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 #:	NDA 200-603
Supplement #:	S-29
Drug Name:	Latuda (lurasidone HCl) tablets: 20mg, 40mg, 60mg, 80mg
Indication(s):	Treatment of major depressive episodes associated with bipolar I disorder
Applicant:	Sunovion Pharmaceuticals
Date(s):	Submission date: 5/5/2017, PDUFA date: 3/5/2017
Review Priority:	Standard
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Keywords: mixed models**,** sensitivity analyses, data imputation

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1 EXECUTIVE SUMMARY

Sunovion Pharmaceuticals submitted study D1050326 under NDA 200603, S-29, to fulfill PREA requirement 2058-1 to investigate the efficacy of flexible dose LATUDA® (lurasidone HCl) (20mg-80mg) for the treatment of bipolar depression in children and adolescents aged 10-17 years. Subjects treated with lurasidone showed an average reduction in Children's Depression Rating Scale – Rating (CDRS-R) of -5.7 (95% CI: -8.4, -3.0, $p < 0.0001$). In addition, lurasidone improved the clinical global impression of the severity of bipolar depression (CGI-BP-S depression score) with a mean improvement of -0.44 (95% CI: -0.66, -0.22, $p < 0.0001$). Study D1050326 met its primary outcome and supports the efficacy of lurasidone for the treatment of bipolar depression in children and adolescents.

2 INTRODUCTION

The Sponsor submitted this sNDA for the use of Latuda (lurasidone HCl) in the treatment of major depressive episodes associated with bipolar I disorder in pediatric subjects. Reference is made to the original NDA, 200603 – lurasidone indicated for treatment of schizophrenia – and supplements S-010 and S-011 for the treatment of depressive episodes associated with bipolar 1 in adults. This sNDA fulfills the Pediatric Research Equity Act (PREA) requirement (2058-1) from the approval letter dated June 28, 2013.

The study contained in this sNDA is the third study of lurasidone in a pediatric population. The other studies were for the indications of schizophrenia and irritability related to autism. The study in schizophrenia was positive; therefore, lurasidone's indication was expanded to include schizophrenia in pediatric subjects. Pediatric exclusivity was granted for schizophrenia. However, the study of irritability related to autism was negative. No indication for autism related irritability was added to the label.

2.1 Overview

This sNDA contains a single phase 3, multi-center, double-blind, placebo-controlled, flexible dose, parallel-group study designed to evaluate the efficacy and safety of lurasidone in children and adolescents with bipolar I depression. Lurasidone dose ranged from 20mg per day to 80mg per day.

The original protocol was reviewed under IND 103427.

Table 1: List of all studies included in analysis

	Phase and Design	Treatment Period	# of Subjects per Arm	Study Population
D1060326	*Phase 3 - MC, R, DB, PG, PC trial*	*6 weeks*	*lurasidone/ 176 placebo/ 174*	*subjects aged 10-17 with bipolar I depression*

* MC: multi-center, R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled

2.2 Data Sources

The following data sources were considered in this review:

a) Applicant's study report (\\CDSESUB1\evsprod\NDA200603\0165\m5\53-clin-stud-rep\535-rep-effic-safety-stud\bipolar-depression\5351-stud-rep-contr\d1050326\d1050326-body.pdf)
b) Applicant's trial protocol (\\cdsesub1\evsprod\nda200603\0165\m5\53-clin-stud-rep\535-rep-effic-safety-stud\bipolar-depression\5351-stud-rep-contr\d1050326\d1050326-e3-16-1-01.pdf)
c) Data sets (\\CDSESUB1\evsprod\NDA200603\0166\m5\datasets\d1050326\analysis\adam\datasets)

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d) Software code (\\CDSESUB1\evsprod\NDA200603\0166\m5\datasets\d1050326\analysis\adam\programs)

e) Response to FDA information request (\\CDSESUB1\evsprod\NDA200603\0168\m5\datasets\d1050326\analysis\adam\programs)

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The Sponsor submitted all necessary analysis datasets and SAS programs. This reviewer found the datasets acceptable. However, the originally submitted SAS programs were not sufficient to recreate the sensitivity analyses for the primary endpoint. After an information request, the Sponsor submitted a commented version of the SAS programs. With these updates, this Reviewer recreated the primary results from the Clinical Study Report. In addition, the Sponsor submitted necessary Data Safety and Monitoring Board (DSMB) minutes and interim analysis reports.

3.2 Evaluation of Efficacy

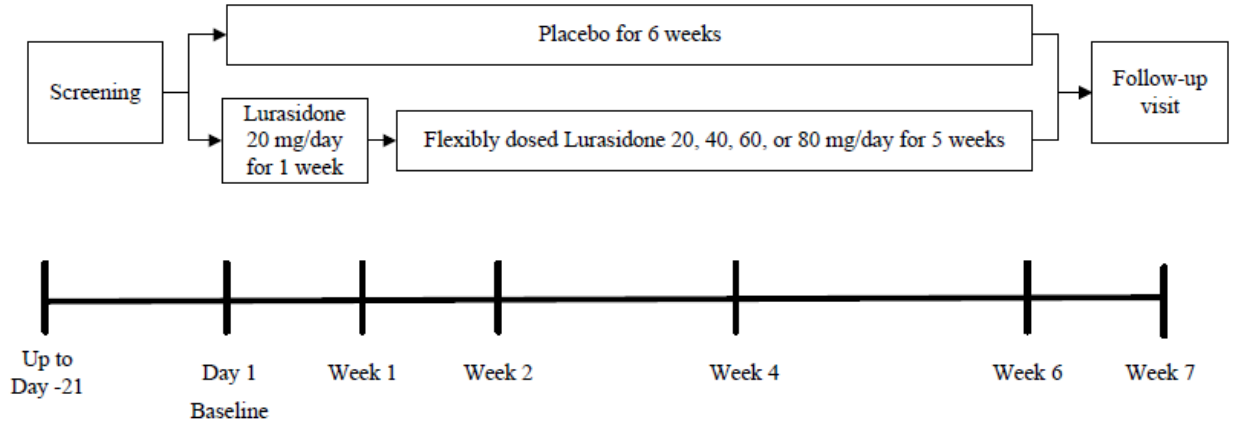
3.2.1 Study Design and Endpoints

D1050326 was a six week, double-blind, randomized, placebo-controlled study. The study was conducted at 64 sites in 11 countries (Bulgaria, Columbia, France, Hungary, Mexico, Philippines, Poland, Russia, South Korea, Ukraine, and United States). This study evaluated the efficacy and safety of flexibly dosed lurasidone (20 to 80 mg/day) compared to placebo in pediatric subjects (10-17 years old) for the treatment of depressive episodes. Subjects were randomized at a 1:1 ratio to either placebo or lurasidone. Randomization was stratified by age (10 to 14 years old; 15 to 17 years old) and stimulant use at baseline.

Lurasidone dose started at 20 mg per day for all subjects. After 7 days of 20 mg lurasidone per day, lurasidone dose can be increased up to 80 mg per day at the discretion of the Investigator to optimize both efficacy and tolerability. If necessary, efficacy driven dose changes occurred at the weekly visits. Dose reductions for safety or tolerability were made at any time.

The primary endpoint was change from baseline to week 6 in depressive symptoms as measured by Children's Depression Rating Scale, Revised (CDRS-R) total score. CDRS-R total score is the sum of 17 items that evaluates the presence and severity of depressive symptoms. CDRS-R score ranges from 17-113. The key secondary endpoint was change from baseline to week 6 in Clinical Global Impression – Bipolar Version, Severity of Illness (CGI-BP-S) score (depression item). CGI-BP-S is a clinician rated 7-point score that reflects severity of depressive symptoms. Both the primary and key secondary endpoints were observed at baseline (day 1), weeks 1, 2, 4, and 6. A follow-up visit was scheduled for week 7.

Figure 1: Study Design Schematic of D1050326



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

3.2.2 Statistical Methodologies

Sponsor's Methods
Study D1050326 was designed to have 85% power to detect a 5.0 point treatment effect in CDRS-R between the lurasidone arm and placebo arm at week 6 using a t-test with 5% type I error rate. Assuming a common standard deviation of 14.2 units, the Sponsor calculated a sample size of 145 subjects. The Sponsor enrolled 170 subjects per arm to allow for a 15% dropout rate.

A blinded, sample size re-assessment was conducted when 90% of subjects were enrolled. If the observed standard deviation was greater than 14.2, the sample size is modified. No alpha adjustment is needed because the interim assessment is blinded. An external, independent, blinded statistician from the Independent Statistical Analysis Center (ISAC) of the DSMB conducted the analysis.

All efficacy analyses were conducted using the Intent-to-Treat (ITT) population. The ITT population consisted of all randomized subjects who received at least one dose of lurasidone.

For both the primary endpoint of change in CDRS-R score from baseline to week 6 and key secondary endpoint of change in CGI-BP-S depression from baseline to week 6, the primary analysis was a MMRM analysis. The model included fixed effect terms for treatment, categorical visit (weeks 1 to 6), treatment-by-visit interaction, baseline CDRS-R score, pooled country, and age stratum. The pooled country term grouped countries into eight groups: (1) United States; (2) Ukraine; (3) Russia; (4) Mexico; (5) Bulgaria; (6) Colombia; (7) France, Hungary, Poland; and (8) South Korea, Philippines. The age stratum term divided subjects into groups: 10 to 14 years, and 15 to 17 years. An unstructured covariance matrix was pre-specified. The model was fit using restricted maximum likelihood (REML). If the unstructured covariance matrix model did not converge, a spatial exponential covariance pattern model was used along

with robust standard errors. The lurasidone treatment effect was the least squares (LS) mean difference at week 6 from this MMRM model. Statistical significance is assessed using the LS means *p*-value.

The primary analysis model assumed that missing data is missing at random (MAR). Two pre-planned sensitivity analyses are both pattern mixture models (PMM). The first PMM used placebo-based multiple imputation. This model assumed that a dropout's CDRS-R trajectory behaved similarly to a placebo patient after dropout. The second PMM analyzed the effect of dropout pattern. This model extended the primary analysis model to incorporate a fixed effect of dropout pattern (completers or dropouts).

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Of the 350 subjects, 174 subjects were randomized to placebo and 176 subjects were randomized to flexible dose lurasidone. Three subjects were randomized but not dosed (2 in placebo arm and 1 in the lurasidone arm) yielding a safety population of 347 subjects. The ITT population consisted of 343 subjects. In the lurasidone arm, one patient withdrew consent and one patient discontinued for lack of efficacy. In the placebo arm, one patient was lost to follow-up and one patient was withdrawn because of a protocol violation. Twenty-five subjects dropped out of the double-blind (DB) phase. Additional details of patient disposition are presented in Table 2.

Table 2: Subject Disposition (All Randomized Subjects)

	Placebo (N=174) n (%)	Lurasidone 20-80 mg (N=176) n (%)	Total (N=350) n (%)
Number randomized	174 (100.0)	176 (100.0)	350 (100.0)
Number randomized, but not dosed	2 (1.1)	1 (0.6)	3 (0.9)
Number in the ITT population	170 (97.7)	173 (98.3)	343 (98.0)
Number in the PP population	152 (87.4)	149 (84.7)	301 (86.0)
Number in the Safety population	172 (98.9)	175 (99.4)	347 (99.1)
Number who completed the 6-Week DB Phase	156 (89.7)	162 (92.0)	318 (90.9)
Number who completed the 6-Week DB Phase and entered into the open-label extension Study D1050302	150 (86.2)	156 (88.6)	306 (87.4)
Number who discontinued during the DB Phase by primary reason for discontinuation	18 (10.3)	14 (8.0)	32 (9.1)
Lack of Efficacy	3 (1.7)	3 (1.7)	6 (1.7)
Adverse Event	3 (1.7)	3 (1.7)	6 (1.7)
Lost to Follow-Up	3 (1.7)	3 (1.7)	6 (1.7)
Protocol Violation	2 (1.1)	1 (0.6)	3 (0.9)
Withdrawal of Consent	6 (3.4)	3 (1.7)	9 (2.6)

Other	1 (0.6)	1 (0.6)	2 (0.6)

Source: Recreated from Sponsor's data using Sponsor's submitted code. Matches Sponsor's Table 14.1.1.3.

In the ITT population, half the subjects were female (51% male vs. 49% female). Subjects' ages ranged from 10 to 17 years, with a mean age of 14.2 years. Randomization was stratified on age with strata 10-14 years and 15-17 years. Most subjects were white (74.9%), 10.4% of subjects were black or African American, and 14.8% of subjects were Asian or other. Most subjects were from outside the United States (US) (56.8% Non-US vs. 43.9% US). No other meaningful differences were observed among treatment groups for any of the other demographic variables. See Table 3 for additional demographic characteristics.

Table 3: Demographic Characteristics (ITT Population)

Characteristic	Placebo (N=170)	Lurasidone 20-80 mg (N=173)	Total (N=343)
Gender, n (%)	170	173	343
Male	87 (51.2)	88 (50.9)	175 (51.0)
Female	83 (48.8)	85 (49.1)	168 (49.0)
Age (years)			
n	170	173	343
Mean (SD)	14.3 (2.05)	14.2 (2.19)	14.2 (2.12)
Median	14.5	14.0	14.0
Min, Max	10, 17	10, 17	10, 17
Age Stratum, n (%)	170	173	343
10-14 years old	85 (50.0)	88 (50.9)	173 (50.4)
15-17 years old	85 (50.0)	85 (49.1)	170 (49.6)
Age Group 1, n (%)	170	173	343
10-12 years old	37 (21.8)	38 (22.0)	75 (21.9)
13-17 years old	133 (78.2)	135 (78.0)	268 (78.1)
Race, n (%)	170	173	343
American Indian or Alaska Native	0	2 (1.2)	2 (0.6)
Asian	4 (2.4)	7 (4.0)	11 (3.2)
Black or African American	18 (10.6)	15 (8.7)	33 (9.6)
Native Hawaiian or Other Pacific Islander	0	0	0
White	125 (73.5)	134 (77.5)	259 (75.5)
Other	23 (13.5)	15 (8.7)	38 (11.1)
Ethnicity, n (%)	170	173	343
Hispanic or Latino	33 (19.4)	31 (17.9)	64 (18.7)
Not Hispanic or Latino	137 (80.6)	142 (82.1)	279 (81.3)
Country, n (%)	170	173	343
US	73 (42.9)	74 (42.8)	147 (42.9)
Non-US	97 (57.1)	99 (57.2)	196 (57.1)
Region, n (%)	170	173	343
North America	73 (42.9)	74 (42.8)	147 (42.9)
South America	24 (14.1)	22 (12.7)	46 (13.4)
Europe	70 (41.2)	71 (41.0)	141 (41.1)

Asia	3 (1.8)	6 (3.5)	9 (2.6)
Screening BMI (kg/m^2)			
n	170	173	343
Mean (SD)	21.37 (3.49)	21.52 (3.35)	21.45 (3.42)
Median	21.02	21.34	21.26
Min, Max	14.7, 32.8	14.2, 28.6	14.2, 32.8
Screening BMI Percentile			
n	170	173	343
Mean (SD)	61.52 (30.18)	64.88 (28.96)	63.21 (29.58)
Median	66.056	69.607	69.069
Min, Max	2.29, 99.94	1.25, 99.44	1.25, 99.94
Category, n (%)			
< 3th percentile	1 (0.6)	2 (1.2)	3 (0.9)
3th to 85th percentile	112 (65.9)	105 (60.7)	217 (63.3)
> 85th to 97th percentile	49 (28.8)	61 (35.3)	110 (32.1)
> 97th percentile	8 (4.7)	5 (2.9)	13 (3.8)
Screening BMI Z-score			
n	170	173	343
Mean (SD)	0.43 (1.046)	0.52 (1.019)	0.48 (1.032)
Median	0.41	0.51	0.50
Min, Max	-2.0, 3.2	-2.2, 2.5	-2.2, 3.2
Baseline Weight (kg)			
n	170	173	343
Mean (SD)	57.0 (13.51)	56.5 (13.03)	56.8 (13.26)
Median	55.3	56.3	56.0
Min, Max	25, 96	29, 88	25, 96
Screening Height (cm)			
n	170	173	343
Mean (SD)	162.16 (11.194)	161.14 (11.388)	161.64 (11.288)
Median	162.80	162.00	162.00
Min, Max	130.0, 186.2	130.0, 190.0	130.0, 190.0

Source: Recreated from Sponsor's data using Sponsor's submitted code. Matches Sponsor's Table 14.1.2.3.

At baseline, subjects had a baseline CDRS-R total score of 58.9 with a range in scores from 44 to 82. CDRS-R scores range from 17 to 113. Baseline CGI-BP-S depression scores range from 3 to 6 with a mean score of 4.5 out of a maximum of 7.

Table 4: Baseline CDRS-R Total Score and Baseline CGI-BP-S Depression Score (ITT Population)

Characteristic	Placebo (N=170)	Lurasidone 20-80 mg (N=173)	Total (N=343)
Baseline CDRS-R Total Score			
n	170	173	343
Mean (SD)	58.6 (8.26)	59.2 (8.24)	58.9 (8.24)
Median	57.5	59.0	58.0
Min, Max	45, 82	44, 80	44, 82
Baseline CGI-BP-S Depression			
n	170	173	343
Mean (SD)	4.5 (0.57)	4.6 (0.65)	4.5 (0.61)
Median	4.0	5.0	4.0

Min, Max	4, 6	3, 6	3, 6

Source: Recreated from Sponsor's data using Sponsor's submitted code. Matches Sponsor's Table 14.1.2.3.

3.2.4 Results and Conclusions

Sponsor's Results

The primary efficacy endpoint of change from baseline to week 6 in CDRS-R total score reached statistical significance for flexible dose lurasidone compared to placebo ($p < 0.0001$). At week 6, mean CDRS-R total score in the lurasidone arm declined by 5.7 (95% CI[1]: -8.4, -3.0) points more than the placebo arm. The key secondary endpoint of change from baseline to week 6 in CGI-BP-S depression score was also statistically significant for flexible dose lurasidone compared to placebo ($p < 0.0001$). Detailed results are found in Table 5. P-values were compared to an alpha level of 0.05. Throughout this Section, negative change indicates improvement.

Table 5: CDRS-R Total Score and CGI-S-BP Depression Score at Six Weeks (ITT Population)

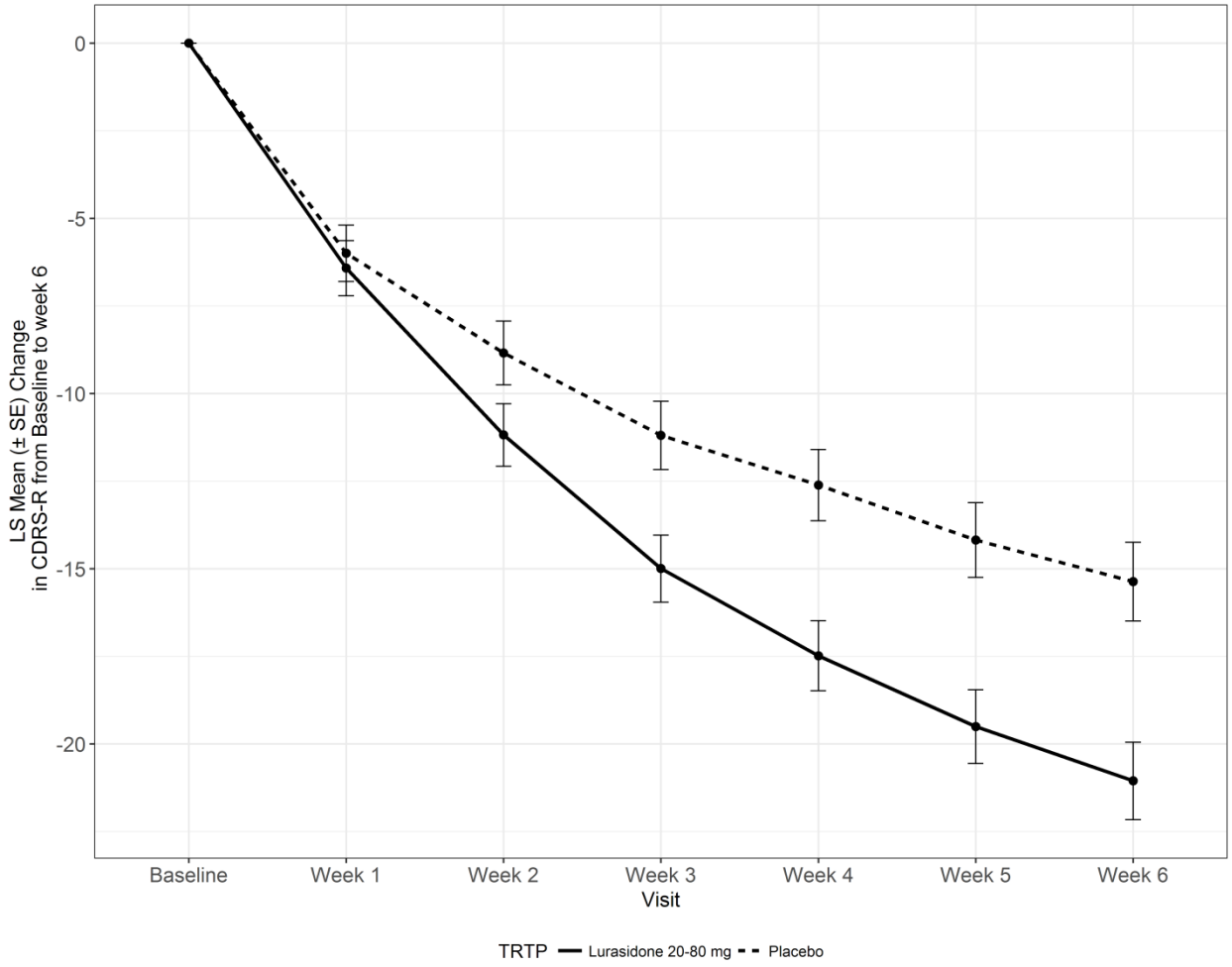
Endpoints	N	LS Mean (SE)	N	LS Mean (SE)	LS Mean Difference	Adjusted p-value
Primary Endpoint						
Change in CDRS-R Total Score	157	-15.3 (1.08)	161	-21.0 (1.06)	-5.7 (-8.4, -3.0)	<0.0001
Key Secondary						
Change in CGI-BP-S Depression Score	157	-1.05 (0.087)	162	-1.49 (0.085)	-0.44 (-0.66, -0.22)	<0.0001

Source: Recreated from Sponsor's data using Sponsor's submitted code. Matches Sponsor's Table 14.2.1.0.0.

Over the six week study period, the mean CDRS-R total score declined from baseline in both arms, see Figure 2. The lurasidone arm was statistically significantly different from placebo at week 2. Lurasidone arm remained separated from the placebo arm through week 6. Weekly least square (LS) means are presented in Table 6.

[1] Confidence interval is abbreviated CI.

Figure 2: CDRS-R Total Score - LS Mean (± SE) Change from Baseline over Time - Mixed Model for Repeated Measures (ITT Population)



Source: Reviewer

Table 6: CDRD-S Total Score - Change from Baseline over Time - Mixed Model for Repeated Measures (ITT Population)

CDRS-R Total Score	Placebo (N=170)	Lurasidone 20-80 mg (N=173)
Week 1		
n	170	173
LS Mean (SE)	-5.9 (0.74)	-6.3 (0.72)
Difference of LS Mean (SE) (vs. Placebo)		-0.5 (0.85)
95% CI of Difference (a)		(-2.1, 1.2)
Effect Size (vs. Placebo) (b)		0.06
p-value (vs. Placebo) (a)		0.5926
Week 2		
n	169	171
LS Mean (SE)	-8.7 (0.86)	-11.1 (0.84)
Difference of LS Mean (SE) (vs. Placebo)		-2.4 (1.04)
95% CI of Difference (a)		(-4.4, -0.3)

Effect Size (vs. Placebo) (b)		0.25
p-value (vs. Placebo) (a)		0.0238
Week 3		
n	167	167
LS Mean (SE)	-11.1 (0.92)	-14.9 (0.90)
Difference of LS Mean (SE) (vs. Placebo)		-3.8 (1.14)
95% CI of Difference (a)		(-6.1, -1.6)
Effect Size (vs. Placebo) (b)		0.36
p-value (vs. Placebo) (a)		0.0009
Week 4		
n	165	161
LS Mean (SE)	-12.5 (0.96)	-17.4 (0.95)
Difference of LS Mean (SE) (vs. Placebo)		-4.9 (1.22)
95% CI of Difference (a)		(-7.3, -2.5)
Effect Size (vs. Placebo) (b)		0.44
p-value (vs. Placebo) (a)		<0.0001
Week 5		
n	159	161
LS Mean (SE)	-14.1 (1.02)	-19.4 (1.00)
Difference of LS Mean (SE) (vs. Placebo)		-5.3 (1.30)
95% CI of Difference (a)		(-7.9, -2.8)
Effect Size (vs. Placebo) (b)		0.45
p-value (vs. Placebo) (a)		<0.0001
Week 6		
n	157	161
LS Mean (SE)	-15.3 (1.08)	-21.0 (1.06)
Difference of LS Mean (SE) (vs. Placebo)		-5.7 (1.39)
95% CI of Difference (a)		(-8.4, -3.0)
Effect Size (vs. Placebo) (b)		0.45
p-value (vs. Placebo) (a)		<0.0001

Source: Recreated from Sponsor's data using Sponsor's submitted code. Matches Sponsor's Table 14.2.1.1.1.

Two sensitivity analyses assessed departures from the missing at random (MAR) assumption from MMRM. The first sensitivity analysis used pattern mixture model (PMM1) with placebo-based multiple imputation, results found in Table 7. The week 6 LS mean difference from PMM1 was -5.4 (95% CI: -8.1, -2.7). The small difference in LS means (0.3) between PMM1 and MMRM showed that the primary MMRM is not sensitive to violations of MAR assumption.

The second sensitivity analysis was a pattern mixture model (PMM2) with two dropout patterns (completers and dropouts). The completers population consisted of all subjects who completed the six weeks of the study. The dropouts population consisted of all subjects who dropped out at any visit after week 1. PMM2 results were compared to a random effect model (REM) without any dropout pattern and a continuous time variable. In REM, the treatment effect (lurasidone by time interaction) was -2.7. In PMM2, the overall estimate of treatment effect (weighted average of the completer and dropout treatment effects) was -2.6. The pattern specific treatment effects were -2.7 for the completers and -1.2 for the dropouts. Detailed results are presented in Table 8

Reviewer's Note: The Sponsor interprets the results of PMM2 to indicate that REM is robust to patient dropout because the average PMM2 treatment effect is numerically close to the REM

treatment effect (difference = 0.1). This Review expected this result because the study had <10% missing data. However, the treatment effect differed by 1.5 units between the completer and dropout pattern.

Table 7: Sensitivity Analysis - Pattern Mixture Model with Placebo-based Multiple Imputation - CDRS-R Total Score (ITT Population)

	Statistic	Placebo (N=170)	Lurasidone 20-80 mg (N=173)
PMM with Placebo-based Multiple Imputation Result at Week 6	LS Mean (SE)	-15.3 (1.08)	-20.7 (1.07)
	Difference from Placebo		
	LS Mean Difference (SE)		-5.4 (1.39)
	LS Mean Difference 95% CI		(-8.1, -2.7)
	p-value		0.0001
MMRM Result at Week 6	LS Mean (SE)	-15.3 (1.08)	-21.0 (1.06)
	Difference from Placebo		
	LS Mean Difference (SE)		-5.7 (1.39)
	LS Mean Difference 95% CI		(-8.4, -3.0)
	p-value		<0.0001

Source: Recreated from Sponsor's data using Sponsor's submitted code. Matches Sponsor's Table 14.2.1.1.4.

Table 8: Sensitivity Analysis - Pattern Mixture Model with Two Patterns (Completers and Dropouts) - CDRS-R Total Score (ITT Population)

	Statistic	Intercept	Time	Lurasidone	Time* Lurasidone
REM	Model Estimate (SE)	56.9 (1.60)	-4.1 (0.94)	1.5 (1.01)	-2.7 (0.60)
	95% CI	(53.8, 60.1)	(-5.9, -2.2)	(-0.5, 3.5)	(-3.8, -1.5)
	p-value	<0.0001	<0.0001	0.1438	<0.0001
PMM Overall	Model Estimate (SE)	57.0 (1.60)	-4.1 (0.95)	1.4 (1.01)	-2.6 (0.60)
	95% CI	(53.9, 60.2)	(-6.0, -2.3)	(-0.5, 3.4)	(-3.8, -1.4)
	p-value	<0.0001	<0.0001	0.1523	<0.0001
PMM Completers	Model Estimate (SE)	56.7 (1.66)	-4.1 (0.98)	1.7 (1.05)	-2.7 (0.61)
	95% CI	(53.5, 60.0)	(-6.0, -2.2)	(-0.3, 3.8)	(-3.9, -1.5)
	p-value	<0.0001	<0.0001	0.0989	<0.0001
PMM Dropouts	Model Estimate (SE)	60.7 (5.84)	-4.5 (3.82)	-2.6 (3.85)	-1.2 (2.58)
	95% CI	(49.2, 72.1)	(-12.0, 3.0)	(-10.2, 4.9)	(-6.2, 3.9)
	p-value	<0.0001	0.2349	0.4957	0.6517

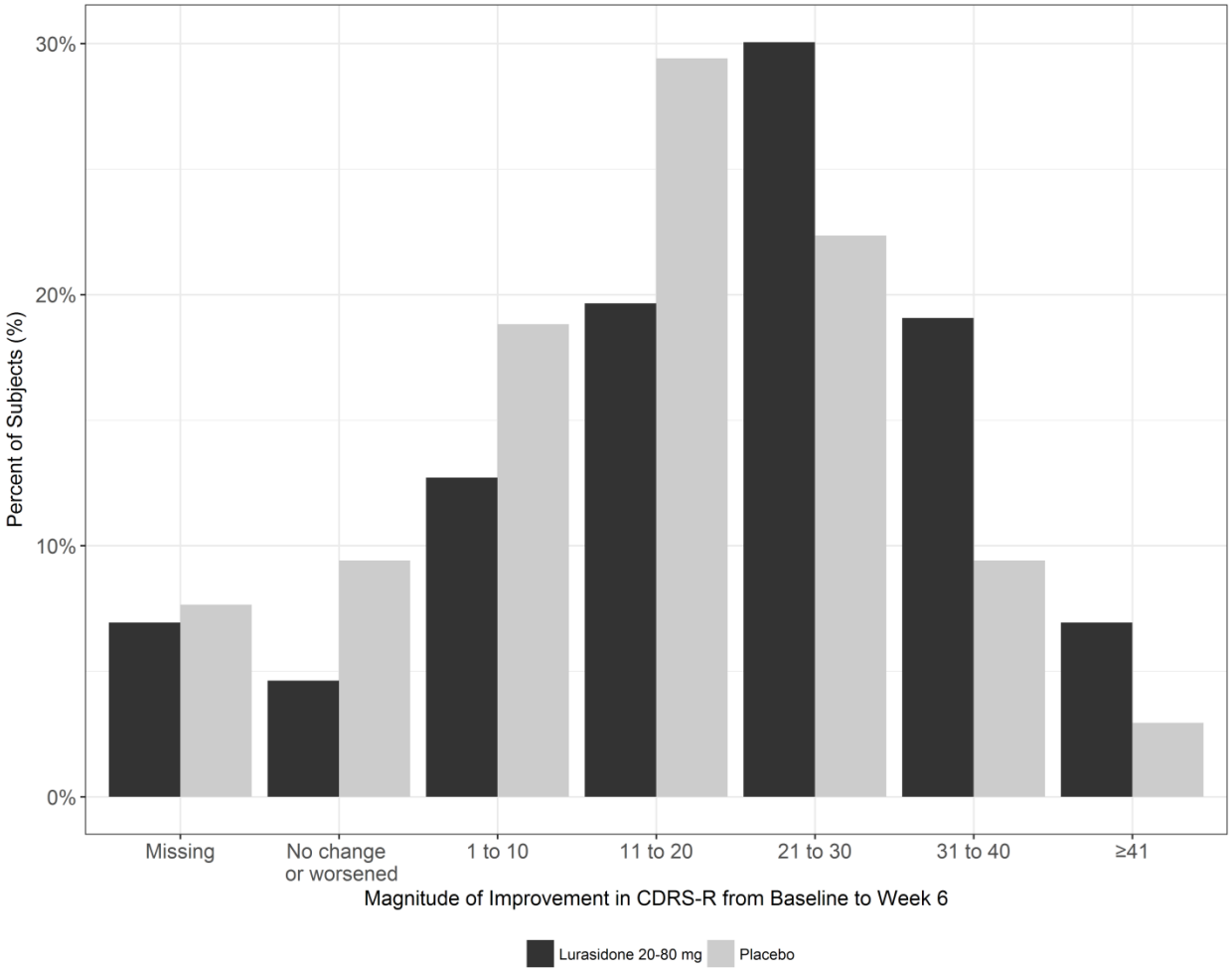
Source: Recreated from Sponsor's data using Sponsor's submitted code. Matches Sponsor's Table 14.2.1.1.5.

Reviewer's Results

This Reviewer recreated the results for the primary and key secondary endpoints in Study D10050326. In addition, this Reviewer verified the results of the pre-planned, blinded interim analysis conducted on June 10, 2016 by the blinded statistician. All patients enrolled before May 30, 2016 were included in this analysis. The mean change from baseline to week 6 was -18.7 with a standard deviation (SD) of 13.7. Because this SD was less than the assumed SD = 14.2, the blinded statistician recommended no sample size increase.

Figure 3 summarizes the response distribution of patients with bipolar depression to lurasidone to aid in the analysis of lurasidone's usefulness in treating bipolar depression. A patient can have one of three types of response: symptom improvement (measured as a positive change at week 6 in CDRS-R), worsening, or dropout out of the study. A useful drug's response distribution shows greater quantitative improvement (larger change from baseline CDRS-R scores) compared to placebo. In addition, a useful drug has fewer patients with worsening CDRS-R or no change in CDSR-R. The missing data category consists of patients where the drug is useful but still dropped out before the final study assessment and patients where the drug is not useful and dropped out because of the lack of usefulness. In Study D10050326, only 32 patients dropped out of the study. In Table 2, note that the frequency of dropout reasons is similar for both lurasidone and placebo. For visual clarity, all missing data is plotted in the same category. In Figure 3, the lurasidone arm's response distribution is shifted towards greater magnitude of improvement in CDRS-R scores compared to the placebo arm's response distribution. Dropout rates are similar between the two study arms, and dropout rates are low (<10%) in both arms. Because the dropout rate is low, the positive efficacy finding for lurasidone supports the usefulness of lurasidone in children ages 10-17.

Figure 3: Percentage of Subjects with Specified Magnitude of Change in CDRS-R Total Score (ITT Population)



Source: Reviewer

3.3 Evaluation of Safety

This review does not evaluate safety. Please refer to the clinical review for an evaluation of safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This section contains the results of this Reviewer's subgroup analyses. These exploratory analyses used the primary efficacy model (MMRM) with the addition of a subgroup by treatment interaction term. The week 6, LS mean, difference between lurasidone and placebo estimated the subgroup treatment effects as seen in Table 9.

Table 9: Subgroup Analysis - CDRS-R Total Score - Change from Baseline over Time for Specific Subgroups - Mixed Model for Repeated Measures (ITT Population)

Subgroup		Treatment Arm	Sample Size	Mean (SD)	LS Mean Difference from Baseline (SE)	LS Mean Difference from Placebo (95% CI)
Country	Bulgaria	Lurasidone	9	68.11 (10.24)	-10.50 (-18.97, -2.02)	5.57 (-6.54, 17.68)
		Placebo	8	67.13 (8.89)	-16.07 (-24.84, -7.29)	
	Colombia	Lurasidone	7	52.86 (6.18)	-25.84 (-35.20, -16.49)	-2.62 (-16.33, 11.08)
		Placebo	7	57.71 (12.46)	-23.22 (-33.26, -13.18)	
	Hungary, France, Poland	Lurasidone	8	61.25 (9.92)	-25.55 (-34.29, -16.81)	-5.34 (-17.68, 7.00)
		Placebo	8	60.50 (4.41)	-20.21 (-28.97, -11.45)	
	Korea, Philippines	Lurasidone	6	49.17 (4.45)	-16.22 (-26.41, -6.04)	6.68 (-10.84, 24.20)
		Placebo	3	63.33 (5.51)	-22.91 (-37.20, -8.61)	
	Mexico	Lurasidone	15	60.93 (9.92)	-21.35 (-27.91, -14.79)	-4.44 (-13.34, 4.47)
		Placebo	17	62.24 (11.16)	-16.91 (-22.97, -10.84)	
	Russia	Lurasidone	21	62.48 (8.08)	-23.42 (-28.85, -17.98)	-10.49 (-18.10, -2.87)
		Placebo	21	62.67 (6.95)	-12.93 (-18.39, -7.47)	
	Ukraine	Lurasidone	33	58.33 (6.79)	-20.10 (-24.45, -15.76)	-10.82 (-16.95, -4.70)
		Placebo	33	59.76 (6.24)	-9.28 (-13.72, -4.84)	
	United States	Lurasidone	74	58.49 (7.10)	-23.32 (-26.34, -20.30)	-4.09 (-8.30, 0.12)
		Placebo	73	54.78 (6.75)	-19.23 (-22.25, -16.21)	
Region	Non-US	Lurasidone	99	59.79 (8.99)	-20.91 (-23.53, -18.29)	-6.54 (-10.17, -2.91)
		Placebo	97	61.45 (8.16)	-14.37 (-17.06, -11.69)	
	US	Lurasidone	74	58.49 (7.10)	-23.40 (-26.48, -20.32)	-4.20 (-8.49, 0.097)
		Placebo	73	54.78 (6.75)	-19.21 (-22.28, -16.13)	
Age	10-12 years old	Lurasidone	38	59.08 (8.07)	-19.55 (-23.82, -15.29)	-3.71 (-9.70, 2.28)
		Placebo	37	56.84 (7.91)	-15.85 (-20.24, -11.45)	
	13-17 years old	Lurasidone	135	59.27 (8.31)	-21.40 (-23.72, -19.08)	-6.18 (-9.27, -3.10)
		Placebo	133	59.08 (8.31)	-15.22 (-17.56, -12.88)	
Age Strata	10-14 years old	Lurasidone	88	58.92 (7.98)	-18.84 (-21.70, -15.98)	-2.30 (-6.16, 1.56)
		Placebo	85	57.78 (7.73)	-16.55 (-19.43, -13.65)	
	15-17 years old	Lurasidone	85	59.55 (8.53)	-23.07 (-25.88, 20.26)	-9.01 (-12.84, -5.18)
		Placebo	85	59.40 (8.73)	-14.06 (-16.89, -11.23)	
Gender	Female	Lurasidone	85	61.02 (8.34)	-20.85 (-23.82, -17.88)	-5.98 (-9.87, -2.09)
		Placebo	83	60.52 (8.46)	-14.87 (-17.88, -11.86)	
	Male	Lurasidone	88	57.50 (7.80)	-21.21 (-24.10, -18.32)	-5.41 (-9.28, -1.54)
		Placebo	87	56.75 (7.67)	-15.80 (-18.71, -12.89)	
Race	Non-white	Lurasidone	39	56.59 (8.48)	-21.86 (-26.10, -17.63)	-2.26 (-7.84, 3.32)
		Placebo	45	58.96 (10.13)	-19.60 (-23.58, -15.62)	
	White	Lurasidone	134	60.00 (8.03)	-20.44 (-22.98, -17.90)	-6.96 (-10.07, -3.84)
		Placebo	125	58.46 (7.51)	-13.48 (-16.11, -10.86)	
Ethnicity	Hispanic or Latino	Lurasidone	31	58.35 (8.67)	-21.28 (-26.38, -16.17)	-5.39 (-11.78, 1.00)
		Placebo	33	60.15 (10.09)	-15.89 (-20.92, -10.85)	
	Not Hispanic or Latino	Lurasidone	142	59.42 (8.16)	-21.12 (-23.60, -18.64)	-5.77 (-8.81, -2.74)
		Placebo	137	58.21 (7.75)	-15.34 (-17.89, -12.80)	
ADHD Medication History	Currently taking ADHD Stimulant	Lurasidone	18	57.17 (8.02)	-12.46 (-18.71, -6.21)	-1.36 (-9.59, 6.87)
		Placebo	21	55.95 (5.72)	-11.10 (-16.85, -5.35)	
	Not currently taking ADHD Stimulant	Lurasidone	155	59.47 (8.25)	-21.79 (-24.02, -19.56)	-6.09 (-8.97, -3.21)
		Placebo	149	58.96 (8.50)	-15.70 (-18.00, 13.40)	
History of Rapid	Non-rapid cycling	Lurasidone	147	59.16 (8.34)	-20.90 (-23.23, -18.56)	-6.12 (-9.10, -3.14)
		Placebo	145	58.70 (8.20)	-14.78 (-17.13, -12.42)	

Cycling Bipolar	Rapid cycling	Lurasidone	26	59.62 (7.78)	-21.80 (-26.81, -16.80)	-3.12 (-10.12, 3.88)
		Placebo	25	57.96 (8.72)	-18.68 (-23.85, -13.51)	

Source: Reviewer.

4.1 Gender, Race, Age, and Geographic Region

Gender: Both males and females had similar treatment effects. The female treatment effect was -5.89, and the male treatment effect was -5.41. The study had generally equal numbers of males (placebo: 87, lurasidone: 88) and females (placebo: 83, lurasidone: 85) in each treatment arm.

Race: Non-white subjects had a smaller treatment effect (-2.26) than white subjects (-6.96). However, the study enrolled far less non-white subjects (placebo: 39, lurasidone: 45) than white subjects (placebo: 125, lurasidone: 134).

Age: Older subjects (age 13-17 years) had a greater treatment effect (-6.18) than younger subjects (age 10-12 years). This age effect was expected, and the Sponsor stratified the study on age (10-14 years vs. 15-17 years) to control for confounding due to age.

Geographic Region: Subjects in the United States (US) had a similar treatment effect (-4.20) compared to the rest of the world (-6.54). Within the non-US subjects, there was country-to-country variability. The Ukraine (-10.82, 66 subjects) and Russia (-10.42, 42 subjects) had the greatest treatment effect. In several regions, Bulgaria (5.57, 17 subjects) and Korea/Philippines (6.68, 9 subjects), the lurasidone arm worsened compared to placebo. However, the sample size was small in these regions.

4.2 Other Special/Subgroup Populations

History of ADHD stimulant medication: Subjects with a history of ADHD stimulant medication had a smaller treatment effect (-1.36) compared to subjects without a history of ADHD medications (-6.09).

Rapid cycling Bipolar Disorder (>3 cycles per 12 months): Subjects with a history of rapid cycling had a smaller treatment effect (-3.12) compared to subjects without rapid cycling (-6.12).

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

No statistical issues affected the primary and key secondary results.

5.2 Collective Evidence

The study D1050326 meet its primary and key secondary objective for demonstrating the efficacy of lurasidone (20mg – 80mg) for the treatment of bipolar depression in subjects aged 10-17 years. At 6 weeks, the lurasidone arm showed a 5.7 point improvement versus placebo as measured by CDRS-S. This result was statistically significant with $p < 0.0001$.

5.3 Conclusions and Recommendations

In study D1050326, flexibly dosed lurasidone (mean dose = 32.5mg, median dose = 30mg) was efficacious for the treatment of bipolar depression in children and adolescents aged 10-17 years old. Both the primary and key secondary endpoints reached statistical significance. This study fulfilled the PREA requirement 2058-1.

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/s/

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