arm (+2.34 ng/mL mean change from baseline for lurasidone 60mg). This finding is consistent with most other antipsychotics and is covered in current labeling. One AE related to increased prolactin (elevated level at screening) was reported in one subject on lurasidone 60mg but was not attributable to study drug. (See Table 20 for subjects with prolactin ≥1XULN, no trend versus placebo.)

Reviewer Comment: There may be a small dose-dependent drug effect of increased prolactin at the 60mg dose in this study.

Table 20 Prolactin Change from Baseline

Change from Baseline to Endpoint in Prolactin (Safety Population)

			Lurasidone		
	Statistics	Placebo (N=49)	20 mg (N=49)	60 mg (N=51)	All (N=100)
Prolactin (ng/mL) - Overall					
Endpoint	n	43	43	48	91
	Baseline Mean (SD)	8.72 (9.551)	7.63 (7.509)	7.53 (8.086)	7.58 (7.776)
	Mean Change (SD)	-0.13 (5.862)	-0.21 (8.983)	2.34 (13.892)	1.13 (11.836)
	Median Change	-0.30	0.10	1.15	0.50
	Min, Max Change	-19.9, 12.3	-35.5, 24.9	-46.2, 66.4	-46.2, 66.4
	p-value[a]		0.9998	0.1930	0.3829
Prolactin - Females (ng/mL)					
Endpoint	n	7	9	8	17
	Baseline Mean (SD)	6.96 (5.843)	5.97 (4.587)	10.91 (9.171)	8.29 (7.334)
	Mean Change (SD)	3.00 (4.914)	1.60 (9.046)	8.88 (25.974)	5.02 (18.711)
	Median Change	3.90	-0.40	4.35	0.50
	Min, Max Change	-4.1, 8.4	-5.6, 24.9	-21.6, 66.4	-21.6, 66.4
Prolactin - Males (ng/mL)					
Endpoint	n	36	34	40	74
	Baseline Mean (SD)	9.06 (10.143)	8.07 (8.106)	6.86 (7.803)	7.41 (7.912)
	Mean Change (SD)	-0.74 (5.895)	-0.69 (9.041)	1.04 (10.049)	0.24 (9.573)
	Median Change	-0.40	0.10	0.90	0.50
	Min, Max Change	-19.9, 12.3	-35.5, 16.2	-46.2, 28.5	-46.2, 28.5

Abbreviations: ANCOVA = analysis of covariance; max = maximum; min = minimum; SD = standard deviation.
Note: Endpoint: the last post-baseline assessment during double-blind treatment period.
[a] p-values from stratified Mantel-Haenszel raw mean score test per Rank ANCOVA. Rank was stratified by age group.
Source: Table 14.3.4.2.1.

Metabolic Chemistry:
Overall, there were small mean increases from baseline by Week 6 for both drug treatment arms versus placebo for fasting total cholesterol, and for the 60mg arm for fasting triglycerides. Fasting glucose did **not** show increases in this 6-week study.

Table 21 Metabolic Chemistry Change from Baseline

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

			Lurasidone		
	Statistics	Placebo (N=49)	20 mg (N=49)	60 mg (N=51)	All (N=100)
Glucose (Overall) (mg/dL)					
Endpoint	n	43	43	50	93
	Baseline Mean (SD)	91.3 (9.69)	88.9 (13.37)	87.1 (8.73)	87.9 (11.09)
	Mean Change (SD)	-1.1 (12.40)	-2.9 (14.02)	0.4 (9.70)	-1.1 (11.94)
	Median Change	-5.0	-1.0	-1.0	-1.0
	Min, Max Change	-21, 40	-57, 19	-18, 25	-57, 25
	p-value[a]	-	0.8520	0.8565	0.9051
Glucose (Fasting) (mg/dL)					
Endpoint	n	36	37	45	82
	Baseline Mean (SD)	90.1 (9.69)	86.4 (7.47)	88.1 (7.24)	87.3 (7.34)
	Mean Change (SD)	-2.0 (12.17)	-0.5 (7.43)	-0.4 (8.35)	-0.5 (7.90)
	Median Change	-5.0	-1.0	-1.0	-1.0
	Min, Max Change	-21, 40	-18, 15	-17, 23	-18, 23
	p-value[a]	-	0.5426	0.5400	0.4548
Cholesterol (Overall) (mg/dL)					
Endpoint	n	43	43	50	93
	Baseline Mean (SD)	152.2 (25.22)	146.8 (25.59)	152.8 (26.38)	150.0 (26.05)
	Mean Change (SD)	-0.1 (20.53)	6.4 (16.98)	7.5 (18.28)	7.0 (17.61)
	Median Change	-4.0	4.0	7.5	6.0
	Min, Max Change	-47, 71	-26, 52	-27, 66	-27, 66
	p-value[a]	-	0.0893	0.0373	0.0264
Cholesterol (Fasting) (mg/dL)					
Endpoint	n	36	37	45	82
	Baseline Mean (SD)	152.9 (27.21)	145.9 (23.89)	153.1 (27.01)	149.9 (25.75)
	Mean Change (SD)	-1.4 (20.37)	8.5 (15.09)	8.7 (18.26)	8.6 (16.81)
	Median Change	-5.0	6.0	8.0	7.0
	Min, Max Change	-47, 71	-26, 39	-27, 66	-27, 66
	p-value[a]	-	0.0126	0.0078	0.0029

	Statistics	Placebo (N=49)	Lurasidone 20 mg (N=49)	Lurasidone 60 mg (N=51)	Lurasidone All (N=100)
HDL Cholesterol (Overall) (mg/dL)					
Endpoint	n	43	43	50	93
	Baseline Mean (SD)	59.2 (14.76)	56.3 (14.11)	53.9 (12.77)	55.0 (13.38)
	Mean Change (SD)	-1.5 (7.59)	1.2 (8.37)	0.6 (7.94)	0.9 (8.10)
	Median Change	-2.0	1.0	0.5	1.0
	Min, Max Change	-26, 18	-16, 31	-17, 26	-17, 31
	p-value[a]	-	0.1946	0.4709	0.2248
HDL Cholesterol (Fasting) (mg/dL)					
Endpoint	n	36	37	45	82
	Baseline Mean (SD)	58.8 (13.52)	56.8 (14.83)	53.7 (12.41)	55.1 (13.55)
	Mean Change (SD)	-1.8 (7.14)	1.1 (7.53)	1.4 (7.78)	1.3 (7.62)
	Median Change	-1.5	1.0	1.0	1.0
	Min, Max Change	-26, 12	-16, 15	-17, 26	-17, 26
	p-value[a]	-	0.1629	0.2129	0.1131
LDL Cholesterol (Overall) (mg/dL)					
Endpoint	n	43	43	50	93
	Baseline Mean (SD)	75.5 (21.68)	74.3 (21.52)	82.3 (22.84)	78.6 (22.48)
	Mean Change (SD)	2.3 (19.22)	5.4 (15.00)	4.5 (13.81)	4.9 (14.30)
	Median Change	1.0	5.0	4.0	5.0
	Min, Max Change	-35, 82	-25, 34	-21, 41	-25, 41
	p-value[a]	-	0.1749	0.2152	0.1218
LDL Cholesterol (Fasting) (mg/dL)					
Endpoint	n	36	37	45	82
	Baseline Mean (SD)	76.9 (23.36)	73.1 (19.47)	83.0 (23.42)	78.5 (22.15)
	Mean Change (SD)	2.4 (19.14)	7.8 (12.90)	5.2 (13.52)	6.4 (13.23)
	Median Change	-1.0	7.0	5.0	5.5
	Min, Max Change	-24, 82	-21, 34	-21, 41	-21, 41
	p-value[a]	-	0.0423	0.1099	0.0397

	Statistics	Placebo (N=49)	Lurasidone 20 mg (N=49)	Lurasidone 60 mg (N=51)	Lurasidone All (N=100)
Triglycerides (Overall) (mg/dL)					
Endpoint	n	43	43	50	93
	Baseline Mean (SD)	87.3 (43.00)	84.9 (45.61)	87.3 (54.11)	86.2 (50.10)
	Mean Change (SD)	-0.1 (53.84)	-1.9 (53.78)	9.8 (41.16)	4.4 (47.50)
	Median Change	-3.0	1.0	15.0	2.0
	Min, Max Change	-100, 225	-236, 183	-137, 93	-236, 183
	p-value[a]	-	0.7147	0.1608	0.2808
Triglycerides (Fasting) (mg/dL)					
Endpoint	n	36	37	45	82
	Baseline Mean (SD)	85.9 (44.07)	84.6 (48.30)	87.1 (56.05)	85.9 (52.39)
	Mean Change (SD)	-8.0 (41.40)	-6.3 (48.14)	8.1 (41.55)	1.6 (44.94)
	Median Change	-4.0	1.0	13.0	2.0
	Min, Max Change	-100, 100	-236, 57	-137, 93	-236, 93
	p-value[a]	-	0.5148	0.1032	0.1813
Hemoglobin A1C (%)					
Endpoint	n	44	43	50	93
	Baseline Mean (SD)	5.08 (0.287)	4.90 (0.260)	4.95 (0.313)	4.93 (0.289)
	Mean Change (SD)	0.01 (0.272)	0.08 (0.240)	0.12 (0.358)	0.10 (0.308)
	Median Change	0.05	0.00	0.10	0.10
	Min, Max Change	-0.8, 0.5	-0.3, 0.7	-0.4, 2.1	-0.4, 2.1
	p-value[a]	-	0.9066	0.5204	0.6614

Table 22 Incidence of Select Markedly Abnormal Lab Values

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

Parameter (unit)	Unit	Placebo n (%)	Lurasidone 20 mg n (%)	Lurasidone 60 mg n (%)	Lurasidone All n (%)
Potassium (mEq/L)	n	44	43	50	93
	≥ 5.5	0	4 (9.3)	2 (4.0)	6 (6.5)
Prolactin (ng/mL)	n	44	43	48	91
	≥ 1 x ULN	3 (6.8)	1 (2.3)	3 (6.3)	4 (4.4)
Cholesterol (mg/dL) - fasting	n	39	38	45	83
	≥ 240	0	0	1 (2.2)	1 (1.2)
Triglycerides (mg/dL) - fasting	n	39	38	45	83
	Female ≥ 170 Male ≥ 200	1 (2.6)	0	3 (6.7)	3 (3.6)
HDL-Cholesterol (mg/dL) - fasting	n	39	38	45	83
	≤ 30	0	1 (2.6)	1 (2.2)	2 (2.4)
LDL Cholesterol (mg/dL) - fasting	n	39	38	45	83
	≥ 160	0	0	0	0

Note: Percentages are based on the number of subjects per time interval.
Source: Table 14.3.4.5.1.

For other electrolytes besides potassium (K+), the only markedly abnormal lab values were one subject each on 20mg and 60mg with sodium ≥150mEq/L (also two on placebo), and two subjects on 20mg, six subjects on 60mg (plus one on 60/40mg) with bicarbonate ≤18mEq/L (also five on placebo).

Reviewer Comment: No clear drug-dependent trends for these chemistry parameters are evident here. For K+, there might be a small drug-related association with abnormal elevation versus placebo, although the study N's are too low to assess significance.

Creatine Kinase:
No increases in mean CK were noted for either dose arm over placebo in this study by Week 6. No CK-related AEs were reported. Only one markedly high CK value ≥450 U/L was noted in the placebo group, and one in the lurasidone 20mg group, none on 60mg. Subject 325052001 in the 20mg group had very high CK of 6807 at screening but by 4 days before study entry was down to 528. At Week 6, they were at 565, so the effect likely was not drug-related, although the original etiology is unclear.

Reviewer Comment: No significant drug-related effects on CK are noted in this study.

Table 23 CK Mean Changes from Baseline

	N	Placebo N=49	N	Lurasidone 20mg N=49	N	Lurasidone 60mg N=44
Mean Change from Baseline at Endpoint	43	+12.7 (71.11)	43	-3.1 (43.13)	42	-12.5 (68.84)

Urinalysis:
Reviewer Comment: No clinically meaningful changes in mean values from Baseline to Week 6 in this study were noted.

Hormonal Parameters:
A shift was seen in six subjects (8%) going from normal to high testosterone on lurasidone (both arms combined, but only 1 subject on 20mg) versus placebo (1 subject, or 3%). Mean changes from baseline for testosterone levels decreased by Week 6 on lurasidone versus placebo and showed no overall significant differences in testosterone level between treatment groups. However, there was a very wide SD range likely due to the much higher baseline testosterone levels in the adolescent age group (368 ng/dL) versus the child group (58 ng/dL). A subgroup analysis by age was done of the adlb.xpt dataset on JMP. At Week 6, the child arms showed mean changes of +4.6 for lurasidone 20mg, +12.8 for 60mg, and -3.2 for placebo.

This might indicate a small dose-dependent increase in testosterone level for subjects ages 6 to 12 years in this study. The adolescent group showed no clear trend at Week 6 (-43 for 20mg, -32 for 60mg, +124 for placebo.)

Table 24 Mean Testosterone Change from Baseline by Age Group in D1050325 (Male Subjects Only)

			CHG (ng/dL)		
TRTP	**AVISIT**	**AGEGR1**	**Mean**	**Std Dev**	**N**
Lurasidone 20 mg	Endpoint	13-17 years old	-42.67	185.34	9
		6-12 years old	4.44	27.58	25
	Week 6	13-17 years old	-42.67	185.34	9
		6-12 years old	4.625	28.15	24
Lurasidone 60 mg	Endpoint	13-17 years old	-32.17	86.31	12
		6-12 years old	45.18	177.58	28
	Week 6	13-17 years old	-32.17	86.31	12
		6-12 years old	12.8	50.42	25
Placebo	Endpoint	13-17 years old	124.5	144.14	10
		6-12 years old	0.12	29.63	26
	Week 6	13-17 years old	124.5	144.14	10
		6-12 years old	-3.24	22.58	21

Table 25 Mean Testosterone Levels by Age Subgroup (Males)

Endpoint	Statistics	Placebo (N=30)	Lurasidone 20 mg (N=29)	Lurasidone 60 mg* (N=30)	Lurasidone All (N=59)
Testosterone (ng/dL) –Male					
6-12 years old	n	26	25	28	53
	Baseline Mean (SD)	60.1 (80.29)	62.3 (101.97)	55.4 (90.83)	58.6 (95.37)
	Mean (SD)	60.2 (91.75)	66.7 (121.10)	100.6 (197.21)	84.6 (165.08)
13-17 years old	n	10	9	12	21
	Baseline Mean (SD)	316.6 (175.34)	385.0 (187.02)	372.6(203.44)	377.9 (191.82)
	Mean (SD)	441.1 (201.80)	342.3 (86.58)	340.4 (183.31)	341.2 (146.56)

One 9 year-old child subject 325013002 on lurasidone 60mg was reported as an AE at the end of the 6-week treatment period for elevated testosterone; their baseline level was 19 ng/dL and it went to 38 at endpoint. These overall serum levels are low even after doubling but again, it might be part of a small dose-dependent increase trend in this age group. (Even excluding this subject, the same mean trends remained present.) However, interpretability is limited due to overall low N's in this study.

I also did a similar subgroup mean change analysis for estradiol in female subjects where mean estradiol in this study was 44 pg/mL in adolescents 13 to 17 years and 17.5 in children 6 to 12 years, but no trends were evident at Week 6 for the child subgroup, with mean change from baseline at -2.6 for lurasidone 20mg, -1.0 for 60mg and -1.0 for placebo, with overall N's being very low (9 subjects total for 20mg, 9 for 60mg, and 8 for placebo, and 3/2/3 respectively in the adolescent age range.) No trends were evident in the adolescent group as well at Week 6 (+0.13 for 20mg, +4.4 for 60mg, +78 for placebo).

Reviewer Comment: There may be a small dose-dependent increase of serum testosterone in male children in this study, but not adolescents, although this finding's interpretability is limited due to low N's and by dispensing error variations in the 60mg

arm, and to other possible background fluctuations in this population per DPMH. Otherwise, there were no clear or significant trends on hormonal parameters measured in this study.

7.4.3 Vital Signs

Vital Signs:
No significant changes in blood pressure or pulse were noted for this study, although the drug arms all trended up slightly from baseline in a dose-dependent fashion. (Only two child subjects on lurasidone 20mg were reported as an AE for BP increase: one 325036014 for systolic (+9 Week 3, +5 Week 6) and one 325036001 for diastolic (+12 week 6); and one child 325011003 on lurasidone 60mg was reported an AE for orthostatic hypotension (-25 SBP Week 3, -12 DBP Week 6.) One subject each on lurasidone 20mg and 60mg were reported as AEs for tachycardia.

Reviewer Comment: There were no clear overall orthostatic hypotension trends in the drug arms versus placebo for the overall study group. However, please see the subgroup analysis in Section 7.5.3.

Table 26 Change in Mean Vital Signs from Baseline

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

			Lurasidone		
	Statistics	Placebo (N=49)	20 mg (N=49)	60 mg (N=51)	All (N=100)
Heart Rate (beats/min), Supine					
Endpoint	n	49	48	51	99
	Baseline Mean (SD)	80.3 (13.60)	81.9 (11.48)	80.3 (12.16)	81.1 (11.80)
	Mean Change (SD)	-1.4 (12.96)	0.7 (13.05)	1.1 (13.66)	0.9 (13.30)
	Median Change	-2.0	2.5	0.0	1.0
	Min, Max Change	-32, 30	-20, 41	-30, 44	-30, 44
Systolic Blood Pressure (mmHg), Supine					
Endpoint	n	49	48	51	99
	Baseline Mean (SD)	108.1 (11.73)	107.1 (12.07)	105.6 (13.10)	106.3 (12.57)
	Mean Change (SD)	-0.2 (11.40)	1.0 (10.18)	2.9 (12.79)	2.0 (11.58)
	Median Change	2.0	0.5	2.0	2.0
	Min, Max Change	-26, 28	-21, 34	-32, 30	-32, 34

	Statistics	Placebo (N=49)	Lurasidone 20 mg (N=49)	Lurasidone 60 mg (N=51)	Lurasidone All (N=100)
Diastolic Blood pressure (mmHg), Supine					
Endpoint	n	49	48	51	99
	Baseline Mean (SD)	66.0 (7.90)	66.9 (7.74)	64.9 (8.64)	65.9 (8.23)
	Mean Change (SD)	-1.1 (8.67)	0.7 (9.10)	2.7 (9.95)	1.7 (9.55)
	Median Change	-1.0	2.0	3.0	2.0
	Min, Max Change	-22, 20	-21, 22	-27, 18	-27, 22
Respiration Rate (breaths/min)					
Endpoint	n	49	48	51	99
	Baseline Mean (SD)	17.5 (2.06)	18.2 (3.68)	17.4 (2.05)	17.8 (2.96)
	Mean Change (SD)	0.2 (2.27)	-0.3 (3.59)	0.4 (2.25)	0.1 (2.98)
	Median Change	0.0	0.0	0.0	0.0
	Min, Max Change	-8, 8	-14, 8	-4, 8	-14, 8
Temperature (C)					
Endpoint	n	49	48	51	99
	Baseline Mean (SD)	36.71 (0.365)	36.70 (0.340)	36.72 (0.309)	36.71 (0.323)
	Mean Change (SD)	-0.01 (0.414)	-0.07 (0.410)	-0.06 (0.419)	-0.06 (0.413)
	Median Change	0.00	0.00	0.00	0.00
	Min, Max Change	-0.8, 1.1	-1.1, 0.8	-1.7, 0.6	-1.7, 0.8

Abbreviations: max = maximum; min = minimum; SD = standard deviation.
Note: Endpoint: the last post-baseline assessment during double-blind treatment period.
Source: Table 14.3.5.1.

Table 27 Incidence of Abnormal Vital Signs

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

Parameter	Placebo (N=49) n (%)	Lurasidone 20 mg (N=49) n (%)	Lurasidone 60 mg (N=51) n (%)	Lurasidone All (N=100) n (%)
Systolic Blood Pressure (mmHg), Supine				
Any Post-Baseline DB Visit	49	48	51	99
Potentially Markedly Low	0	0	0	0
Potentially Markedly High	5 (10.2)	3 (6.3)	5 (9.8)	8 (8.1)

Parameter	Placebo (N=49) n (%)	Lurasidone 20 mg (N=49) n (%)	Lurasidone 60 mg (N=51) n (%)	Lurasidone All (N=100) n (%)
Systolic Blood Pressure (mmHg), Standing				
Any Post-Baseline DB Visit	48	47	51	98
Potentially Markedly Low	1 (2.1)	0	1 (2.0)	1 (1.0)
Potentially Markedly High	1 (2.1)	5 (10.6)	5 (9.8)	10 (10.2)
Orthostatic Systolic Blood Pressure (mmHg)				
Any Post-Baseline DB Visit	48	47	51	98
≥ 20 decrease from supine to standing position	2 (4.2)	1 (2.1)	5 (9.8)	6 (6.1)
Diastolic Blood Pressure (mmHg), Supine				
Any Post-Baseline DB Visit	49	48	51	99
Potentially Markedly Low	1 (2.0)	0	0	0
Potentially Markedly High	3 (6.1)	3 (6.3)	3 (5.9)	6 (6.1)
Diastolic Blood Pressure (mmHg), Standing				
Any Post-Baseline DB Visit	48	47	51	98
Potentially Markedly Low	0	0	0	0
Potentially Markedly High	0	6 (12.8)	6 (11.8)	12 (12.2)
Orthostatic Diastolic Blood Pressure (mmHg)				
Any Post-Baseline DB Visit	48	47	51	98
≥ 10 decrease from supine to standing position	8 (16.7)	9 (19.1)	9 (17.6)	18 (18.4)
Heart Rate (beats/min), Supine				
Any Post-Baseline DB Visit	49	48	51	99
Potentially Markedly Low	3 (6.1)	1 (2.1)	2 (3.9)	3 (3.0)
Potentially Markedly High	1 (2.0)	0	1 (2.0)	1 (1.0)
Heart Rate (beats/min), Standing				
Any Post-Baseline DB Visit	48	48	51	99
Potentially Markedly Low	0	1 (2.1)	2 (3.9)	3 (3.0)
Potentially Markedly High	0	1 (2.1)	0	1 (1.0)

Parameter	Placebo (N=49) n (%)	Lurasidone 20 mg (N=49) n (%)	Lurasidone 60 mg (N=51) n (%)	Lurasidone All (N=100) n (%)
Orthostatic Heart Rate (beats/min)				
Any Post-Baseline DB Visit	48	48	51	99
≥ 20 increase from supine to standing position	12 (25.0)	18 (37.5)	13 (25.5)	31 (31.3)
Temperature (°C)				
Any Post-Baseline DB Visit	49	48	51	99
Potentially Markedly High	0	0	0	0

Abbreviations: DB = double-blind.
Notes: 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.
Notes: Percentages are based on the number of subjects per time interval.
Source: Table 14.3.5.2.1.

Table 28 Markedly Abnormal Cutoff Criteria for Vital Signs

Criteria for Potentially Markedly Abnormal Post-Baseline Vital Signs for Pediatric and Adolescent Subjects

Parameter (unit)	Age (years old)	Markedly Low	Markedly High
SBP (supine, standing) (mmHg)	6-12	Value ≤ 70 and ≥ 20 decrease from baseline	Value ≥ 120 and ≥ 20 increase from baseline
	13-18	Value ≤ 90 and ≥ 20 decrease from baseline	Value ≥ 135 and ≥ 20 increase from baseline
DBP (supine, standing) (mmHg)	6-12	Value ≤ 40 and ≥ 15 decrease from baseline	Value ≥ 80 and ≥ 15 increase from baseline
	13-18	Value ≤ 50 and ≥ 15 decrease from baseline	Value ≥ 90 and ≥ 15 increase from baseline
Pulse rate (supine, standing) (bpm)	6-10	Value ≤ 60 and ≥ 15 decrease from baseline	Value ≥ 135 and ≥ 15 increase from baseline
	11-18	Value ≤ 50 and ≥ 15 decrease from baseline	Value ≥ 120 and ≥ 15 increase from baseline
SBP orthostatic criteria (mmHg)	~	≥ 20 decrease from supine to standing position	NA
DBP orthostatic criteria (mmHg)	~	≥ 10 decrease from supine to standing position	NA
Pulse rate orthostatic criteria (bpm)	~	NA	≥ 20 increase from supine to standing position
Temperature (°C)	~	NA	Value ≥ 38.3°C and ≥ 0.8°C increase from baseline

Abbreviations: NA = not applicable.
Note: ~ means that the abnormal range is applicable for all subjects within age group: 6 to 17 years old.
Source: SAP, Table 9.

Weight:
Reviewer Comment: LS Mean weight for the drug treatment arms showed small increases from baseline by Week 6, and in a dose-dependent fashion from placebo.

Table 29 Weight LS Mean Change from Baseline

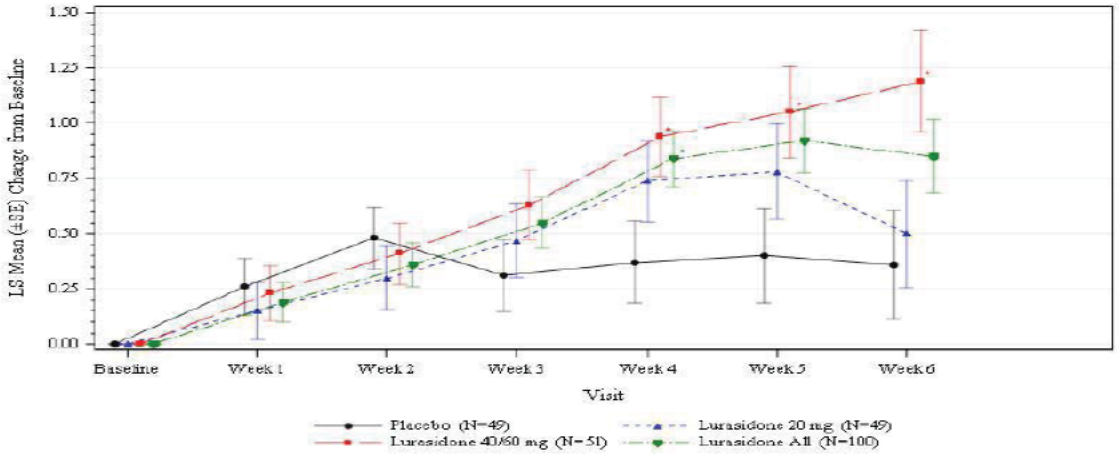
Change from Baseline in Body Weight – Mixed Model for Repeated Measures (Safety Population) (Continued)

Weight (kg)	Placebo (N=49)	20 mg (N=49)	60 mg (N=51)	All (N=100)
Change from Baseline at Week 5				
n	40	43	47	90
LS Mean (SE)	0.40 (0.214)	0.78 (0.214)	1.05 (0.204)	0.92 (0.148)
Difference of LS Mean (SE) (vs. Placebo)		0.38 (0.304)	0.65 (0.295)	0.51 (0.260)
95% CI of Difference		(-0.22, 0.98)	(0.06, 1.23)	(-0.00, 1.03)
p-value (vs. Placebo)		0.2120	0.0296	0.0502
Change from Baseline at Week 6				
n	38	42	47	89
LS Mean (SE)	0.36 (0.244)	0.50 (0.242)	1.19 (0.230)	0.85 (0.167)
Difference of LS Mean (SE) (vs. Placebo)		0.14 (0.345)	0.83 (0.335)	0.49 (0.297)
95% CI of Difference		(-0.54, 0.83)	(0.17, 1.49)	(-0.10, 1.07)
p-value (vs. Placebo)		0.6781	0.0146	0.1032

Abbreviations: CI = confidence intervals; LS = least squares; SE = standard errors.
Notes: 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 center, baseline weight, and treatment-by-visit interaction.
Source: Table 14.3.6.1.1.

Figure 4 Weight LS Mean Change from Baseline

Change from Baseline (LS Mean ± SE) in Body Weight (kg) – Mixed Model for Repeated Measures (Safety Population)



Note: * p<=0.05.
Source: Figure 14.7.1.1.

7.4.4 Electrocardiograms (ECGs)

ECG Parameters:
Incidence of abnormal changes in heart rate and PR intervals were rare, but appeared more in the drug treatment arms (for HR and PR) than placebo. QRS intervals had no incidence of abnormal changes in any arm. Mean changes from baseline by Week 6 were slightly higher for HR, and markedly lower for RR interval for both drug arms versus placebo. Other intervals showed no major trends/changes between drug and placebo.

Table 30 Incidence of Abnormal ECG Values (HR, PR, QRS)

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

ECG Parameter (unit)	Visit	Placebo (N=49) n (%)	Lurasidone 20 mg (N=49) n (%)	Lurasidone 60 mg (N=51) n (%)	Lurasidone All (N=100) n (%)
Heart Rate (bpm) Abnormally High	Baseline	1 (2.0)	4 (8.2)	2 (3.9)	6 (6.0)
	Week 6	0	1 (2.4)	1 (2.2)	2 (2.3)
	Endpoint	0	2 (4.3)	1 (2.0)	3 (3.2)
PR Interval (msec) Abnormally High	Baseline	1 (2.0)	2 (4.1)	2 (3.9)	4 (4.0)
	Week 6	0	2 (4.8)	0	2 (2.3)
	Endpoint	0	2 (4.3)	1 (2.1)	3 (3.2)
QRS Interval (msec) Abnormally High	Baseline	0	0	0	0
	Week 6	0	0	0	0
	Endpoint	0	0	0	0

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 31 Abnormal ECG Cutoffs

Definition of Abnormal ECG Values by Parameter for Pediatric and Adolescent Subjects

ECG parameter (unit)	Age (years old)	Abnormally Low	Abnormally High
HR (bpm)	6 to < 8	< 65	> 115
	8 to < 12	< 55	> 110
	12 to < 16	< 50	> 105
	≥ 16	< 50	> 100
PR interval (msec)	6 to < 8	--	> 160
	8 to < 12	--	> 175
	12 to < 16	--	> 180
	≥ 16	--	> 200
QRS interval (msec)	6 to < 8	--	> 100
	8 to < 12	--	> 105
	12 to < 16	--	> 110
	≥ 16	--	> 120

Table 32 ECG Mean Change from Baseline (LOCF) for HR, RR, PR, QRS, QT

Change from Baseline to Last Observation Carried Forward Endpoint in Electrocardiogram Parameters (Safety Population)

			Lurasidone		
	Statistics	Placebo (N=49)	20 mg (N=49)	60 mg (N=51)	All (N=100)
Heart Rate (beats/min)					
Endpoint	n	44	46	49	95
	Baseline Mean (SD)	80.1 (14.96)	78.0 (15.61)	76.1 (15.16)	77.0 (15.33)
	Mean Change (SD)	-1.3 (15.84)	2.8 (15.46)	3.8 (12.90)	3.4 (14.13)
	Median Change	-2.0	1.0	5.0	3.0
	Min, Max Change	-46, 32	-27, 53	-20, 32	-27, 53
RR Interval (msec)					
Endpoint	n	44	46	49	95
	Baseline Mean (SD)	773.6 (138.11)	798.3 (148.04)	815.9 (146.57)	807.4 (146.76)
	Mean Change (SD)	16.8 (133.30)	-35.2 (137.74)	-40.7 (125.82)	-38.0 (131.05)
	Median Change	16.5	-7.5	-45.0	-24.0
	Min, Max Change	-244, 374	-416, 215	-287, 164	-416, 215
PR Interval (msec)					
Endpoint	n	42	46	48	94
	Baseline Mean (SD)	134.4 (14.87)	137.5 (23.63)	128.9 (18.53)	133.1 (21.50)
	Mean Change (SD)	0.5 (12.48)	-0.5 (9.40)	2.8 (11.23)	1.2 (10.45)
	Median Change	3.0	0.5	2.0	1.0
	Min, Max Change	-26, 38	-24, 30	-20, 34	-24, 34
QRS Interval (msec)					
Endpoint	n	44	46	48	94
	Baseline Mean (SD)	89.2 (8.66)	88.2 (7.33)	87.4 (7.66)	87.8 (7.47)
	Mean Change (SD)	-0.9 (6.07)	-0.7 (6.09)	-0.6 (6.45)	-0.6 (6.24)
	Median Change	-1.5	-2.0	-1.0	-1.5
	Min, Max Change	-17, 12	-13, 19	-15, 16	-15, 19
QT Interval (msec)					
Endpoint	n	44	46	48	94
	Baseline Mean (SD)	366.3 (26.61)	366.3 (31.51)	370.8 (30.34)	368.6 (30.83)
	Mean Change (SD)	2.6 (23.61)	-6.2 (20.66)	-3.0 (25.34)	-4.6 (23.10)
	Median Change	2.5	-5.5	-5.0	-5.0
	Min, Max Change	-48, 54	-52, 36	-68, 43	-68, 43

QTc Parameters:
Mean changes from baseline at endpoint showed a small increase compared to placebo (+0.3) for the 60mg lurasidone arm (+3.2) but not 20mg (-1.1) using the Fridericia method.

One 11yo WM subject (325025008) on placebo at screening had a QTc above 460 (464) which went down to 432 a few days later, and by Week 6 was at 446 (+14). One 10yo WM subject (325024006) on lurasidone 20mg went from 400 at screening to 455 (+55) at Week 6. This subject was reported as an AE of abnormal ECG but did not discontinue medication.

These subjects had QTc above 450 and/or high QTc change from baseline (none led to AEs, and no subjects had QTc values over 500msec):
325023004: 448 screening, 452 baseline, 443 Week 6 (-9) on 20mg.
325006001: 451 screening, 426/434 baseline, 427 Week 6 (-7) on 60mg.
325018004: 459/422 screening, 396 (-26) Week 6 on 60mg.
325002003: 339 screening, 416 Week 6 on 40mg. (+77)
325026005: 410 screening, 423 Week 6 on 40mg. (+13)

Table 33 Incidence of Abnormal QTc Values (>460msec)

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

QTc > 460 msec	Visit	Placebo (N=49) n (%)	Lurasidone 20 mg (N=49) n (%)	Lurasidone 60 mg (N=51) n (%)	Lurasidone All (N=100) n (%)
QTcB - Bazett's Correction Formula (msec)	Baseline	2 (4.1)	1 (2.0)	1 (2.0)	2 (2.0)
	Week 6	0	2 (4.8)	1 (2.2)	3 (3.4)
	Endpoint	2 (4.5)	2 (4.3)	1 (2.1)	3 (3.2)
QTcF - Fridericia's Correction Formula (msec)	Baseline	0	0	0	0
	Week 6	0	0	0	0
	Endpoint	0	0	0	0

Abbreviations: ECG = electrocardiogram.
Note: Percentages are based on the number of subjects per time interval.
Source: Table 14.3.7.5.

QTc Prolongation
QTc > 460 msec
Increase from baseline QTc ≥ 60 msec

Table 34 ECG Mean Change from Baseline for QTc

	Statistics	Placebo (N=49)	Lurasidone 20 mg (N=49)	Lurasidone 60 mg (N=51)	Lurasidone All (N=100)
QTcB - Bazett's Correction Formula (msec)					
Endpoint	n	44	46	48	94
	Baseline Mean (SD)	419.3 (22.93)	412.7 (24.05)	412.6 (26.95)	412.6 (25.44)
	Mean Change (SD)	-1.0 (23.13)	1.8 (25.58)	6.6 (22.91)	4.2 (24.24)
	Median Change	-0.5	-1.5	6.0	4.0
	Min, Max Change	-44, 48	-57, 80	-43, 98	-57, 98
QTcF - Fridericia's Correction Formula (msec)					
Endpoint	n	44	46	48	94
	Baseline Mean (SD)	400.5 (18.05)	396.2 (20.84)	397.7 (22.41)	397.0 (21.55)
	Mean Change (SD)	0.3 (16.25)	-1.1 (16.95)	3.2 (18.60)	1.1 (17.85)
	Median Change	2.0	-1.5	2.5	0.5
	Min, Max Change	-35, 27	-39, 55	-29, 77	-39, 77

Abbreviations: max = maximum; min = minimum; SD = standard deviation.
Note: Endpoint: the last post-baseline assessment during double-blind treatment period.
Source: Table 14.3.7.1.

Reviewer Comment: There may be some slight drug-related effects on ECG, particularly at 60mg (slight QTc prolongation, tachycardia) but none that appear high-risk or as a clear trend.

7.4.5 Special Safety Studies/Clinical Trials

N/A

7.4.6 Immunogenicity

The Sponsor designated seven events as hypersensitivity-related AEs, all occurring on lurasidone (2 on 20mg and 5 on 60mg), none on placebo. They were: urticaria, conjunctivitis, glossodynia, pustular rash, rash, hypersensitivity, and wheezing. (If you include allergic rhinitis/rhinorrhea events, there were 12 total hypersensitivity AEs on drug (4 on 20mg, 8 on 60mg) and none on placebo.)

Reviewer Comment: These event trends point to some possible dose-dependent hypersensitivity risk on lurasidone versus placebo in this population. This issue is already covered in current lurasidone labeling.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The most common AEs that clearly appeared more frequent at the higher dosage (40-60mg) versus the lower dosage (20mg) and greater than placebo were: vomiting and somnolence/sedation. Others that were possibly dose-dependent were: abdominal pain/discomfort, weight increase, nausea, and allergic rhinitis/congestion/rhinorrhea (also hypersensitivity AEs in general). For laboratory parameters, there may be some dose-dependent effect on prolactin, fasting cholesterol, testosterone (in children ages 6 to 12), weight, and blood pressure/pulse.

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. But given that this study was conducted in both children and adolescents, it may be worth looking at some parameters for any obvious age-related trends.

Overall, incidence of abnormal vital signs was slightly higher in the child age group than the adolescent age group on drug versus placebo. Marked high elevation in SBP and DBP were fairly frequent in the child age group on lurasidone (11% supine, 14% standing for SBP, 7% supine and 17% standing for DBP), although for the supine readings elevation on placebo also occurred at similar rates. Orthostatic changes in BP were also more common in children than adolescents on drug versus placebo (7% SBP on drug versus 3% placebo and 21% DBP on drug versus 11% placebo in the child group, lower than placebo for both in the adolescent group). Orthostatic HR changes also occurred more often on drug (31%) versus placebo (20%) in the child group. These trends were not present in the adolescent group. These findings point to some possible orthostatic effects on lurasidone versus placebo in children. (This was not a dose-dependency analysis as incidence was not broken down by dosage.)

Table 35 Incidence of Abnormal Vital Signs by Age Group

Number and Percentage of Subjects with Potentially Markedly Abnormal Post-Baseline Vital Signs (MAPVS) by Age Group (6-12 years, 13-17 years) (Safety Population)

Parameter	6-12 years old		13-17 years old	
	Placebo (N=35) n (%)	Lurasidone (N=72) n (%)	Placebo (N=14) n (%)	Lurasidone (N=28) n (%)
Systolic Blood Pressure (mmHg), Supine				
Potentially Markedly High	5 (14.3)	8 (11.1)	0	0
Systolic Blood Pressure (mmHg), Standing				
Potentially Markedly Low	0	1 (1.4)	1 (7.7)	0
Potentially Markedly High	1 (2.9)	10 (14.1)	0	0
Orthostatic Systolic Blood Pressure (mmHg)				
≥ 20 decrease from supine to standing position	1 (2.9)	5 (7.0)	1 (7.7)	1 (3.7)
Diastolic Blood Pressure (mmHg), Supine				
Potentially Markedly Low	0	0	1 (7.1)	0
Potentially Markedly High	3 (8.6)	5 (6.9)	0	1 (3.7)
Diastolic Blood Pressure (mmHg), Standing				
Potentially Markedly Low	0	0	0	0
Potentially Markedly High	0	12 (16.9)	0	0
Orthostatic Diastolic Blood Pressure (mmHg)				
≥ 10 decrease from supine to standing position	4 (11.4)	15 (21.1)	4 (30.8)	3 (11.1)
Heart Rate (beats/min), Supine				
Potentially Markedly Low	3 (8.6)	3 (4.2)	0	0
Potentially Markedly High	0	1 (1.4)	1 (7.1)	0
Heart Rate (beats/min), Standing				
Potentially Markedly Low	0	3 (4.2)	0	0
Potentially Markedly High	0	1 (1.4)	0	0

Parameter	6-12 years old		13-17 years old	
	Placebo (N=35) n (%)	Lurasidone (N=72) n (%)	Placebo (N=14) n (%)	Lurasidone (N=28) n (%)
Orthostatic Heart Rate (beats/min)				
≥ 20 increase from supine to standing position	7 (20.0)	22 (30.6)	5 (38.5)	9 (33.3)
Temperature (°C)				
Potentially Markedly High	0	0	0	0

Notes: Age is based on the age at screening.
Notes: 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.
Notes: Percentages are based on the number of subjects age group and treatment.
Source: Table 14.3.5.2.2.

In terms of rates of markedly abnormal lab parameters by age group, the only noticeable differences was a higher rate of low bicarbonate in the child group (12%) versus the adolescent group (4%) on drug compared to placebo (however the placebo rate was even higher at 16% in the child group, so likely this finding has no significance.) Also, elevated fasting cholesterol and triglycerides occurred more often on drug in the adolescent group (4% cholesterol, 12% TGs) versus 0% in the child group and near 0% on placebo in both age groups. It is unclear if these rates indicate a slightly higher risk for lipid elevation in the adolescent group versus the child group on lurasidone or if it is just a chance finding, although the elevation did appear possibly dose-dependent (occurred for adolescents on the 60mg dose only.)

Reviewer Comment: Overall, there may be some increased tendency toward orthostatic hypotension in children on lurasidone versus placebo, but not in adolescents; and there may be some increased risk for elevated lipids on lurasidone versus placebo in adolescents, but not in children. However, these trends are of limited interpretability by lack of statistical significance due to low N's in this study.

Table 36 Incidence of Abnormal Lab Values by Age Group

Number and Percentage of Subjects with Potentially Markedly Abnormal Post-Baseline Laboratory Values (PMAPLV) by Age Group (6-12 years, 13-17 years) (Safety)

Age group: 6-12 years old

Category	Laboratory Parameter	Placebo (N=35)	Lurasidone 20 mg (N=36)	Lurasidone 60 mg (N=30)	Lurasidone 40/60 mg (N=36)	Lurasidone All (N=72)
Chemistry	Creatine Kinase (U/L)					
	Any Post-Baseline DB VISIT	31	31	29	35	66
	>=450	0	1 (3.2)	0	0	1 (1.5)
	Lactate Dehydrogenase (U/L)					
	Any Post-Baseline DB VISIT	31	31	29	35	66
	>=3 x ULN	0	0	0	0	0
	Gamma Glutamyl Transferase (U/L)					
	Any Post-Baseline DB VISIT	31	31	29	35	66
	>=150	0	0	0	0	0
	Sodium (mEq/L)					
	Any Post-Baseline DB VISIT	31	31	29	35	66
	<=130	0	0	0	0	0
	>=150	1 (3.2)	1 (3.2)	1 (3.4)	1 (2.9)	2 (3.0)

Age group: 13-17 years old

Category	Laboratory Parameter	Placebo (N=14)	Lurasidone 20 mg (N=13)	Lurasidone 60 mg (N=14)	Lurasidone 40/60 mg (N=15)	Lurasidone All (N=28)
Chemistry	Creatine Kinase (U/L)					
	Any Post-Baseline DB VISIT	13	12	14	15	27
	>=450	1 (7.7)	0	0	0	0
	Lactate Dehydrogenase (U/L)					
	Any Post-Baseline DB VISIT	13	12	14	15	27
	>=3 x ULN	0	0	0	0	0
	Gamma Glutamyl Transferase (U/L)					
	Any Post-Baseline DB VISIT	13	12	14	15	27
	>=150	0	0	0	0	0
	Sodium (mEq/L)					
	Any Post-Baseline DB VISIT	13	12	14	15	27
	<=130	0	0	0	0	0
	>=150	1 (7.7)	0	0	0	0

Ages 6 to 12

Category	Laboratory Parameter	Placebo (N=35)	Lurasidone 20 mg (N=36)	Lurasidone 60 mg (N=30)	Lurasidone 40/60 mg (N=36)	Lurasidone All (N=72)
Chemistry	Potassium (mEq/L)					
	Any Post-Baseline DB VISIT	31	31	29	35	66
	<=3	0	0	0	0	0
	>=5.5	0	3 (9.7)	1 (3.4)	1 (2.9)	4 (6.1)
	Bicarbonate (mEq/L)					
	Any Post-Baseline DB VISIT	31	31	29	35	66
	<18	5 (16.1)	2 (6.5)	5 (17.2)	6 (17.1)	8 (12.1)
	>30	0	0	0	0	0
	Calcium (mg/dL)					
	Any Post-Baseline DB VISIT	31	31	29	35	66
	<8.4	0	0	0	0	0
	>11.5	0	0	0	0	0
	Chloride (mEq/L)					
	Any Post-Baseline DB VISIT	31	31	29	35	66
	<90	0	0	0	0	0
	>115	1 (3.2)	0	0	0	0

Ages 13 to 17

Category	Laboratory Parameter	Placebo (N=14)	Lurasidone 20 mg (N=13)	Lurasidone 60 mg (N=14)	Lurasidone 40/60 mg (N=15)	Lurasidone All (N=28)
Chemistry	Potassium (mEq/L)					
	Any Post-Baseline DB VISIT	13	12	14	15	27
	<=3	0	0	0	0	0
	>=5.5	0	1 (8.3)	1 (7.1)	1 (6.7)	2 (7.4)
	Bicarbonate (mEq/L)					
	Any Post-Baseline DB VISIT	13	12	14	15	27
	<18	0	0	1 (7.1)	1 (6.7)	1 (3.7)
	>30	0	0	0	0	0
	Calcium (mg/dL)					
	Any Post-Baseline DB VISIT	13	12	14	15	27
	<8.4	0	0	0	0	0
	>11.5	0	0	0	0	0
	Chloride (mEq/L)					
	Any Post-Baseline DB VISIT	13	12	14	15	27
	<90	0	0	0	0	0
	>115	0	0	0	0	0

Ages 6 to 12

Category	Laboratory Parameter	Placebo (N=35)	Lurasidone 20 mg (N=36)	Lurasidone 60 mg (N=30)	Lurasidone 40/60 mg (N=36)	Lurasidone All (N=72)
Chemistry	Blood Urea Nitrogen (mg/dL)					
	Any Post-Baseline DB VISIT	31	31	29	35	66
	>=30	0	0	0	0	0
	Glucose (mg/dL) - fasting					
	Any Post-Baseline DB VISIT	27	27	25	31	58
	<=45	0	0	0	0	0
	>=126	0	0	0	0	0
	Glucose (mg/dL) - overall					
	Any Post-Baseline DB VISIT	31	31	29	35	66
	<=45	0	0	0	0	0
	>=200	0	0	0	0	0
	Prolactin (ng/mL)					
	Any Post-Baseline DB VISIT	31	31	28	34	65
	>=1 x ULN	2 (6.5)	1 (3.2)	2 (7.1)	2 (5.9)	3 (4.6)
	Cholesterol (mg/dL) - fasting					
	Any Post-Baseline DB VISIT	27	27	25	31	58
	>=240	0	0	0	0	0

Ages 13 to 17

Category	Laboratory Parameter	Placebo (N=14)	Lurasidone 20 mg (N=13)	Lurasidone 60 mg (N=14)	Lurasidone 40/60 mg (N=15)	Lurasidone All (N=28)
Chemistry	Blood Urea Nitrogen (mg/dL)					
	Any Post-Baseline DB VISIT	13	12	14	15	27
	>=30	0	0	0	0	0
	Glucose (mg/dL) - fasting					
	Any Post-Baseline DB VISIT	12	11	13	14	25
	<=45	0	0	0	0	0
	>=126	0	0	0	0	0
	Glucose (mg/dL) - overall					
	Any Post-Baseline DB VISIT	13	12	14	15	27
	<=45	0	0	0	0	0
	>=200	0	0	0	0	0
	Prolactin (ng/mL)					
	Any Post-Baseline DB VISIT	13	12	13	14	26
	>=1 x ULN	1 (7.7)	0	1 (7.7)	1 (7.1)	1 (3.8)
	Cholesterol (mg/dL) - fasting					
	Any Post-Baseline DB VISIT	12	11	13	14	25
	>=240	0	0	1 (7.7)	1 (7.1)	1 (4.0)

Ages 6 to 12

Category	Laboratory Parameter	Placebo (N=35)	Lurasidone 20 mg (N=36)	Lurasidone 60 mg (N=30)	Lurasidone 40/60 mg (N=36)	Lurasidone All (N=72)
	Triglycerides (mg/dL) - fasting					
	Any Post-Baseline DB VISIT	27	27	25	31	58
	Female: >=170, Male: >=200	1 (3.7)	0	0	0	0
	Cholesterol/HDL-Cholesterol (mg/dL) - fasting					
	Any Post-Baseline DB VISIT	27	27	25	31	58
	<=30	0	0	0	0	0
	LDL Cholesterol (mg/dL) - fasting					
	Any Post-Baseline DB VISIT	27	27	25	31	58
	>=160	0	0	0	0	0

Ages 13 to 17

Category	Laboratory Parameter	Placebo (N=14)	Lurasidone 20 mg (N=13)	Lurasidone 60 mg (N=14)	Lurasidone 40/60 mg (N=15)	Lurasidone All (N=28)
	Triglycerides (mg/dL) - fasting					
	Any Post-Baseline DB VISIT	12	11	13	14	25
	Female: >=170, Male: >=200	0	0	3 (23.1)	3 (21.4)	3 (12.0)
	Cholesterol/HDL-Cholesterol (mg/dL) - fasting					
	Any Post-Baseline DB VISIT	12	11	13	14	25
	<=30	0	1 (9.1)	1 (7.7)	1 (7.1)	2 (8.0)
	LDL Cholesterol (mg/dL) - fasting					
	Any Post-Baseline DB VISIT	12	11	13	14	25
	>=160	0	0	0	0	0

7.5.4 Drug-Disease Interactions

N/A

7.5.5 Drug-Drug Interactions

Concomitant psychotropic medications were not permitted in this study (except occasional prn benzodiazepines) as well as Cytochrome P450 affecting drugs. Other drug-drug interactions did not appear 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 37 BMI Mean Change from Baseline by Age Group in D1050302

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

Table 38 Height Changes by Age Group in D1050302

Measure	Age 13 to 15 Yrs	Age 16 Yrs +
DB Baseline Height	163.72 ± 9.115 cm	170.12 ± 8.031 cm
DB Baseline Z-Score	0.07 ± 1.053	-0.11 ± 0.810
Change in Height at Week 52	3.86 ± 3.728 cm	1.17 ± 1.558 cm
(WHO Growth Chart Average Change in Height at Week 52)	3.60 ± 2.179 cm	0.80 ± 0.677 cm
Change in Height at Endpoint	3.02 ± 3.526 cm	0.96 ± 1.338 cm
(WHO Growth Chart Average Change in Height at Endpoint)	3.07 ± 2.543 cm	0.70 ± 0.666 cm
Mean Change from Baseline at Week 52	0.03 ± 0.413	0.05 ± 0.224
Mean Change from Baseline at Endpoint	0.00 ± 0.353	0.04 ± 0.194

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

N/A

7.7 Additional Submissions / Safety Issues

Barnes Akathisia Rating Scale (BARS):
Mean BARS total scores were very low in general in this study (less than 0.40 on a 9-point scale) for all treatment groups. No significant trends were evident from the results.

Table 39 BARS Mean Change from Baseline

	Placebo	N	Lurasidone 20mg	N	Lurasidone 60mg	N
BARS Total Score Mean Change from Baseline to Endpoint	0.0±1.21	35	0.1±0.59	38	-0.1±0.60	36

Source: Table 14.3.8.2.1

Abnormal Involuntary Movement Scale (AIMS):
Mean AIMS scores were extremely low overall in this study (less than 0.30 on a 28-point scale) across all treatment groups.

Table 40 AIMS Mean Change from Baseline

	Placebo	N	Lurasidone 20mg	N	Lurasidone 60mg	N
AIMS Total Score Mean Change from Baseline to Endpoint	-0.2±1.03	49	-0.1±0.67	48	-0.1±0.45	44

Source: Table 14.3.9.2.1

Simpson-Angus Scale (SAS):
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.

Table 41 SAS Mean Change from Baseline

	Placebo	N	Lurasidone 20mg	N	Lurasidone 60mg	N
SAS Total Score Mean	-0.01±0.112	48	-0.01±0.054	48	-0.04±0.125	44

Change from Baseline to Endpoint						

Source: Table 14.3.10.2.1

Tanner Staging:
No unusual stage changes were noted for Tanner staging in males or females in this study.

Menstrual Cyclicity:
No unusual findings were noted.

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 42 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

- Negative study for use of lurasidone in children and adolescents with autistic disorder for irritability in Section 8.4.
- Common AE tables, generally in keeping with adult study AEs and expected parameter effects (increases in prolactin, fasting lipids, weight, hypersensitivity reactions) except for **vomiting** which occurred at markedly higher rate than other lurasidone trials, particularly in children ages 6 to 12.

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