U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 200603
Supplement #:	S-27
Drug Name:	Latuda (lurasidone HC1)
Indication(s):	Children and Adolescent Subjects with Irritability Associated with Autistic Disorder
Applicant:	Sunovion Pharmaceuticals Inc.
Date(s):	Receipt Date: July 29, 2016 PDUFA Date: January 29, 2017
Review Priority:	Priority
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1 EXECUTIVE SUMMARY

This study randomized 150 subjects in a ratio 1:1:1 to placebo, 20 mg lurasidone, or 60 mg lurasidone. The primary endpoint was the change from Baseline in ABC irritability subscale score at Week 6. A blinded sample size recalculation was performed based on the primary endpoint at 90% of the initially planned enrollment for both trials. This trial showed sufficient power at the interim analysis, so sample size was not increased. Despite the sufficient power to detect a treatment effect of at least 7 points in ABC irritability subscale score, the study did not demonstrate efficacy of lurasidone over placebo in children and adolescent subjects with irritability associated with autistic disorders. Neither lurasidone dose met the primary objective in this trial.

2 INTRODUCTION

2.1 Overview

Reference is made to the original NDA for the use of Latuda (lurasidone HC1) as a treatment of schizophrenia in adult patients, which was approved in 2010. The sponsor submitted this sNDA as a Prior Approval Supplement Submission to satisfy the Written Request for pediatric patients with irritability associated with autistic disorder. This sNDA includes a Phase 3, multicenter, randomized, parallel, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of 2 fixed doses of lurasidone (20 mg and 60 mg/day q.d.) for 6 weeks compared with placebo in pediatric subjects with irritability associated with autistic disorder.

The original protocol of this study was reviewed under IND 61292.

Table 1: List of All Studies Included in Analysis

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
D1050325	*Phase 3*	*6 weeks*	-	*50 subjects in placebo, 49 subjects in 20 mg/day Latuda, and 51 subjects in 60 mg/day Latuda*	*patients with irritability associated with autistic disorder (6 to 17 years old)*

2.2 Data Sources

The following data sources were considered in this review:
a) Applicant's study report
(\\CDSESUB1\evsprod\NDA200603\0143\m5\53-clin-stud-rep\535-rep-effic-safety-stud\schizophre\5351-stud-rep-contr\d1050325\d1050325-bodycopy.pdf)
b) Applicant's trial protocol
(\\CDSESUB1\evsprod\NDA200603\0143\m5\53-clin-stud-rep\535-rep-effic-safety-stud\schizophre\5351-stud-rep-contr\d1050325\d1050325-e3-16-1-01.pdf)
c) Data sets
(\\CDSESUB1\evsprod\NDA200603\0143\m5\datasets\d1050325\analysis\adam\datasets)
(\\CDSESUB1\evsprod\NDA200603\0143\m5\datasets\d1050325\tabulations\sdtm)
d) Software code
(\\CDSESUB1\evsprod\NDA200603\0145\m5\datasets\d1050325\analysis\adam\programs)
e) Response to FDA information request
(\\CDSESUB1\evsprod\NDA200603\0145\m1\us)

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The sponsor has complied with our requests for providing necessary datasets, definition files, and statistical programs for their analyses. This reviewer found the quality of their submissions acceptable and was able to replicate the primary results from the sponsor's Clinical Study Report (CSR).

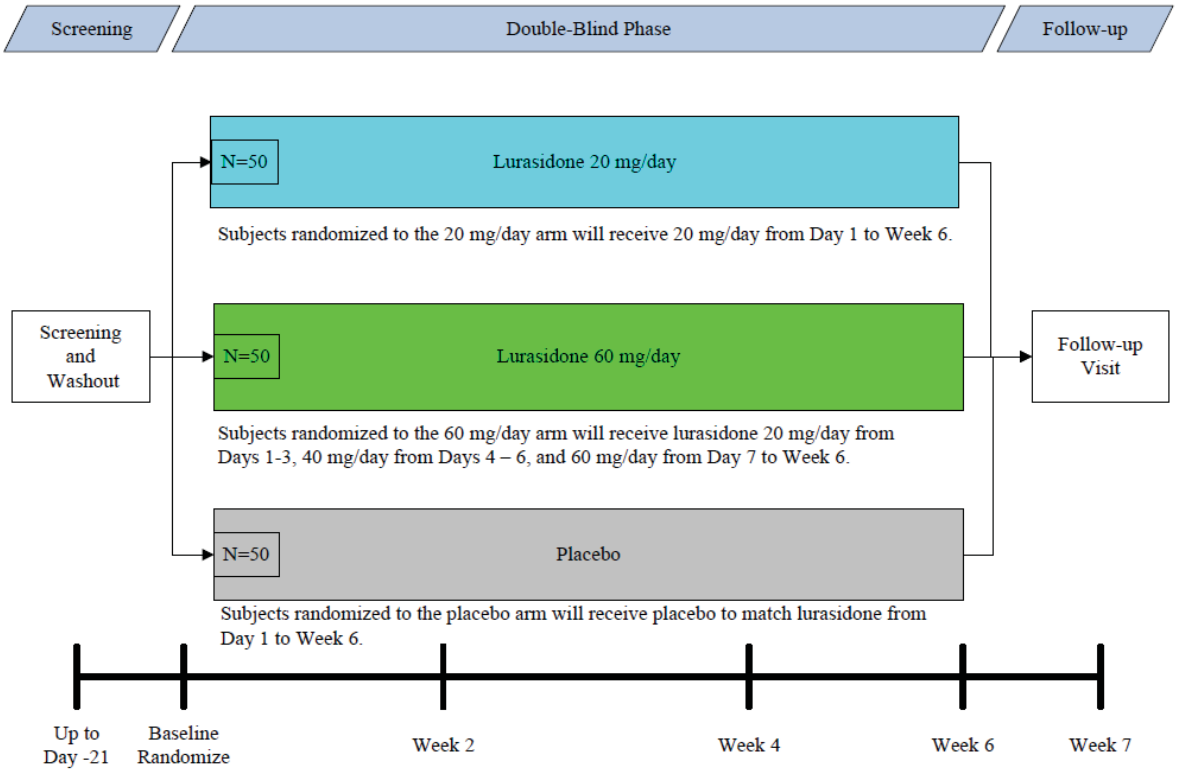
3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

DI050325 was a randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of 2 fixed doses of lurasidone (20 mg and 60 mg/day q.d.) for 6 weeks compared with placebo in pediatric subjects (6-17 years old) with irritability associated with autistic disorder. The study was conducted at 40 clinical sites in the United States.

The study was comprised of a 21-day screening period and a 6-week double-blind treatment period. Following the screening period, subjects who continue to meet entry criteria were randomly assigned to 1 of 3 double-blind treatment arms: lurasidone 20 mg/day, lurasidone 60 mg/day, or placebo (1:1:1 ratio). Subjects who met eligibility criteria were randomly assigned to receive lurasidone 20 mg/day, lurasidone 60 mg/day, or matching placebo in a double-blind fashion (1:1:1). The randomization was balanced using permuted blocks with age stratification criteria: children (6-12 years old at screening visit) vs. adolescents (13-17 years old at screening visit).

Figure 1: Study Design of DI050325



[Source: Figure 1 on page 24 of clinical study report.]

Subjects randomized to the 20 mg/day arm were to receive 20 mg/day from Day 1 to Week 6 Visit. Subjects randomized to the 60 mg/day arm were to receive lurasidone 20 mg/day from Days 1-3, 40 mg/day from Days 4-6 and 60 mg/day from Day 7 to Week 6 Visit. Subjects randomized to the placebo arm were to receive placebo to match lurasidone from Day 1 to Week 6 Visit. Subjects who completed the 6-week treatment phase of the study were eligible to participate in a separate 104-week open-label extension study (D1050302).

The primary efficacy rating scale was the change from Baseline to Week 6 in the ABC irritability subscale. The ABC irritability subscale rates symptoms such as “injures self”, “aggressive to other children and adults”, “irritable”, “temper outbursts”, “depressed mood”, “mood changes”, and “yells or screams inappropriately”. It was calculated as summing of items 2, 4, 8, 10, 14, 19, 25, 29, 34, 36, 41, 47, 50, 52, and 57; as a result, the ABC irritability subscale score ranged from 0 to 45. In general, higher values of the ABC subscale scores represented greater severity of illness.

Secondary efficacy endpoints include

- 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.

3.2.2 Statistical Methodologies

The sample size calculation was based on the results from a Monte Carlo computer simulation. Dunnett’s procedure was used to adjust for the multiple comparisons of two lurasidone doses vs. placebo for the sample size calculation. Assuming a mean difference of 7.0 points of the change in the ABC irritability subscale score at Week 6 for both lurasidone groups over the placebo group and a common standard deviation (SD) of 11 units (i.e., effect size=0.64), a sample size of 40 subjects per group would provide at least 85% power to reject at least one of the null hypotheses of no difference from placebo in lurasidone doses. An upward adjustment of approximately 20% was assumed to compensate for subjects who were randomized but do not provide any ABC irritability subscale post-Baseline efficacy measures. Thus, a total sample of approximately 150 subjects (50 subjects per group) was randomized with a ratio of 1:1:1 for placebo, lurasidone 20 mg/day and 60 mg/day respectively.

The primary efficacy analyses of lurasidone 20 mg/day vs placebo and lurasidone 60 mg/day vs placebo were performed for the change from Baseline in the ABC irritability subscale score at Week 6 using a likelihood-based mixed model for repeated measures (MMRM) model. The response (dependent) variable was the change from Baseline in the ABC irritability subscale score assessed on weekly visits (Weeks 1 to 6). Specifically, the MMRM model included fixed effects terms for treatment, visit (as a categorical variable), pooled center, the ABC irritability score at Baseline, and treatment-by-visit interaction. Restricted maximum likelihood estimation method was applied using unstructured covariance model. A robust sandwich estimator for the standard error of the fixed effects and a spatial exponential covariance pattern model was used in case that the model could not be converged. The spatial exponential model was selected for the analysis of data with unequally spaced time points. The likelihood based mixed effects model can accommodate incomplete data under the assumption of ignorable attrition. The treatment differences (each lurasidone group minus placebo) in the Least-Squares means (LS means), their 2-sided 95% CIs, and the associated p-values were estimated based on this model. In addition,

descriptive statistics (mean, SD, 95% CI) were provided for the ABC irritability subscale score and change from Baseline by study visit for each treatment group.

The primary and secondary efficacy analyses all used the MMRM Method, which took into account the missing data as an integral part of the analyses. The likelihood-based mixed-effects model can accommodate incomplete data under the assumption of ignorable attrition. In addition to the model-based missing data approach of the MMRM model, the primary and secondary efficacy analyses were also analyzed using a pattern mixture model (PMM) with placebo-based multiple imputation method and a random effects pattern mixture (REM) model as sensitivity analyses.

The blinded sample size recalculation was performed when about 90% subject were enrolled. The sample size would be recalculated based on whether the estimated pooled SD from all available subjects at sample size re-assessment was considerably larger than the assumption (SD=11). A total of 136 subjects had been randomized as of 03 Sep 2014 (the 135th and 136th subjects were randomized on a same day). The sample size re-assessment was conducted by a blinded statistician from the ISAC based on a data snapshot taken on 10 Sep 2014 from the clinical database (Medidata RAVE).

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 150 subjects were randomized to treatment with placebo (N=50), lurasidone 20 mg/day (N=49), or lurasidone 60 mg/day (N=51). A total of 148 subjects were included in the ITT population: 99 subjects in the combined lurasidone group and 49 subjects in the placebo group.

A total of 128 subjects (85.3%) completed the 6-week double-blind phase of the study. The proportion of subjects completing the study was higher in the combined lurasidone group (90.0%) than the placebo group (76.0%). Overall, 22 subjects (14.7%) discontinued from the study. A total of 8 (5.3%) subjects discontinued the study due to an adverse event; 4 subjects (4.0%) in the combined lurasidone group and 4 subjects (8.0%) in the placebo group. A total of 7 (4.7%) subjects discontinued the study due to withdrawal of consent; 1 subject (1.0%) in the combined lurasidone group and 6 subjects (12.0%) in the placebo group. No other primary reason accounted for ≥ 3% of subjects discontinuing from the study.

Table 2: Subject Disposition (All Randomized Subjects)

	Placeo (N=50) n (%)	Lurasido			Total (N=150) n (%)
		20 mg (N=49) n (%)	60 mg (N=51) n (%)	All (N=100) n (%)	
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)

[Source: Table 12 on page 58 of clinical study report.]

Of the 149 subjects in the Safety population, 122 (81.9%) were male and 27 (18.1%) were female. Subject age ranged from 6 to 17 years, with a mean age of 10.7 years. The majority of subjects were aged 6-12 (71.8%) and the remainders were 13-17 (28.2%). The majority of subjects were White (77.2%), followed by Black or African American (16.1%). Two subjects were of Asian race (1.3%), 2 subjects were of American Indian or Alaska Native race (1.3%), and 6 subjects identified their race as Other (4.0%). In the placebo group, 85.7% of subjects were White and 10.2% were Black or African American, while in the combined lurasidone group 73.0% of subjects were White and 19.0% were Black or African American. No other meaningful differences were observed among treatment groups for any of the other demographic variables.

Table 3: Demographic Characteristics (Intent-to-Treat 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)

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. on clinical study report.]

3.2.4 Results and Conclusions

3.2.4.1 Sponsor's Analysis: Primary Efficacy Analysis and Sensitivity Analysis

The primary objective was not met for both lurasidone doses. Although the decreases in the ABC irritability subscale scores from Baseline to Week 6 were greater in the lurasidone groups, these treatment differences were not statistically significant from placebo: -1.9 (95% CI: -6.1, 2.2; p = 0.3592) for the lurasidone 60 mg/day group and -1.3 (95% CI: -5.6, 3.0; p = 0.5463) for the lurasidone 20 mg/day group. Additionally, while the decreases in the ABC irritability subscale score were greater in the lurasidone groups at each post-Baseline visit, there was no significant treatment difference at any time point in the study as shown in Table 4 and Figure 2.

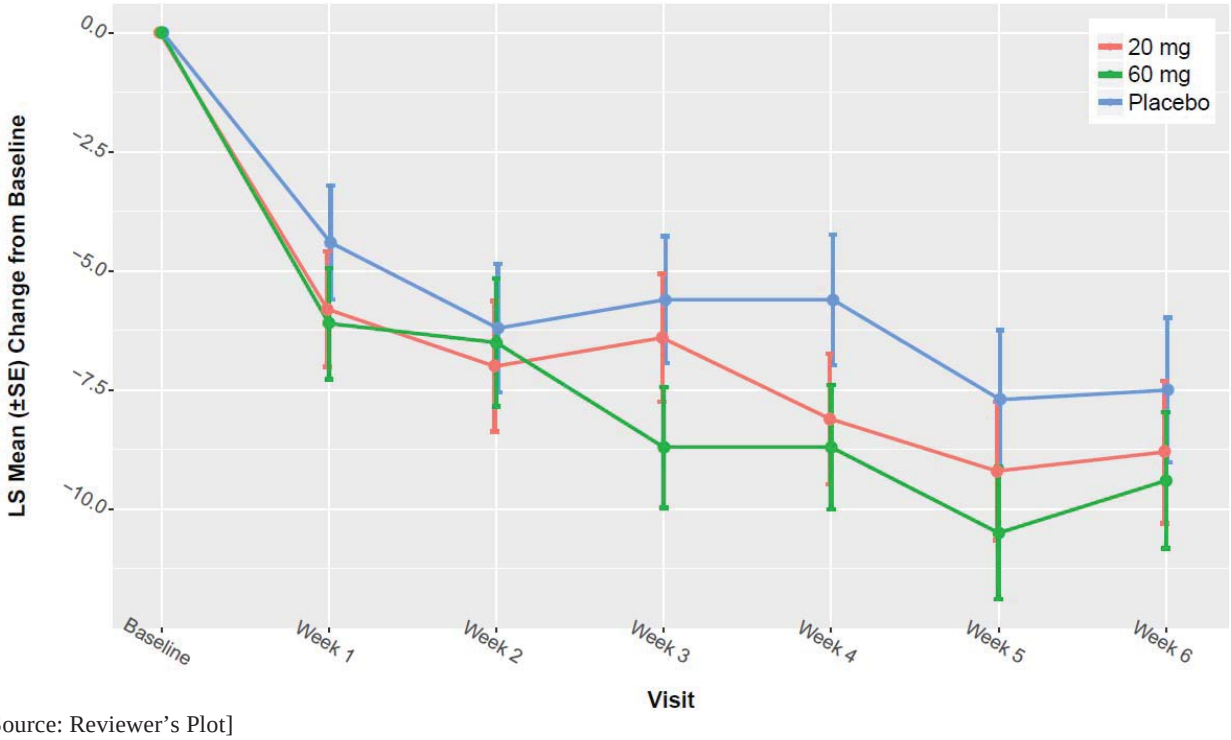
Table 4: Change from Baseline in the Aberrant Behavior Checklist (ABC) Irritability Subscale Score – Mixed Model for Repeated Measures (Intent-to-Treat Population)

ABC Irritability Subscale Score	Placebo (N=49)	Lurasidone 20 mg (N=48)	Lurasidone 60 mg (N=51)
Change from Baseline to Week 1			
n	47	48	51
LS Mean (SE)	-4.4 (1.19)	-5.8 (1.21)	-6.1 (1.17)
Difference of LS Mean (SE) (vs. Placebo)		-1.3 (1.71)	-1.7 (1.67)
95% CI of Difference		(-4.7, 2.0)	(-5.0, 1.6)
p-value (vs. Placebo)		0.4323	0.3202
Change from Baseline to Week 2			
n	47	46	48
LS Mean (SE)	-6.2 (1.35)	-7.0 (1.37)	-6.5 (1.34)
Difference of LS Mean (SE) (vs. Placebo)		-0.8 (1.94)	-0.3 (1.90)
95% CI of Difference		(-4.6, 3.0)	(-4.0, 3.5)
p-value (vs. Placebo)		0.6804	0.8809
Change from Baseline to Week 3			
n	42	43	50
LS Mean (SE)	-5.6 (1.33)	-6.4 (1.34)	-8.7 (1.27)
Difference of LS Mean (SE) (vs. Placebo)		-0.9 (1.90)	-3.1 (1.83)
95% CI of Difference		(-4.6, 2.9)	(-6.8, 0.5)
p-value (vs. Placebo)		0.6475	0.0890
Change from Baseline to Week 4			
n	41	43	47
LS Mean (SE)	-5.6 (1.37)	-8.1 (1.37)	-8.7 (1.31)

Difference of LS Mean (SE) (vs. Placebo)		-2.5 (1.95)	-3.1 (1.89)
95% CI of Difference		(-6.4, 1.3)	(-6.8, 0.7)
p-value (vs. Placebo)		0.1972	0.1055
Change from Baseline to Week 5			
n	40	43	47
LS Mean (SE)	-7.7 (1.46)	-9.2 (1.45)	-10.5 (1.39)
Difference of LS Mean (SE) (vs. Placebo)		-1.5 (2.07)	-2.8 (2.01)
95% CI of Difference		(-5.6, 2.6)	(-6.8, 1.2)
p-value (vs. Placebo)		0.4634	0.1661
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 22 on page 79 of clinical study report.]

Figure 2: Change from Baseline (LS Mean ± SE) in the Aberrant Behavior Checklist (ABC) Irritability Subscale Score over Time- Mixed Model for Repeated Measures (Intent-to-Treat Population)



[Source: Reviewer's Plot]

Two sensitivity analyses were conducted to assess the missing at random (MAR) assumption underlying the primary efficacy MMRM analyses (ITT population). A PMM using a placebo-based multiple imputation method was performed to explore the robustness of the MMRM results for the primary efficacy variable for the ITT population. The results of this analysis shown in Table 5 were in line with MMRM results for the primary efficacy variable; thus, the sponsor concluded that the MMRM results (primary analyses) were robust.

A second sensitivity analysis based on random effect pattern mixture model with two patterns (completers, dropouts) was performed to assess the impact on treatment group comparisons. The PMM model showed very similar numerical estimates to the overall REM model, indicating that the dropout status did not alter the overall results with respect to the treatment comparisons. The estimates, standard errors, and p-values from the PMM and REM models were very similar for the primary efficacy variable. Therefore, the sponsor indicated that MAR was a reasonable assumption when analyzing the primary efficacy variable.

Table 5: Sensitivity Analysis: Pattern Mixture Model with Placebo-Based Multiple Imputation for Primary Efficacy Analysis of Aberrant Behavior Checklist (ABC) Irritability Subscale Score (ITT Population)

Analysis	Statistic	Placebo (N=49)	Lurasidone 20 mg (N=48)	Lurasidone 60 mg (N=51)
PMM with Placebo-based Multiple Imputation Result at Week 6	LS Mean (SE)	-7.4 (1.59)	-8.7 (1.56)	-9.3 (1.49)
	Difference from Placebo			
	LS Mean Difference (SE)		-1.3 (2.22)	-1.9 (2.16)
	LS Mean Difference 95% CI		(-5.7, 3.0)	(-6.2, 2.3)
	p-value		0.5521	0.3729
MMRM Result at Week 6	LS Mean (SE)	-7.5 (1.52)	-8.8 (1.50)	-9.4 (1.43)
	Difference from Placebo			
	LS Mean Difference (SE)		-1.3 (2.15)	-1.9 (2.09)
	LS Mean Difference 95% CI		(-5.6, 3.0)	(-6.1, 2.2)
	p-value		0.5463	0.3592

**$p \leq 0.01$
Abbreviations: ITT = Intent-to-Treat; LS = least squares; MMRM = Mixed Model Repeated Measure; PMM = Pattern Mixed Model; SE = standard error.
Note: PMM (Pattern mixture model): 1000 placebo-based multiple imputations using a monotone regression imputation method.
Note: MMRM (Mixed Model for Repeated Measures), based on the fixed effects for treatment, pooled country, visit as a categorical variable, baseline score, and treatment by visit interaction, assuming an unstructured covariance matrix.
[Source: Table 14.2.1.1.4 on clinical study report.]

Table 6: Sensitivity Analysis: Random Effects Pattern Mixture Model with Two Patterns (Completers and Dropouts) for Primary Efficacy Analysis of Aberrant Behavior Checklist (ABC) Irritability Subscale Score (ITT Population)

Analysis	Statistic	Intercept	Time	Lurasidone 20 mg	Lurasidone 60 mg	Time* Lurasidone 20 mg	Time* Lurasidone 60 mg
REM	Model Estimate (SE)	28.3 (0.93)	-3.2 (0.60)	-1.0 (1.31)	-1.9 (1.29)	-0.4 (0.84)	-0.7 (0.82)
	95% CI	(26.5, 30.1)	(-4.4, -2.0)	(-3.6, 1.5)	(-4.4, 0.6)	(-2.0, 1.3)	(-2.3, 0.9)
	p-value	<0.001**	<0.001**	0.431	0.142	0.644	0.395
PMM Overall	Model Estimate (SE)	28.3 (0.94)	-3.1 (0.62)	-1.0 (1.35)	-1.9 (1.34)	-0.2 (0.87)	-0.6 (0.84)
	95% CI	(26.4,30.1)	(-4.4,-1.9)	(-3.7,1.6)	(-4.5,0.8)	(-1.9,1.5)	(-2.3,1.0)
	p-value	<0.001**	<0.001**	0.447	0.165	0.785	0.464
PMM Completers	Model Estimate (SE)	28.2 (1.05)	-3.3 (0.65)	-1.2 (1.44)	-1.8 (1.41)	-0.4 (0.89)	-0.7 (0.87)
	95% CI	(26.1, 30.2)	(-4.6, -2.0)	(-4.0, 1.6)	(-4.5, 1.0)	(-2.1, 1.3)	(-2.4, 1.1)
	p-value	<0.001**	<0.001**	0.415	0.212	0.657	0.453
PMM Dropouts	Model Estimate (SE)	28.5 (2.05)	-2.6 (1.59)	0.3 (3.71)	-3.0 (3.98)	1.1 (3.25)	-0.2 (3.16)
	95% CI	(24.5, 32.5)	(-5.7, 0.5)	(-7.0, 7.5)	(-10.8, 4.8)	(-5.2, 7.5)	(-6.4, 6.0)
	p-value	<0.001**	0.099	0.944	0.448	0.73	0.959

Note: REM = Random effects model without dropout pattern; PMM Overall = Overall random effects pattern mixture model using a weighted average of the parameter estimates for each dropout pattern (completers and dropouts); PMM Completers = Random effects pattern mixture model for completers only; PMM Dropouts = Random effects pattern mixture model for dropouts only. Time = sqrt (analysis visit). * p<=0.05; ** p<=0.01.
[Source: Table 14.2.1.1.5 on clinical study report.]

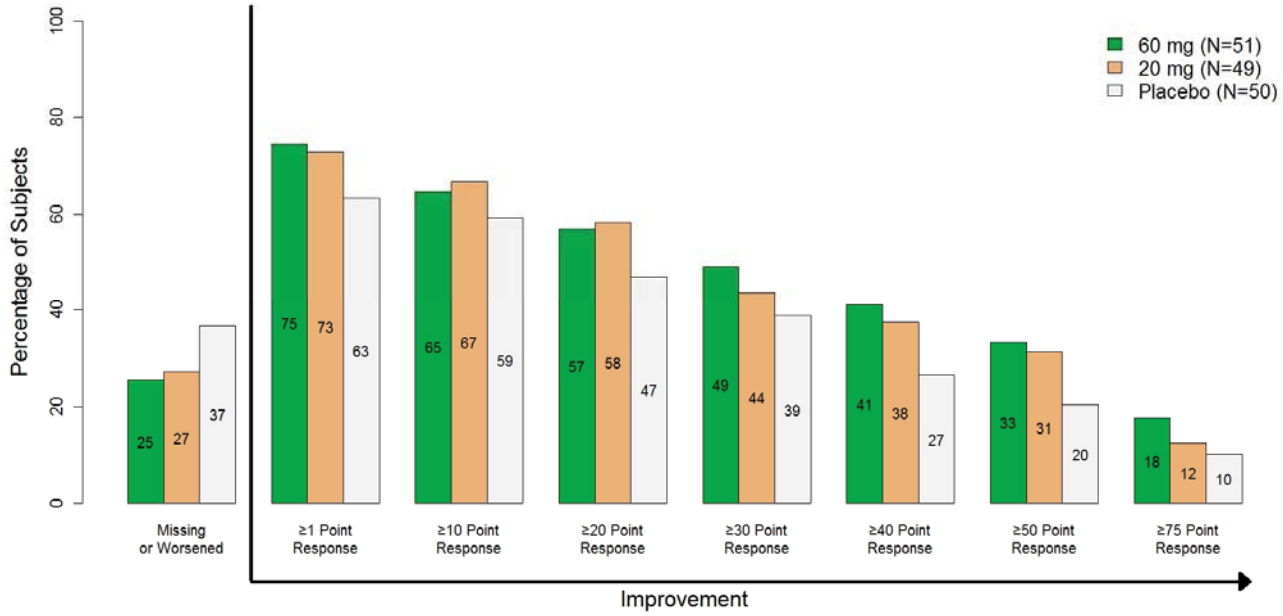
3.2.4.3 Reviewer's Results and Comments

This reviewer confirms the sponsor's analysis results for the primary endpoint. The sensitivity analyses as presented in Tables 5 and 6 were confirmed as well. Based on this reviewer's analysis, Figure 3 shows that the percentages of subjects with different magnitudes of improvement on the primary endpoint in both drug arms were consistently larger than that in the placebo group. The placebo group has a much larger dropout rate.

At the interim look on Sep 10, 2014, 136 subjects had been randomized and 132 subjects had at least one value for change from Baseline in ABC irritability subscale score. By that time, there were 117 subjects who either completed (97 subjects) or discontinued early from the study (20 subjects); of those, 115 subjects had value(s) for change from Baseline in ABC irritability subscale score. By using the LOCF approach, the estimated SD was 9.72 based on the 132 subjects and 9.93 based on the 115 subjects. Since the estimated pooled SD was smaller than the assumed SD=11 based on either data set, the independent statistical analysis center (ISAC) of the Data and Safety Monitoring Board (DSMB) recommended no sample size increase. Based on the estimated pooled SD derived from either data set at the interim look, the calculated powers to conclude at least one effective dose were >92% assuming a treatment difference of 7 points.

Despite the sufficient power to detect a treatment effect of at least 7 points, the final analysis did not demonstrate superiority to placebo group in either of the treatment groups. The magnitudes of the observed treatment effects were less than 2 points, as compared with the postulated magnitude (7 points). The p-values from the primary analyses were 0.55 and 0.36 for 20 mg lurasidone group and 60 mg lurasidone, respectively. This study did not demonstrate efficacy of lurasidone over placebo in treating children and adolescent subjects with irritability associated with autistic disorder.

Figure 3: Percentage of Subjects with Specific Magnitude of ABC Irritability Subscale Score Improvement at Week 6



[Source: Reviewer's Plot]
Numbers on the bars represent percentage of subjects

3.3 Evaluation of Safety

Safety was not evaluated in this review. Please refer to the clinical review for details on the safety evaluation.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The purpose of the following subgroup analyses was to assess the consistency of treatment effects across subgroups. The change from Baseline to Week 6 in the ABC irritability subscale score was examined by age group, gender and race to explore whether there was a consistent treatment effect across subgroups. Mean differences from placebo in ABC irritability subscale score for age group, gender, race, and geographic region are shown in Table 7. The trends appeared consistent in favor of lurasidone across subgroups. In terms of dose response relationship, there was a noticeable trend in favor of 60 mg for the adolescents group, as compared to the seemly-flat trend for the children subgroup. Since the majority (71.8%) of the patient population in this trial was children, the overall treatment effects were largely driven by this subgroup.

Table 7: ABC Irritability Subscale Score: Subgroup Analysis by Age group, Gender and Race in Changes from Baseline to Week 6 (ITT LOCF)

Subgroup Treatment	Treatment	n	LS Mean (SE)	Difference of LS Mean (95% CI) (vs. Placebo)
Age Group				
Age 6-12 at Screening	**Lurasidone 20 mg**	36	-8.7 (1.64)	-1.6 (-6.2, 3.1)
	Lurasidone 60 mg	35	-8.4 (1.66)	-1.3 (-5.9, 3.4)
	Placebo	35	-7.1 (1.68)	-
Age 13-17 at Screening	**Lurasidone 20 mg**	12	-9.2 (2.87)	-2.9 (-10.7, 4.9)
	Lurasidone 60 mg	15	-12.1 (2.56)	-5.8 (-13.1, 1.5)
	Placebo	14	-6.2 (2.64)	-
Gender				
Male	**Lurasidone 20 mg**	38	-8.2 (1.60)	-1.6 (-6.1, 2.8)
	Lurasidone 60 mg	43	-9.2 (1.51)	-2.7 (-7.0, 1.7)
	Placebo	40	-6.5 (1.56)	-
Female	**Lurasidone 20 mg**	10	-11.0 (3.18)	-2.5 (-11.6, 6.5)
	Lurasidone 60 mg	8	-10.9 (3.52)	-2.4 (-11.9, 7.1)
	Placebo	9	-8.4 (3.27)	-
Race				
White	**Lurasidone 20 mg**	34	-8.6 (1.70)	-1.3 (-5.9, 3.2)
	Lurasidone 60 mg	38	-8.7 (1.64)	-1.4 (-5.8, 2.9)
	Placebo	42	-7.3 (2.17)	-
Black or African American	**Lurasidone 20 mg**	10	-7.3 (3.16)	-2.2 (-13.0, 8.6)
	Lurasidone 60 mg	9	-9.5 (3.32)	-4.3 (-15.3, 6.6)
	Placebo	5	-5.1 (4.43)	-
Other	**Lurasidone 20 mg**	4	-11.0 (12.19)	-
	Lurasidone 60 mg	3	-14.3 (8.14)	-
	Placebo	1	-13.0 (-)	-
Asian	**Lurasidone 20 mg**		-	-
	Lurasidone 60 mg	1	1.0 (-)	-

	Placebo	1	1.0 (-)	-

Note: LS Means, LS Mean Difference, associated 95% CI and p-value are based on model with treatment, pooled country, subgroup, treatment-by-subgroup interaction as fixed factors, and baseline ABC irritability score as a covariate.
[Source: Tables 14.2.1.7.1, 14.2.1.7.2 and 14.2.1.7. 3 on clinical study report.]

In order to investigate why lurasidone looks more effective in adolescents than in children, the reviewer further summarized dropouts by age group. It was found that all of the dropouts (11 subjects) were from children subgroup; 8 subjects (7.5%) discontinued due to an adverse event and 3 subjects (2.8%) discontinued due to lack of efficacy. However, the small sample size in the adolescents group can limit interpretation. The caution should be taken in interpreting whether the dropouts diluted the efficacy outcome in children group.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There are no statistical issues that impact the overall conclusions.

5.2 Collective Evidence

This study did not meet the primary objective for both lurasidone doses. The difference in the change from Baseline in ABC irritability subscale score at Week 6 between 20 mg lurasidone group and placebo group was -1.3 points and was not statistically significant (p-value = 0.55). For the 60 mg lurasidone group, this difference was -1.9 points and was not statistically significant (p-value = 0.36).

5.3 Conclusions and Recommendations

This study had sufficient power to detect a treatment effect of at least 7 points in ABC irritability subscale score, but did not demonstrate efficacy of lurasidone over placebo in children and adolescent subjects with irritability associated with autistic disorder.

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

/s/

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12/15/2016

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