Cross-Discipline Team Leader Review

Date	{See Appended Electronic Signature Page}
From	CDR Javier A. Muniz, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA 200603 S-029
Applicant	Sunovion Pharmaceuticals
Date of Submission	May 5, 2017
PDUFA Goal Date	March 5, 2018
Proprietary Name / **Established (USAN) names**	Latuda lurasidone
Dosage forms / Strength	20 mg, 40 mg, 60 mg, 80 mg, and 120 mg tablets
Proposed Indication(s)	Treatment of major depressive episodes associated with bipolar I disorder in pediatric patients aged 10 and older
Recommended:	Approval

1. Introduction and Background

Lurasidone (Latuda) is an atypical antipsychotic first approved in October, 2010. It is indicated for the treatment of schizophrenia in adults and pediatric patients aged 13 to 17 years. Lurasidone is also approved for the treatment of major depressive episodes associated with bipolar I disorder (bipolar depression) in adults, alone or as adjunctive treatment with lithium or valproate. The recommended starting dose is 40 mg/day for adults and adolescents with schizophrenia, with a recommended maximum dose of 160 mg/day and 80 mg/day, respectively. The recommended starting dose for adult patients with bipolar depression is 20 mg/day, with a maximum dose of 120 mg/day.

Lurasidone was approved for bipolar depression in adults on June 28, 2013. Among the Post-Marketing Requirements (PMRs) outlined in the approval letter, the Applicant (Sunovion) was instructed to conduct a controlled efficacy and safety study of lurasidone in the treatment of pediatric patients (ages 10 to 17 years) with a diagnosis of depressive episode associated with bipolar disorder (PMR 2058-1). This sNDA is intended to fulfill this requirement and expand the bipolar depression indication to include monotherapy for pediatric patients aged 10 and older. This submission is primarily supported by Study D1050326, a Phase 3, 6-week, multi-center, double-blind, placebo-controlled, flexible-dose, parallel-group trial designed to evaluate the efficacy and safety of lurasidone in pediatric patients aged 10 and above with bipolar depression.

The efficacy trial submitted with 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. Lurasidone is approved for pediatric schizophrenia; however, the trial exploring the effects of lurasidone in irritability related to autism was negative and the drug is not approved for this indication. Patients from all three trials were enrolled into Study D1050302, an open-

label, 104-week, multicenter, lurasidone long-term safety trial in pediatric patients. Study D1050302 was designed to fulfill PMR 2058-2 (described in the adult bipolar depression monotherapy approval letter, dated June, 2013). Study D1050302 is currently ongoing and only preliminary results were submitted with this application.

2. CMC/Device

No new CMC information was submitted with this application.

3. Nonclinical Pharmacology/Toxicology

No new non-clinical information was submitted with this application.

4. Clinical Pharmacology/Biopharmaceutics

This submission includes the results for Study D1050300, a pediatric pharmacokinetic (PK) study to satisfy PMR 1701-1. However, the complete study report for this trial was previously reviewed and found to be acceptable by the Office of Clinical Pharmacology (OCP) reviewer, Praveen Balimane, PhD, in Supplement 26 and 27. The PK results are currently included in the product's existing label. Dr. Balimane recommends approval of this supplement from an OCP perspective.

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical- Efficacy

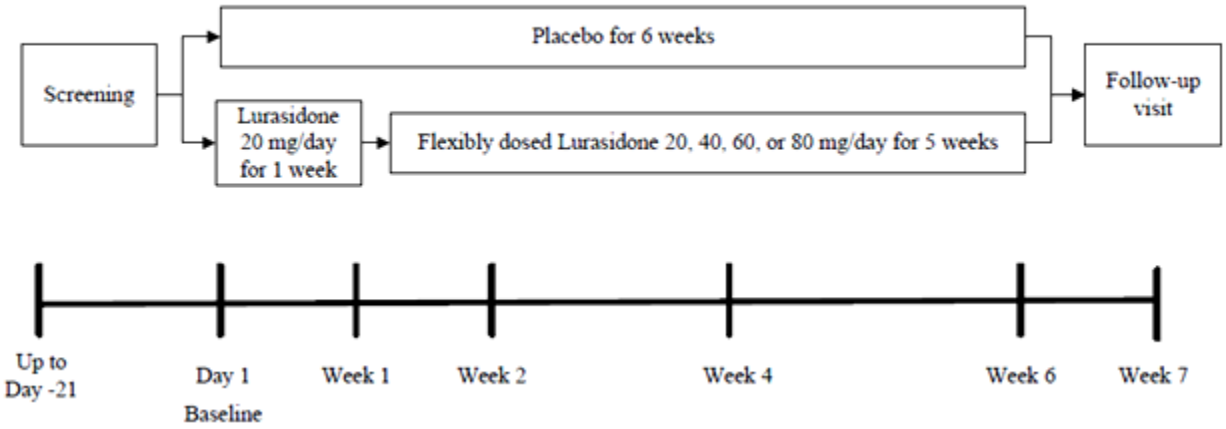
Nancy Dickinson, PharmD, was the clinical reviewer for this sNDA; she recommends approval.

The Applicant seeks to expand the bipolar depression indication to pediatric patients aged 10 and older based on the results of Study D1050326, a 6-week, multi-center, double-blind, placebo-controlled, flexible dose, parallel-group study designed to evaluate the efficacy and safety of lurasidone for the proposed indication.

The original protocol was reviewed under IND 103427 and the trial design is virtually identical to the trial conducted to gain the bipolar depression indication for adults (see Figure 1). The study was conducted at 64 sites in 11 countries (Bulgaria, Colombia, France, Hungary,

Mexico, Philippines, Poland, Russia, South Korea, Ukraine, and the US). 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 associated with bipolar I disorder. 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.

Figure 1: Study Design Schematic, Study D1050326



[Source: Study D1050326's CSR, Figure 1, page 26.]

Lurasidone was started at a 20 mg/day oral dose in all subjects. After seven days of 20 mg/day, the dose could be increased up to a maximum of 80 mg per day at the discretion of the Investigator. If necessary, efficacy-driven dose changes were permitted at the weekly visits. Dose reductions for safety or tolerability were also allowed.

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. The CDRS-R is one of the most widely used rating scales for assessing depression severity and change in depressive symptoms for clinical research trials in children and adolescents with depression. It is a 17-item scale, with items ranging from 1 to 5 or 1 to 7 (possible total score from 17 to 113), rated by a clinician via interviews with the child and parent. A score of ≥40 is indicative of depression, whereas a score ≤28 is often used to define remission (minimal or no symptoms). 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). The 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), Week 1, 2, 4, and 6. A follow-up visit was scheduled for Week 7.

A total of 350 subjects were randomized, 174 subjects to placebo and 176 to lurasidone. Three subjects were randomized but not dosed (two in the placebo arm and one 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.

In the ITT population, gender distribution was similar (51% male vs. 49% female). 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 (56.8% Non-US vs. 43.9% US). No other meaningful differences were observed among treatment groups for any of the other demographic variables. The overall demographics of the patient population in this study support applicability of the study results to the United States population. At baseline, subjects had a CDRS-R mean total score of 58.9 with a range in scores from 44 to 82. Baseline CGI-BP-S depression scores ranged from three to six with a mean score of 4.5.

In the Applicant's analysis, 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 : -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 ($p < 0.0001$). Efficacy results are summarized in Table 1 below.

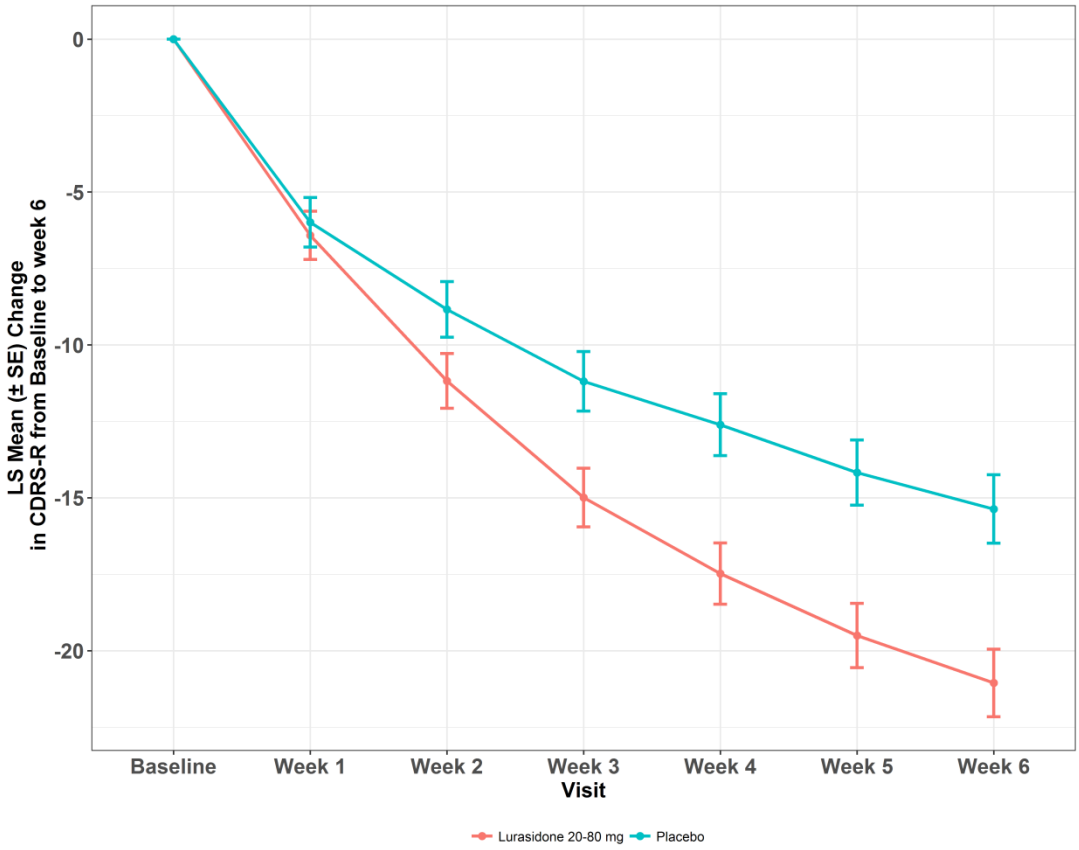
Table 1: CDRS-R Total Score and CGI-S-BP Depression Score at Six Weeks (ITT Population)

Endpoints	Placebo N	LS Mean (SE)	Lur 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: Biostatistics review, Table 5, page 11]
Recreated from submitted data by the biostatistical reviewer. Matches Applicant's Table 14.2.1.0.0
Lur=lurasidone

Over the six weeks of the study, the mean CDRS-R total score declined from baseline in both arms (see **Error! Reference source not found.**). The lurasidone arm was statistically significantly different from placebo at Week 2.

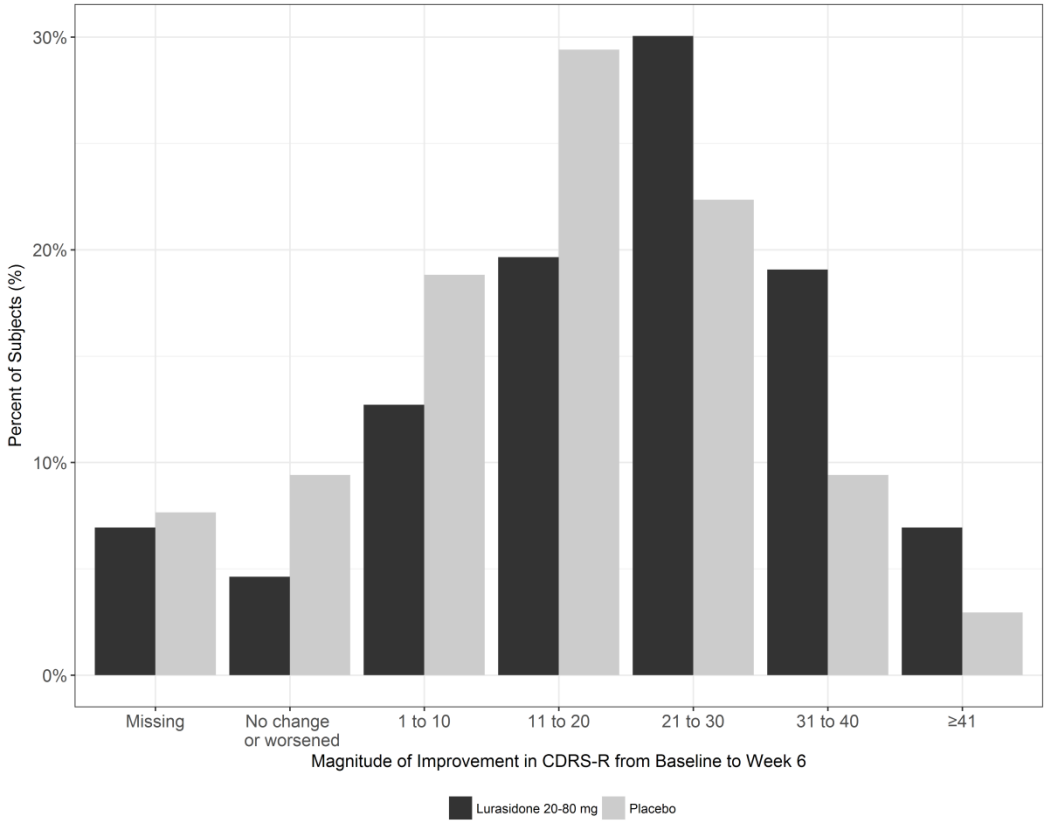
Figure 2: CDRS-R Total Score - LS Mean (± SE) Change from Baseline over Time - Mixed Model for Repeated Measures (ITT Population)



[Source: Dr. Andrew Potter, Biostatistics review, Figure 2, page 12]

Dr. Andrew Potter was the biostatistical reviewer for this supplement. Dr. Potter was able to replicate the results for the primary and key secondary endpoints in Study D1050326 as well as the Applicant's sensitivity analyses. In his review, Dr. Potter summarizes the response distribution of patients with bipolar depression to lurasidone (see Figure 3).

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



[Source: Dr. Andrew Potter, Biostatistics review, Figure 3, page 16]

Additionally, Dr. Potter conducted various exploratory subgroup analyses to include analyses by gender, age, psychiatric history, geographic region, etc. Of note, subjects in the United States had a similar treatment effect (-4.20) compared to the rest of the world (-6.54).

In his review, Dr. Potter concludes: "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." Dr. Potter recommends approval of this supplement.

7. Safety

In general, the safety data submitted with this sNDA are consistent with the known safety profile of lurasidone.

No deaths occurred during Study D1050326. No serious adverse events (SAEs) occurred in more than one subject. Treatment-emergent AEs occurring in more than 5% of patients treated with lurasidone and at a rate at least twice as common as placebo were nausea, headache, weight gain, and insomnia. No suicidal or self-injurious behavior occurred in patients treated

with lurasidone. The rate of treatment-emergent mania was similar between the placebo and the lurasidone arms.

Study D1050302 is a 104-week open-label trial designed to assess the long-term safety profile of lurasidone (dosed 20-80 mg per day) in pediatric patients recruited from the pediatric schizophrenia (Study D1050301), bipolar depression (Study D1050326), and autism trials. This study was scheduled for completion last December, 2017. The Applicant submitted preliminary data for 619 patients participating in this trial with a cutoff date of October, 2016. Additionally, the 120-day safety update submitted with this application focused on the available safety data from 305 patients recruited from Study D1050326 with a cutoff date of May, 2017. It should be noted that although the final report for Study D1050302 has not been submitted for review, the Applicant presented acceptable long-term data to make an approval determination for this sNDA, including lurasidone exposure of 153 patients for ≥ 52 weeks.

Dr. Dickinson reviewed the high-level safety data (i.e., deaths, SAEs, etc.) provided in the 120-day safety update. There were no deaths reported. Most SAEs occurred in the Psychiatric Disorders System Organ Class, likely representing exacerbations of the underlying illness being treated. For pediatric patients, metabolic AEs are of particular interest to us; 32 (10.5%) subjects reported metabolic treatment-emergent AEs. The most common metabolic event was weight increased, reported by 24 (7.9%) subjects. The available long-term safety data for Study D1050302 is generally consistent with lurasidone's known safety profile and the safety data submitted with Study D1050326.

Furthermore, the Division of Pharmacovigilance (DPV) in the Office of Surveillance and Epidemiology (OSE) conducted a review of postmarketing lurasidone AEs in the FDA Adverse Event Reporting System (FAERS) and the medical literature to provide additional safety information in pediatric patients less than 18 years of age. No concerning trends or safety findings were identified in DPV's review or the postmarketing data.

Dr. Dickinson's notes that, in general, older pediatric patients (13 to 17 years of age) appear to tolerate lurasidone better and have lower rates of drug discontinuation. Her review of the safety data submitted with this supplement, as well as the available pediatric postmarketing reports included in DPV's review, revealed no safety findings that would require a labeling revision, preclude approval of this supplement, or necessitate other regulatory action.

8. Advisory Committee Meeting

No advisory committee meeting was held for this supplemental application. The evaluation of the safety data did not reveal safety issues that were unexpected for this class, and the design and results of the efficacy trial did not pose concerns.

9. Pediatrics

As previously discussed, Study D1050326 was conducted to fulfill PMR 2058-1. In addition, the Applicant has the following outstanding pediatric Post-Marketing Requirements:

- 2058-2: A long-term, open-label safety study of study of lurasidone in the treatment of pediatric patients (ages 10 to 17 years) with a diagnosis of depressive episode associated with bipolar disorder

Study D1050302 is currently ongoing and it is intended to fulfill this PMR.

10. Other Relevant Regulatory Issues

The review team did not request for the Office of Scientific Investigations (OSI) to investigate any of the clinical sites.

Dr. Richard Jackson, a sub-investigator at one of the clinical sites, declared that he received honoraria and expense reimbursement from Sunovion totaling (b) (6) between 2011 and 2015 related to speaking engagements and trainings. The Applicant explained that Dr. Jackson's compensation did not exceed $25,000 in 2013, when he became a sub-investigator for Study D1050326. Any potential conflict of interest was avoided as the Applicant did not include clinical data from Dr. Jackson's study site (Site 041) in the submission.

11. Labeling

Labeling was updated to include a description of Study D1050326 in the Clinical Studies section. In addition, modifications were made throughout the label for consistency with recent class labeling changes. The Applicant agreed to these changes.

12. Recommendations/Risk Benefit Assessment

Sufficient information has been submitted to conclude that lurasidone is safe and effective for the treatment of bipolar depression in pediatric patients aged 10 and above. No new safety signals were identified that would alter the overall benefit-risk assessment for this drug. The label and the medication guide have been negotiated to current Division standards. The review team has unanimously recommended approval of this supplement; I agree with their recommendation. This application should be approved by the PDUFA date.

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

/s/

JAVIER A MUNIZ
03/05/2018

MITCHELL V Mathis
03/05/2018