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-26
Drug Name:	Latuda (lurasidone HC1)
Indication(s):	Adolescent subjects with acute schizophrenia
Applicant:	Sunovion Pharmaceuticals Inc.
Date(s):	Receipt Date: July 29, 2016
	PDUFA Date: January 29, 2017
Review Priority:	Priority
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Keywords:

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1 EXECUTIVE SUMMARY

Both lurasidone doses (40 mg and 80 mg q.d.) showed statistically significant improvement in change from baseline on both the primary (PANSS Total Score at Week 6) and the key secondary endpoints (CGI-S score) compared with placebo after multiple comparison adjustment using Hochberg's procedure. The least square mean differences when compared to placebo group were -8.0 and -7.7 points in PANSS Total Score for 40 mg and 80 mg lurasidone treatment group, and were -0.47 and -0.42 points in CGI-S score. However, the results did not suggest additional improvement of the 80 mg over the 40 mg dose whether on the primary or the key secondary endpoint. In addition, the observed treatment differences in CGI-S appeared to be very small. Whether or not it is clinically relevant is deferred to the clinical review team.

2 INTRODUCTION

2.1 Overview

Lurasidone was approved in 2010 as a treatment of schizophrenia in adult patients. Under Pediatric Research Equity Act (PREA), the sponsor is required to assess the safety and effectiveness of the product for the claimed indication in pediatric patients. This sNDA is intended to fulfill this requirement, as well as the Written Request to qualify for exclusivity. This supplement 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 (40 mg and 80 mg/day q.d.) for 6 weeks compared with placebo in adolescent subjects with acute schizophrenia. This study is the focus of the statistical review.

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

Table 1: List of All Studies Included in Analysis

Protocol ID	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
D1050301	*Phase 3*	*6 weeks*	-	*112 subjects in placebo, 108 subjects in 40 mg/day Latuda, and 106 subjects in 80 mg/day Latuda*	*adolescent patients (13 to 17 years old) with schizophrenia*

2.2 Data Sources

The following data sources were considered in this review:

a) Applicant's study report
(\\CDSESUB1\evsprod\NDA200603\0142\m5\53-clin-stud-rep\535-rep-effic-safety-stud\schizophre\5351-stud-rep-contr\d1050301\d1050301-bodycopy.pdf)

b) Applicant's trial protocol
(\\CDSESUB1\evsprod\NDA200603\0142\m5\53-clin-stud-rep\535-rep-effic-safety-stud\schizophre\5351-stud-rep-contr\d1050301\d1050301-e3-16-1-01.pdf)

c) Data sets
(\\CDSESUB1\evsprod\NDA200603\0142\m5\datasets\d1050301\analysis\adam\datasets)
(\\CDSESUB1\evsprod\NDA200603\0142\m5\datasets\d1050301\tabulations\sdtm)

d) Software code
(\\CDSESUB1\evsprod\NDA200603\0145\m5\datasets\d1050301\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).

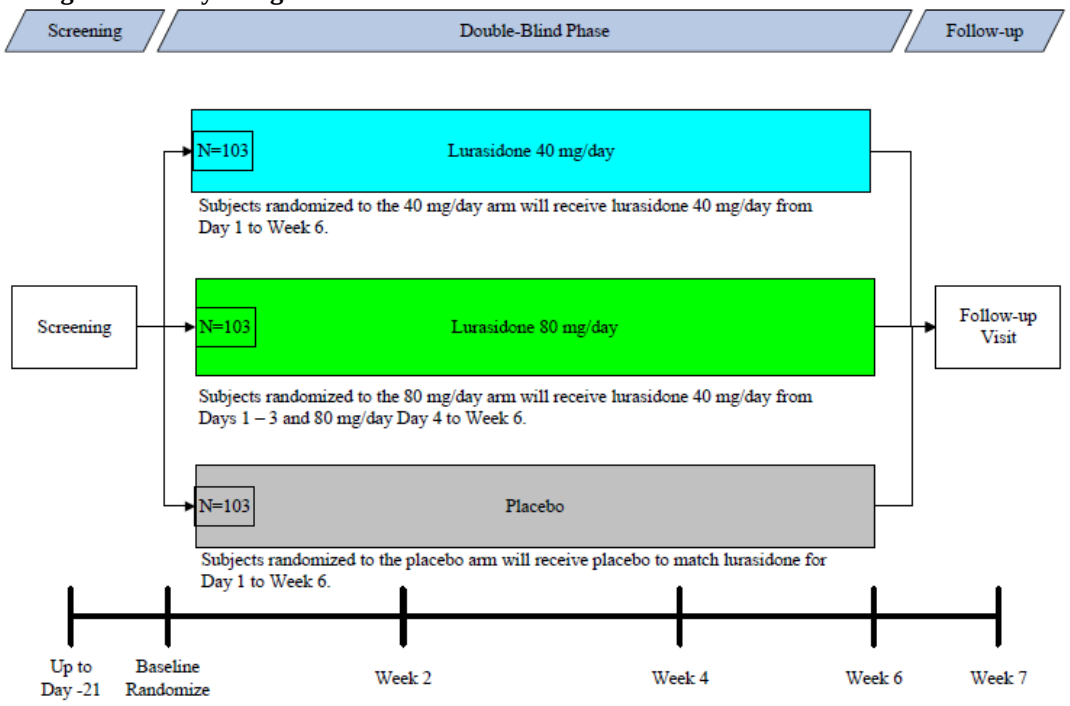
3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

DI050301 was a 6-week, multicenter, double-blind, randomized, parallel-group, placebo-controlled clinical trial compared fixed doses of lurasidone (40 mg/day or 80 mg/day) with placebo in in-patient, outpatient, or partially hospitalized adolescent subjects with acute schizophrenia. The study was conducted at 72 sites in 14 countries.

The study was comprised of a 21-day Screening period, a Baseline assessment, and a 6-week double-blind treatment period. Following the screening period, subjects who continued to meet entry criteria were randomly assigned to 1 of 3 double-blind treatment arms: lurasidone 40 mg/day, lurasidone 80 mg/day, or placebo (1:1:1 ratio). Subjects who meet eligibility criteria are randomly assigned to receive either lurasidone 40 mg/day, lurasidone 80 mg/day, or matching placebo in a double-blind fashion (1:1:1). The randomization was balanced using permuted blocks with 2 stratification criteria applied, as follows: (1) age group (13-15 years old at screening visit, 16-17 years old at screening visit); and (2) countries.

Figure 1: Study Design of DI050301



[Source: Figure 1 on page 26 of clinical study report.]

Subjects randomized to the 40 mg/day arm were treated with lurasidone 40 mg/day from Day 1 to the Week 6 Visit. Subjects randomized to the 80 mg/day arm were treated with lurasidone 40 mg/day from Days 1 to 3, and 80 mg/day from Day 4 to the Week 6 Visit. Subjects randomized to the placebo arm received placebo to match lurasidone from Day 1 to Week 6 Visit. Subjects who were deemed ineligible to continue in the study for any reason, including worsening of symptoms, would be discontinued and provided access to standard treatments per the clinical judgment of the investigator and in accordance with standard medical practice. Subjects who completed the 6-week treatment phase of the study would be eligible to participate in a separate 104-week open-label extension study (D1050302).

The primary efficacy rating scale was the PANSS. The PANSS is a 30-item clinician-rated instrument for assessing the symptoms of schizophrenia. Possible ratings on each of the 30 items were 1 (absent); 2 (minimal); 3 (mild); 4 (moderate); 5 (moderate-severe); 6 (severe); 7 (extreme). Possible total scores ranged from 30 (all symptoms absent) to 210 (all symptoms extreme). As a result, the total score may range from 30 to 210, positive and negative sub-scores may range from 7 to 49, and the general psychopathology sub-scores may range from 16 to 112. The primary efficacy endpoint was the change from Baseline in the Positive and Negative Syndrome Scale (PANSS) Total Score at Week 6.

The key secondary endpoint is change from Baseline in Clinical Global Impression Severity (CGI-S) scale at Week 6. CGI-S is a 7-point clinician-rated scale for assessing the global severity of the subject's illness. Possible ratings were 1 (normal, not ill); 2 (minimally ill); 3 (mildly ill); 4 (moderately ill); 5 (markedly ill); 6 (severely ill); 7 (very severely ill).

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 lurasidone differs from placebo by 6.0 points (SD=18, effect size 0.333) and 8.5 points (SD=18, effect size=0.472) in the change from baseline in PANSS total score at Week 6 for lurasidone 40 mg/day and 80 mg/day doses respectively, a sample size of 87 subjects per group would provide at least 85% power to reject at least one of the null hypotheses of no difference between placebo and lurasidone doses. An upward adjustment of approximately 15% is assumed to compensate for subjects who are randomized but do not provide any PANSS post-baseline efficacy measures. Thus, a total sample of approximately 309 subjects (103 subjects per group) was planned to be randomized with a ratio of 1:1:1 for placebo, lurasidone 40 mg/day and 80 mg/day respectively. The sample size calculation was based on the results from a Monte Carlo computer simulation.

The primary analysis population for the efficacy analysis was the Intent-to-Treat (ITT) population. The primary efficacy analyses of the primary efficacy endpoint (the change from Baseline in PANSS total score at Week 6) were performed using a likelihood-based mixed model for repeated measures (MMRM) model. The response (dependent) variable was the change from Baseline in PANSS total score assessed on Day 4 and other weekly visits (Weeks 1 to 6). Specifically, the MMRM model included fixed-effects terms for treatment, visit (as a categorical variable), pooled country, age group (stratification factor), PANSS total score at Baseline, and treatment-by-visit interaction. A restricted maximum likelihood estimation method was applied using an unstructured covariance model. A robust sandwich estimator for the standard error of the fixed effects and a spatial exponential covariance pattern model were used in cases where the model could not be converged. The spatial exponential model was selected for the analysis of data with unequally spaced timepoints. 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 PANSS total score and change from Baseline by study visit for each treatment group.

The change from Baseline in CGI-S at Week 6 (the key secondary efficacy endpoint), for treatment comparisons of lurasidone 40 mg/day and 80 mg/day versus placebo, was analyzed using a similar MMRM model described for the primary variable (i.e., with fixed effects terms for treatment, visit as

a categorical variable, pooled country, age group (stratification factor), CGI-S score at Baseline, and treatment-by-visit interaction).

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 is considerably larger than the assumption (SD=18). By 15 Oct 2015, 281 subjects were randomized; among those, 5 subjects were randomized on 15 Oct 2015. The sample size re-assessment was conducted by a blinded statistician from ISAC, based on a data snapshot taken on 26 Oct 2015 from MediData Rave (clinical database) for subjects who signed the informed consent form by 15 Oct 2015.

The hypotheses associated with the primary and key secondary variables for efficacy claim were grouped into 2 hierarchical families:

- Family 1 (F1): lurasidone 40 mg/day versus placebo (H1) and lurasidone 80 mg/day versus placebo (H2) based on change from Baseline in the PANSS total score at Week 6 (Endpoint 1).

- Family 2 (F2): lurasidone 40 mg/day versus placebo (H3) and lurasidone 80 mg/day versus placebo (H4) based on change from Baseline in CGI-S at Week 6 (Endpoint 2).

The truncated Hochberg-based gatekeeping procedure described in Procedure 3B by Dmitrienko et al were applied to control the study-wise Type 1 error rate at 5% (two-sided) for the hypotheses in Families 1 and 2. γ, a pre-defined truncation parameter in Family 1, is to determine α propagation rule and ranges from 0 to 1 (exclusive). The optimal value of the truncation parameter was chosen to maximize and balance the power in F1 and F2. For Study D1050301, γ was chosen as 0.5.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 327 subjects were randomized to treatment with placebo (N=113), lurasidone 40 mg/day (N=108), or lurasidone 80 mg/day (N=106). Of the 327 randomized subjects, 326 (99.7%) were included in the ITT populations; the remaining one subject was never dosed with study drug.

Seventeen (5.2%) subjects discontinued the study due to an AE, with the highest proportion of subjects in the placebo group (8.0%) and the lowest proportion in the lurasidone 80 mg/day group (2.8%). Seven (2.1%) subjects withdrew due to lack of efficacy, with the highest proportion of subjects in the placebo group (3.5%) and 1.4% for the two lurasidone groups combined. One (0.3%) subject, receiving placebo, discontinued because of a protocol violation.

Table 2: Subject Disposition (All Randomized Subjects)

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

Abbreviations: DB = double-blind; ITT = Intent-to-Treat; PP = Per Protocol.
Note: Unless otherwise specified, numbers of subjects for each treatment group and frequency counts are per planned treatment. Percentages are calculated with the number of subjects in each treatment group as denominator.
[Source: Table 16 on page 75 of clinical study report.]

Approximately 2/3 of the study population were male (63.4%) and approximately 1/3 were female (36.6%). The mean age was 15.4 ± 1.35 years. Approximately 2/3 were White (66.1%) and 86.5% were non-Hispanic/Latino. Approximately 2/3 were from countries outside the United States (66.3%), with more than half (53.7%) from Europe.

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

Characteristic	Placebo (N=112)	Lurasidone		Total (N=326)
		40 mg (N=110)	80 mg (N=104)	
Gender, n (%)	112	108	106	326
Male	71 (63.4)	67 (60.9)	70 (67.3)	208 (63.8)
Female	41 (36.6)	41 (38.0)	36 (34)	118 (36.2)
Age (years)				
n	112	108	106	326
Mean (SD)	15.3 (1.37)	15.5 (1.33)	15.3 (1.36)	15.4 (1.35)
Median	16.0	16.0	15.0	16.0
Min, Max	13, 17	13, 17	13, 17	13, 17
Category, n (%)				
13-15 years old	55 (49.1)	50 (45.5)	55 (52.9)	160 (49.1)
16-17 years old	57 (50.9)	58 (53.7)	51 (48.1)	166 (50.9)
Race, n (%)	112	108	106	326
American Indian or Alaska Native	0	0	0	0
Asian	5 (4.5)	6 (5.5)	4 (3.8)	15 (4.6)
Black or African American	22 (19.6)	19 (17.6)	19 (17.9)	60 (18.4)
Native Hawaiian or Other Pacific Islander	0	0	0	0
White	74 (66.1)	72 (66.7)	74 (69.8)	220 (67.5)
Other	11 (9.8)	11 (10.2)	9 (8.5)	31 (9.5)
Ethnicity, n (%)	112	108	106	326
Hispanic or Latino	13 (11.6)	12 (11.1)	19 (17.9)	44 (13.5)
Not Hispanic or Latino	99 (88.4)	96 (88.9)	87 (82.1)	282 (86.5)
Country, n (%)	112	108	106	326
US	37 (33.0)	36 (33.3)	37 (34.9)	110 (33.7)
Non-US	75 (67.0)	72 (65.5)	69 (65.1)	216 (66.3)
Region, n (%)	112	108	106	326
North America	37 (33.0)	36 (33.3)	37 (34.9)	110 (33.7)
South America	9 (8.0)	9 (8.2)	8 (7.5)	26 (8.0)
Europe	61 (54.5)	57 (51.8)	57 (54.8)	175 (53.7)
Asia	5 (4.5)	6 (5.6)	4 (3.8)	15 (4.6)
Baseline PANSS Total Score				
n	93	94	91	278
Mean (SD)	93.7 (11.10)	93.9 (10.75)	93.8 (10.91)	93.8 (10.88)
Median	93.0	92.0	93.0	93.0
Min, Max	70, 119	73, 119	73, 118	70, 119

[Source: Table 14.1.2.1 on clinical study report.]

3.2.4 Results and Conclusions

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

The LS mean change (± SE) from Baseline to Week 6 for the PANSS total score based on an MMRM model was -18.3 ± 1.60 for the lurasidone 80 mg/day group, -18.6 ± 1.59 for the lurasidone 40 mg/day group, and -10.5 ± 1.59 for the placebo group. Both doses showed statistically significant improvement in change from baseline in PANSS total score at Week 6 compared with placebo after applying Hochberg's procedure for multiple treatment comparisons (80mg: adjusted p = 0.0008; 40mg: adjusted p = 0.0006) as in Table 4.

Table 4: Change from Baseline in PANSS Total Score over Time – Mixed Model for Repeated Measures (ITT Population)

PANSS Total Score	Placebo (N=112)	Lurasidone 40 mg (N=108)	Lurasidone 80 mg (N=106)
Day 4			
n	112	106	106
LS Mean (SE)	-2.2 (0.65)	-3.2 (0.67)	-2.7 (0.68)
Difference of LS Mean (SE) (vs. Placebo)		-1.0 (0.84)	-0.5 (0.85)
95% CI of Difference		(-2.7, 0.7)	(-2.2, 1.1)
p-value (vs. Placebo)		0.2406	0.5284
Week 1			
n	111	106	104
LS Mean (SE)	-4.3 (0.99)	-7.4 (1.01)	-7.3 (1.03)
Difference of LS Mean (SE) (vs. Placebo)		-3.1 (1.36)	-3.0 (1.37)
95% CI of Difference		(-5.8, -0.5)	(-5.7, -0.3)
p-value (vs. Placebo)		0.0220	0.0280
Week 2			
n	103	106	104
LS Mean (SE)	-6.9 (1.22)	-11.2 (1.23)	-10.6 (1.25)
Difference of LS Mean (SE) (vs. Placebo)		-4.4 (1.69)	-3.8 (1.70)
95% CI of Difference		(-7.7, -1.1)	(-7.1, -0.4)
p-value (vs. Placebo)		0.0100	0.0278
Week 3			
n	99	102	102
LS Mean (SE)	-8.5 (1.29)	-14.7 (1.30)	-12.2 (1.31)
Difference of LS Mean (SE) (vs. Placebo)		-6.2 (1.79)	-3.7 (1.80)
95% CI of Difference		(-9.7, -2.7)	(-7.2, -0.2)
p-value (vs. Placebo)		0.0006	0.0405
Week 4			

n	96	99	99
LS Mean (SE)	-9.2 (1.46)	-17.1 (1.46)	-15.7 (1.47)
Difference of LS Mean (SE) (vs. Placebo)		-7.9 (2.03)	-6.5 (2.04)
95% CI of Difference		(-11.9, -3.9)	(-10.5, -2.5)
p-value (vs. Placebo)		0.0001	0.0016
Week 5			
n	95	97	98
LS Mean (SE)	-10.4 (1.52)	-17.4 (1.52)	-16.1 (1.53)
Difference of LS Mean (SE) (vs. Placebo)		-7.0 (2.11)	-5.7 (2.11)
95% CI of Difference		(-11.2, -2.9)	(-9.9, -1.6)
p-value (vs. Placebo)		0.0010	0.0070
Week 6			
n	93	96	97
LS Mean (SE)	-10.5 (1.59)	-18.6 (1.59)	-18.3 (1.60)
Difference of LS Mean (SE) (vs. Placebo)		-8.0 (2.21)	-7.7 (2.22)
95% CI of Difference		(-12.4, -3.7)	(-12.1, -3.4)
p-value (vs. Placebo)		0.0003	0.0006

Abbreviations: CI = confidence interval; ITT = Intent-to-Treat; LS = Least Squares; PANSS = Positive and Negative Symptoms Scale; SE = standard error.

Note: LS Mean, LS mean difference, and the associated 95% CI and p-value for change from baseline are based on Mixed Model for Repeated Measures with fixed effects terms for treatment, visit (as a categorical variable), pooled country, age strata, PANSS total score at baseline, and treatment-by-visit interaction.

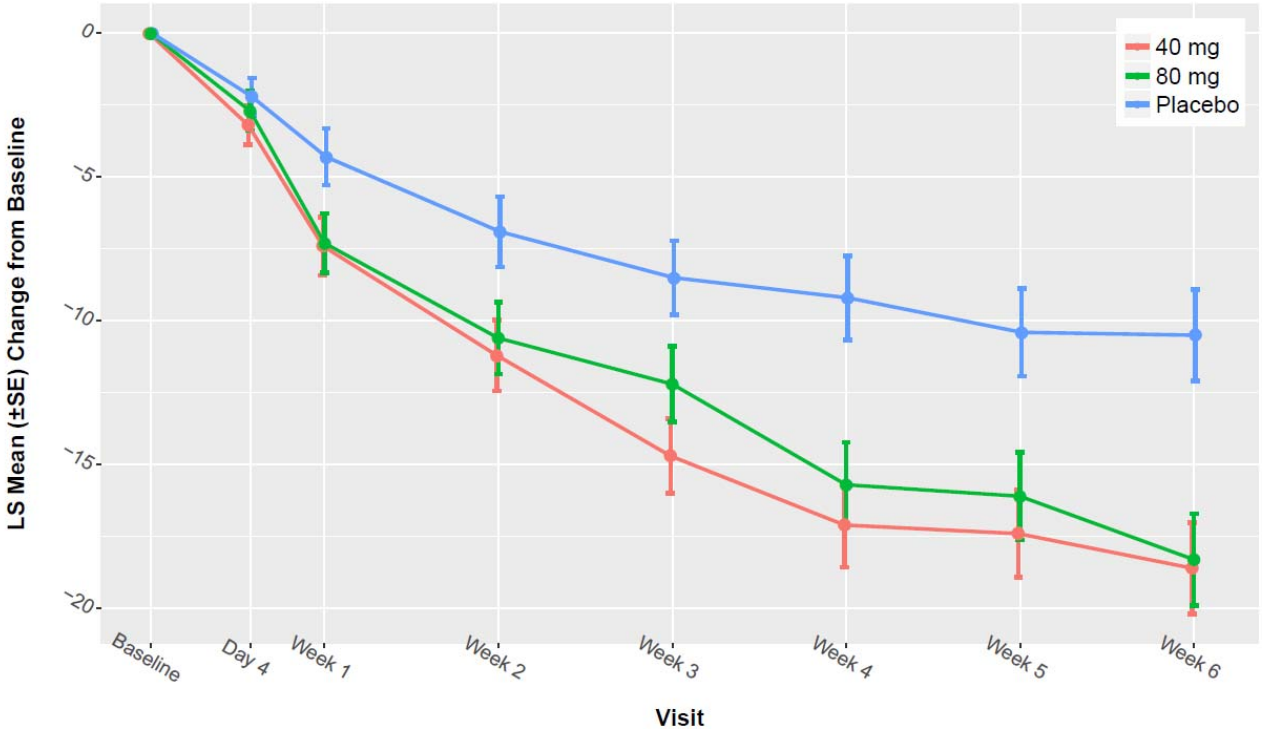
Note: Higher values of PANSS total score represent greater severity of illness.

[Source: Table 22 on page 88 of clinical study report.]

As shown in Figure 2, the LS mean decreases in the PANSS total score in both lurasidone groups were numerically greater than placebo beginning at Week 1 and continuing through Week 6. In both lurasidone treatment groups, the mean decreases were generally stable from Week 4 to Week 6, and the further decreases were small after Week 4. Overall, compared to placebo, it appears that both doses of lurasidone improved the PANSS total score after 6 weeks of treatment.

Two sensitivity analyses were conducted for verifying 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.

Figure 2: PANSS Total Score: LS Mean (±SE) Change from Baseline over Time – Mixed Model for Repeated Measure (ITT Population, Observed)



[Source: Reviewer's Plot]

Table 5: Sensitivity Analysis: Pattern Mixture Model with Placebo-Based Multiple Imputation for Primary Efficacy Analysis of PANSS Total Score (ITT Population)

Analysis	Statistic	Placebo (N=112)	Lurasidone 40 mg (N=108)	Lurasidone 80 mg (N=106)
PMM with Placebo-based Multiple Imputation Result at Week 6	LS Mean (SE)	-10.4 (1.66)	-18.6 (1.63)	-18.1 (1.64)
	Difference from Placebo			
	LS Mean Difference (SE)		-8.2 (2.29)	-7.8 (2.27)
	LS Mean Difference 95% CI		(-12.7, -3.7)	(-12.2, -3.3)
	p-value		0.0003**	0.0006**
MMRM Result at Week 6	LS Mean (SE)	-10.5 (1.59)	-18.6 (1.59)	-18.3 (1.60)
	Difference from Placebo			
	LS Mean Difference (SE)		-8.0 (2.21)	-7.7 (2.22)
	LS Mean Difference 95% CI		(-12.4, -3.7)	(-12.1, -3.4)
	p-value		0.0003**	0.0006**

**$p \leq 0.01$
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, age strata, visit as a categorical variable, baseline score, and treatment by visit interaction, assuming an unstructured covariance matrix.
[Source: Table 27 on page 98 of clinical study report.]

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 6: Sensitivity Analysis: Random Effects Pattern Mixture Model with Two Patterns (Completers and Dropouts) for Primary Efficacy Analysis of PANSS Total Score (ITT Population)

Analysis	Statistic	Intercept	Time	Lurasidone 40 mg	Lurasidone 80 mg	Time* Lurasidone 40 mg	Time* Lurasidone 80 mg
REM	Model Estimate (SE)	93.0 (1.14)	-4.8 (0.69)	2.3 (1.63)	1.8 (1.64)	-3.8 (0.97)	-3.2 (0.98)
	95% CI	(90.8, 95.3)	(-6.1, -3.4)	(-0.9, 5.5)	(-1.5, 5.0)	(-5.7, -1.9)	(-5.1, -1.2)
	p-value	<0.0001**	<0.0001**	0.1677	0.2857	0.0001**	0.0014**
PMM Overall	Model Estimate (SE)	92.8 (1.15)	-4.3 (0.74)	2.4 (1.65)	1.7 (1.66)	-3.7 (0.97)	-2.8 (0.95)
	95% CI	(90.5,95.0)	(-5.8,-2.8)	(-0.9,5.6)	(-1.5,5.0)	(-5.6,-1.8)	(-4.6,-0.9)
	p-value	<0.0001**	<0.0001**	0.1543	0.2959	0.0001**	0.0038**
PMM Completers	Model Estimate (SE)	93.1 (1.25)	-5.8 (0.71)	1.8 (1.76)	1.6 (1.76)	-3.0 (0.99)	-2.8 (0.99)
	95% CI	(90.7, 95.6)	(-7.1, -4.4)	(-1.6, 5.3)	(-1.9, 5.0)	(-4.9, -1.0)	(-4.8, -0.9)
	p-value	<0.0001**	<0.0001**	0.3000	0.3665	0.0029**	0.0044**
PMM Dropouts	Model Estimate (SE)	91.1 (2.86)	2.8 (2.00)	6.6 (4.57)	3.1 (4.84)	-9.5 (3.08)	-2.0 (3.25)
	95% CI	(85.5, 96.7)	(-1.1, 6.7)	(-2.4, 15.5)	(-6.4, 12.6)	(-15.5, -3.4)	(-8.4, 4.4)
	p-value	<0.0001**	0.1571	0.1507	0.5191	0.0021**	0.5403

**p≤0.01
Abbreviations: CI = confidence interval; ITT = Intent-to-Treat; PANSS= Positive and Negative Syndrome Scale; PMM = Pattern Mixed Model; REM = Random Effects Model; SE = standard error.
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. Note: Time = sqrt (analysis visit).
[Source: Table 28 on page 99 of clinical study report]

3.2.4.3 Sponsor's analyses: Key Secondary Efficacy Variable

The key secondary endpoint was the change in CGI-S score from Baseline to Week 6. As the primary objective was met for both of the Lurasidone doses, confirmative testing for the key secondary endpoint was performed. The improvement in the CGI-S scores at Week 6 were statistically significantly different from placebo for both the lurasidone 80 mg/day (-0.42 ± 0.130, p = 0.0015, adjusted p = 0.0015) and lurasidone 40 mg/day (-0.47 ± 0.130, p = 0.0003; adjusted p = 0.0008) treatment groups. Thus, treatment with lurasidone demonstrated a statistically significant improvement over placebo in the CGI-S after 6 weeks of treatment.

Table 7: Change from Baseline in the Clinical Global Impression – Severity (CGI-S) at Week 6-Mixed Model for Repeated Measures (ITT Population)

PANSS Total Score	Placebo (N=112)	Lurasidone 40 mg (N=108)	Lurasidone 80 mg (N=106)
Week 6			
n	93	96	97
LS Mean (SE)	-0.50 (0.094)	-0.97 (0.093)	-0.92 (0.093)
Difference of LS Mean (SE) (vs. Placebo)		-0.47 (0.130)	-0.42 (0.130)
95% CI of Difference		(-0.73, -0.22)	(-0.67, -0.16)
p-value (vs. Placebo)		0.0003	0.0015

Abbreviations: CGI-S = Clinical Global Impression – Severity; CI = confidence interval; ITT = Intent-to-Treat; LS= least squares; SE = standard error.

Note: LS Mean, LS mean difference, and the associated 95% CI and p-value for change from baseline are based on Mixed Model for Repeated Measures with fixed effects terms for treatment, visit (as a categorical variable), pooled country, age strata, CGI-S scores at baseline, and treatment-by-visit interaction.

Note: Higher values of CGI-S scores represent greater severity of illness. [Source: Table 29 on page 101 of clinical study report.]

3.2.4.4 Reviewer's Results and Comments

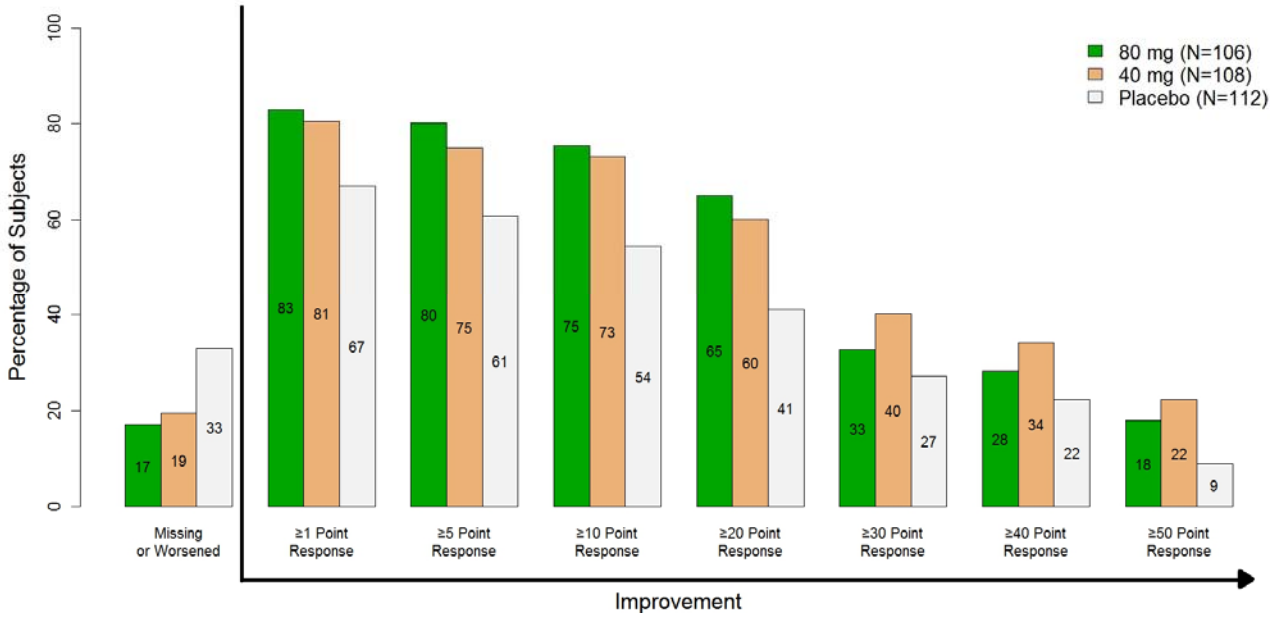
This reviewer confirmed the sponsor's analysis results for the primary and key secondary endpoints. The sensitivity analyses as presented in Tables 5 and 6 were confirmed as well.

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. Table 7 shows that the results did not suggest additional improvement from the 80 mg over the 40 mg dose on the primary or the key secondary endpoint. In addition, the observed treatment differences in CGI-S appeared to be very small. Whether or not it is clinically relevant is deferred to the clinical review team.

At the interim look on Oct 15, 2015, 281 subjects had been randomized and 279 subjects had at least one value for change from Baseline in PANSS total score. By that time, there were 240 subjects who either completed (206 subjects) or discontinued early from the study (34 subjects); of those, 239 subjects had value(s) for change from Baseline in PANSS total score. By using the LOCF approach, the estimated SD was 16.37 based on the 279 subjects and 16.72 based on the 239 subjects. Since the estimated pooled SD was smaller than the assumed SD=18 based on either data set at the interim look, 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, the calculated powers to conclude at least one effective dose were >93% and >68% assuming a treatment difference of 8.5 points and 6.0 points, respectively. Regardless of the power calculation, which depends on several unverifiable assumptions, both treatment arms were still highly statistically significant in this trial when compared with the control arm.

Figure 3: Percentage of Subjects with Specific Magnitude of PANSS Total Score Improvement at Week 6



[Source: Reviewer's Plot]
Numbers on the bars represent percentages 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, Age, and Geographic Region

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 PANSS total score was examined by age group, gender, race, and geographic region to explore whether there was a consistent treatment effect across subgroups. Mean differences from placebo in PANSS total score for age group, gender, race, and geographic region were shown in Table 8. The trends appeared consistent in favor of lurasidone across subgroups. The results did not suggest apparent treatment-by-subgroup interactions with respect to age, gender, race or geographic region.

Table 8: PANSS Total Score: Subgroup Analysis by Age group, Gender, Race, and Geographic Region 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 13-15 at Screening	**Lurasidone 40 mg**	49	-18.0 (2.51)	-7.9 (-14.1, -1.6)
	Lurasidone 80 mg	54	-17.8 (2.39)	-7.6 (-13.7, -1.6)
	Placebo	55	-10.1 (2.34)	-
Age 16-17 at Screening	**Lurasidone 40 mg**	59	-16.2 (2.17)	-8.5 (-14.4, -2.6)
	Lurasidone 80 mg	52	-15.7 (2.37)	-8.0 (-14.1, -1.8)
	Placebo	57	-7.7 (2.22)	-
Gender				
Male	**Lurasidone 40 mg**	67	-17.2 (2.11)	-10.1(-15.6, -4.7)
	Lurasidone 80 mg	70	-16.4 (2.07)	-9.3 (-14.7, -3.9)
	Placebo	71	-7.1 (2.07)	-
Female	**Lurasidone 40 mg**	41	-16.9 (2.67)	-4.9 (-12.0, 2.1)
	Lurasidone 80 mg	36	-17.2 (2.89)	-5.3 (-12.6, 2.1)
	Placebo	41	-11.9 (2.60)	-
Race				
White	**Lurasidone 40 mg**	72	-15.3 (2.22)	-8.1(-13.3, -2.9)
	Lurasidone 80 mg	74	-15.2 (2.18)	-8.0(-13.2, -2.8)
	Placebo	74	-7.3 (2.17)	-
Black or African American	**Lurasidone 40 mg**	19	-11.0 (4.38)	-0.2 (-10.1, 9.6)
	Lurasidone 80 mg	19	-15.0 (4.38)	-4.2 (-14.1, 5.7)
	Placebo	22	-10.8 (4.14)	-
Other	**Lurasidone 40 mg**	11	-31.7 (6.75)	-14.8 (-28.3, -1.4)
	Lurasidone 80 mg	9	-25.9 (6.99)	-9.0 (-23.3, 5.2)
	Placebo	11	-16.8 (6.78)	-

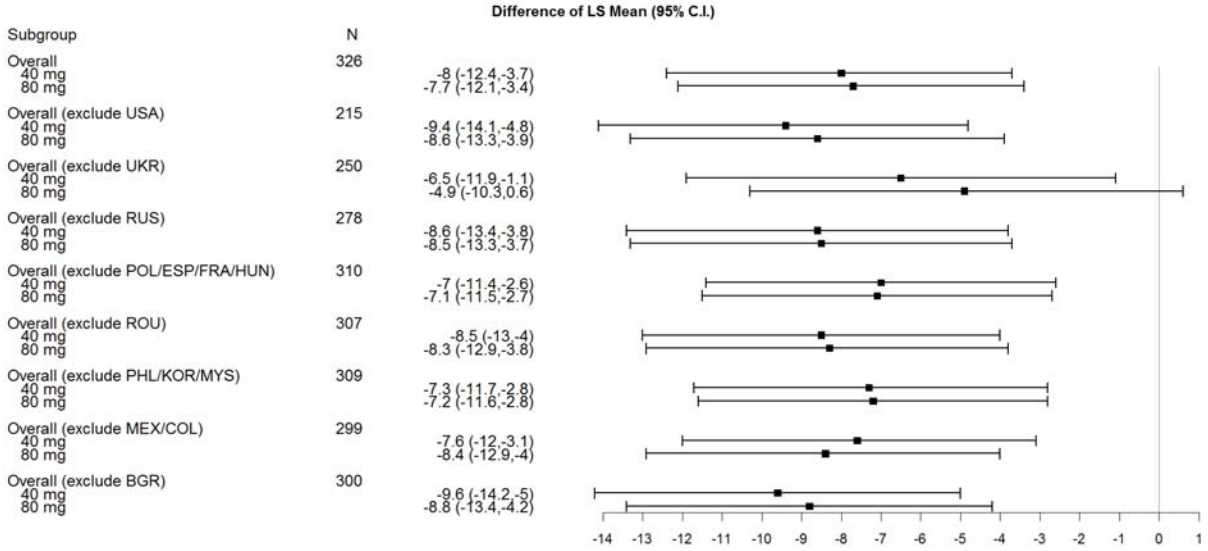
Asian	**Lurasidone 40 mg**	6	-22.5 (15.58)	-
	Lurasidone 80 mg	4	-18.3 (18.39)	-
	Placebo	5	3.6 (13.43)	-
Geographic Region				
US	**Lurasidone 40 mg**	36	-19.8 (2.69)	-5.7 (-13.1, 1.7)
	Lurasidone 80 mg	37	-19.8 (2.66)	-5.7 (-13.0, 1.7)
	Placebo	37	-14.1 (2.67)	-
Non-US	**Lurasidone 40 mg**	72	-17.3 (1.91)	-9.5 (-14.7, -4.3)
	Lurasidone 80 mg	69	-16.8 (1.94)	-9.0 (-14.2, -3.7)
	Placebo	75	-7.8 (1.86)	-

Note: LS Means, LS Mean Difference, associated 95% CI and p-value are based on an ANCOVA model with treatment, pooled country, age strata, subgroup, treatment-by-subgroup interaction as fixed factors, and baseline PANSS total score as a covariate.
[Source: Tables 14.2.1.7.1, 14.2.1.7.2, 14.2.1.7.3 and 14.2.1.7.7 of clinical study report.]

4.2 Country

This reviewer also conducted an additional exploratory subgroup analysis (by excluding one country) in change from Baseline to Week 6 in the PANSS total score to display the treatment effect by each country. Figure 4 is the forest plot that treatment effect seemed consistent overall. Again, the 80 mg dose did not look more effective than the 40 mg dose regardless of which country was removed from the analysis set.

Figure 4: Treatment Effects Relative to Placebo: Subgroup Analyses (by excluding one country) in Changes from Baseline to Week 6 in PANSS Total Score (ITT LOCF)



Note: "N" represents the number of patients after each country was removed from the analysis set. LS Mean Difference, associated 95% CI and p-value are based on the MMRM with fixed effects for treatment, pooled country, age strata, and visit as a categorical variable, baseline score, and treatment by visit interaction, assuming an unstructured covariance matrix.
[Source: Reviewer's Plot]

In order to investigate how treatment effects were influenced by country, this reviewer removed the covariate "country" from the primary MMRM model. The results of this analysis shown in Table 9 were consistent with the primary analysis results in Table 4, which suggested that country had little impact on treatment effects. It also suggested that the apparent "nearly-flat" dose response could not be attributed by country.

Table 9: Change from Baseline in PANSS Total Score at Week 6 – Mixed Model for Repeated Measures by Excluding the Covariate "Country" (ITT Population)

Analysis	Statistic	Placebo (N=112)	Lurasidone 40 mg (N=108)	Lurasidone 80 mg (N=106)
MMRM Result by excluding the Covariate "Country" at Week 6	LS Mean (SE)	-10.8 (1.57)	-18.9 (1.56)	-18.7 (1.57)
	Difference from Placebo			
	LS Mean Difference (SE)		-8.1 (2.22)	-7.9 (2.22)
	LS Mean Difference 95% CI		(-12.5, -3.8)	(-12.2, -3.5)
	p-value		0.0003**	0.0005**

**$p \leq 0.01$
Abbreviations: ITT = Intent-to-Treat; LS = least squares; MMRM = Mixed Model Repeated Measure; PMM = Pattern Mixed Model; SE = standard error.
Note: MMRM (Mixed Model for Repeated Measures), based on the fixed effects for treatment, age strata, visit as a categorical variable, baseline score, and treatment by visit interaction, assuming an unstructured covariance matrix.
[Source: Reviewer's Table]

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There are no statistical issues that impact the overall conclusions.

5.2 Collective Evidence

Both lurasidone doses (40 mg and 80 mg q.d.) showed statistically significant improvement in change from baseline in PANSS Total Score at Week 6 compared with placebo after multiple comparison adjustment using Hochberg's procedure. The least square mean differences when compared to placebo group were -8.0 and -7.7 points in PANSS Total Score for 40 mg and 80 mg lurasidone treatment group, and were -0.47 and -0.42 points in CGI-S score. Various sensitivity analyses showed consistent results in the primary and the key secondary endpoint. However, when compared to placebo, 80 mg dose didn't seem to have a greater observed treatment effect than 40 mg dose whether on the primary or the key secondary endpoint. The exploratory subgroup analyses by country also suggested that the apparent "nearly-flat" dose response could not be attributed by country.

5.3 Conclusions and Recommendations

Both lurasidone treatment groups showed statistical significance when compared with the placebo group on the primary and the key secondary endpoint. However, the results did not suggest additional benefit of the 80 mg over the 40 mg dose whether on the primary or the key secondary endpoint. In addition, the observed treatment differences in CGI-S appeared to be very small. Whether or not it is clinically relevant is deferred to the clinical review team.

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/s/

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