# CLINICAL REVIEW

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| **Application Type** | NDA |
| **Application Number(s)** | 200603 S-029 |
| **Priority or Standard** | Standard |
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| **Division/Office** | Division of Psychiatry Products/ ODE 1 |
| **Reviewer Name(s)** | Nancy Dickinson |
| **Review Completion Date** | 3/5/18 |
| **Established/Proper Name** | lurasidone |
| **(Proposed) Trade Name** | Latuda |
| **Applicant** | Sunovion |
| **Dosage Form(s)** | Tablet |
| **Applicant Proposed Dosing Regimen(s)** | One tablet QD |
| **Applicant Proposed Indication(s)/Population(s)** | Treatment of bipolar I depression in children and adolescent patients (aged 10 to 17 years) |
| **Recommendation on Regulatory Action** | Approval |
| **Recommended Indication(s)/Population(s)** (if applicable) | Treatment of depressive episodes associated with Bipolar I Disorder (bipolar depression) in pediatric patients (aged 10 to 17 years) |

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## Glossary

| | |
|---|---|
| AE | adverse event |
| AR | adverse reaction |
| BPCA | Best Pharmaceuticals for Children Act |
| BRF | Benefit Risk Framework |
| CDRS-R | Children's Depression Rating Scale, Revised |
| CDER | Center for Drug Evaluation and Research |
| CDTL | Cross-Discipline Team Leader |
| CFR | Code of Federal Regulations |
| CMC | chemistry, manufacturing, and controls |
| COSTART | Coding Symbols for Thesaurus of Adverse Reaction Terms |
| CRF | case report form |
| CRO | contract research organization |
| CRT | clinical review template |
| CSR | clinical study report |
| CSS | Controlled Substance Staff |
| DMC | data monitoring committee |
| ECG | electrocardiogram |
| eCTD | electronic common technical document |
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act of 2007 |
| FDASIA | Food and Drug Administration Safety and Innovation Act |
| GCP | good clinical practice |
| GRMP | good review management practice |
| ICH | International Council for Harmonization |
| IND | Investigational New Drug Application |
| ISS | integrated summary of safety |
| ITT | intent to treat |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NDA | new drug application |
| NME | new molecular entity |
| OCS | Office of Computational Science |
| OPQ | Office of Pharmaceutical Quality |
| OSE | Office of Surveillance and Epidemiology |
| OSI | Office of Scientific Investigation |
| PBRER | Periodic Benefit-Risk Evaluation Report |
| PD | pharmacodynamics |
| PI | prescribing information or package insert |

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|---|---|
| PK | pharmacokinetics |
| PMR | postmarketing requirement |
| PPI | patient package insert |
| PREA | Pediatric Research Equity Act |
| PRO | patient reported outcome |
| PSUR | Periodic Safety Update report |
| REMS | risk evaluation and mitigation strategy |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SOC | standard of care |
| TEAE | treatment emergent adverse event |

# 1. Executive Summary

## 1.1. Product Introduction

Lurasidone (Latuda; NDA 200603) is an atypical antipsychotic first approved in October, 2010. It is indicated for the treatment of schizophrenia in adults and pediatric patients 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. Lurasidone is available in 20, 40, 60, 80, and 120 mg tablets. 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, titrating up to 120 mg/day.

The purpose of this supplemental NDA is to seek approval of lurasidone in the treatment of children and adolescents (10 to 17 years) with bipolar depression as monotherapy. The Applicant conducted the pediatric trial to meet a postmarking requirement (PMR 2058-1). For bipolar I depression in pediatric patients, the recommended starting dose of lurasidone is 20 mg given once daily. Initial dose titration is not required, but the dose may be increased after one week based on efficacy to a maximum recommended dose of 80 mg/day.

I recommend approval for this efficacy supplement, Supplement 029. The efficacy of luradisone for the treatment of bipolar depression in pediatric patients (10 to 17 years) was adequately demonstrated. No safety findings could be identified that would preclude approval of lurasidone for this indication in pediatric bipolar patients.

## 1.1. Benefit-Risk Assessment

**Benefit-Risk Integrated Assessment**

Bipolar I disorder is a serious, chronic psychiatric condition that may lead to significant distress, substance abuse, violence, and suicide if left untreated. The goal of treating bipolar depression is remission of depression without precipitation of mania or hypomania. Although there are various treatments approved for bipolar I disorder, there are only three atypical antipsychotics specifically approved for the treatment of depressive episodes associated with bipolar I disorder in adults. The drugs are olanzapine/fluoxetine, quetiapine, and lurasidone. Olanzapine/fluoxetine and quetiapine are approved in pediatric patients (10 to 17 years) for treatment of acute bipolar depression.

In the pediatric population, lurasidone was effective based on a 6-week efficacy trial and partial efficacy extrapolation from the study of bipolar depression in adults. The efficacy trial was well-designed and robustly positive (p-value < 0.0001) on the primary and key secondary endpoints.

My review of safety for lurasidone in pediatric patients (10 to 17 years) indicate that lurasidone is relatively well-tolerated. The most common adverse reactions compared to placebo were nausea (16%), somnolence (9%), weight gain (7%), and vomiting (6%). These finding are consistent with the lurasidone label for other indications. In the 6-week efficacy trial, lurasidone generally demonstrated low risk of metabolic adverse events (e.g., hyperglycemia, dyslipidemia, weight gain, etc.). Monitoring the weight gain over time in pediatric patients would be required because lurasidone is expected to be taken chronically to treat the depressive episodes in bipolar I disorder.

No deaths were reported in data from long-term open-label safety study. The most serious adverse events were reported in Psychiatric Disorder (8.1%) and Injury System Organ Classes (2.7%), (n=619). My analysis of the long-term data submitted and the 120-day safety update identified no new safety signals beyond those seen in the 6-week efficacy study. There was a higher incidence of adverse events leading to discontinuation in younger patients (10 to 12 years, [16.1%]) compared to adolescents (13 to 17, [7.4%]).

I concluded that the risk-benefit ratio of lurasidone for treatment of bipolar depression in pediatric patients (10 to 17 years) is considered favorable. Approval is recommended.

**Benefit-Risk Dimensions**

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of Condition | • Bipolar I disorder is a serious, chronic psychiatric illness affecting 2% of adults and approximately 0.5% of pediatric patients.<br>• Bipolar I disorder is underdiagnosed in pediatric patients due to comorbidities, such as ADHD and possible presentation of depressive episodes first.<br>• Patients with bipolar I disorder cycle through episodes of mania and depression. The depressive episodes may last three times longer than the manic episodes.<br>• The risk of suicide in bipolar I disorder is twice that of unipolar depression.<br>• If untreated, bipolar I disorder may lead to substance abuse, violence, and suicide.<br>• About 50% of patients with bipolar I disorder have a history of a suicide attempt. | Bipolar I disorder is a serious, chronic psychiatric illness presenting with cycles of mania and depression. Patients with bipolar I disorder are at high risk for suicidality, especially if untreated with medication. |
| Current Treatment Options | • Three atypical antipsychotics are specifically approved for the treatment of depressive episodes in bipolar I disorder in adults: lurasidone, quetiapine, and olanzapine/fluoxetine.<br>• Two of those are approved for pediatric patients (10 to 17 years).<br>• Atypical antipsychotics are increasingly becoming first-line treatment.<br>• Due to the risk of triggering a manic or mixed episode, antidepressants are not preferred, but may be used adjunctly if patients are acutely suicidal.<br>• Mood stabilizers treat the manic episodes, but should be taken chronically. The addition of lithium, valproate, carbamazepine, or lamotrigine may be helpful for bipolar depression. | Atypical antipsychotics, mood stabilizers, and sometimes antidepressants are used to treat bipolar I disorder. Only two drugs are approved for treatment of bipolar depression in pediatric patients. Those are quetiapine and olanzapine/fluoxetine. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Benefit | • Lurasidone demonstrated robust efficacy on primary and key secondary endpoints in pediatric patients.<br>• Lurasidone has a low incidence of metabolic syndrome adverse events.<br>• The dose is convenient, once daily.<br>• Relatively well-tolerated.<br>• There was no difference in extrapyramidal symptoms (EPS) between lurasidone and placebo. | Lurasidone demonstrated robust efficacy in a 6-week study in pediatric patients. The drug is already approved for depressive episodes in bipolar I disorder in adults. During the short-term efficacy study, lurasidone demonstrated a low incidence of metabolic adverse events. |
| Risk and Risk Management | • The risk of common antipsychotic adverse effects (especially extrapyramidal symptoms [EPS], and metabolic syndrome) remains, despite low incidence of akathisia and weight gain seen in the 6-week efficacy trial.<br>• The postmarket adverse event review in pediatric patients < 18 years listed some events to monitor, but no labeling changes are necessary.<br>• Both somnolence (9%) and insomnia (5%) were reported.<br>• Nausea was the most reported adverse reaction with lurasidone. Based on the food effect study, lurasidone should be taken with a 350 kcal meal, but food appears to not decrease the nausea. | Although relatively low incidence of weight gain and EPS, lurasidone is still an atypical antipsychotic with class adverse events. A patient's weight gain over time should be monitored by the prescriber. Postmarket adverse event monitoring should be conducted. Administration may be moved to once daily in the morning or evening in case of somnolence or insomnia. |

# 2. Therapeutic Context

## 2.1. Analysis of Condition

The lifetime prevalence of bipolar disorder in the United States is over 2% for adults. The U.S. prevalence in pediatric patients is 0.5% but may be confounded by comorbidity with Attention Deficit Hyperactivity Disorder, as some symptoms overlap.

In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), bipolar disorder encompasses seven types of bipolar disorder. The bipolar I disorder criteria in the DSM-5 represent the modern understanding of the classic manic-depressive disorder. Patients with bipolar I disorder must experience a manic episode that may be followed by depressive episodes. A patient with bipolar I disorder may spend up to three weeks depressed for every one week they are manic. The goal of treating bipolar depression is remission of depression without precipitation of mania, mixed episodes, or hypomania. Research has shown that antidepressant use for the bipolar depression may trigger manic episodes or rapid cycling. Bipolar I disorder is a serious condition that may lead to substance abuse, violence, and suicide if not treated. About 50% of patients with bipolar I disorder have a history of a suicide attempt.

## 2.2. Analysis of Current Treatment Options

The mainstay of pharmacotherapy for bipolar disorder is a mood stabilizer, such as lithium, lamotrigine, and valproate, although these drugs are not FDA-approved for bipolar depression. Depressive episodes in bipolar I disorder may be challenging to treat due to the risk of triggering a switch to mania from the addition of an antidepressant. If the patient's bipolar depression does not respond to one mood stabilizer, a second one or an atypical antipsychotic may be added. Atypical antipsychotics may also be first-line treatment for bipolar depression.

In 2013, FDA approved the first two drugs, atypical antipsychotics, for the pediatric indication of treatment for depressive episodes in bipolar I disorder. Lurasidone gained the indication for adults in 2013. Table 1 compares the three approved drugs to treat bipolar depression. Generally, lurasidone poses a low risk of metabolic adverse events (hyperglycemia, dyslipidemia, and weight gain) in adults.

**Table 1: FDA-approved drugs for depressive episodes in bipolar I disorder**

| Product (s) Name | Relevant Indication | Year of Approval | Route and Frequency of Administration | Efficacy Information | Important Safety and Tolerability Issues |
|---|---|---|---|---|---|
| Latuda (lurasidone) | Bipolar depression | 2013 | Oral tablet 20 to 120mg/day Take with 350 calorie meal. | adults | DDI with strong CYP3A4 inhibitors; low risk of metabolic syndrome |
| Symbyax (Olanzapine and fluoxetine) | Acute Bipolar depression with fluoxetine | 2013 (pediatric) | capsules 3mg/25mg to 12mg/50mg | Adults Pediatrics (10 to 17) | High risk of Metabolic syndrome |
| quetiapine | Acute bipolar depression | 2013 (pediatric) | Oral tablet 300 mg | Adults Children adolescents | Moderate risk of metabolic syndrome |

(Source: Reviewer modified from Pharmacist's Letter)

# 3. Regulatory Background

## 3.1. U.S. Regulatory Actions and Marketing History

Latuda (lurasidone), NDA 200603, was approved October 28, 2010, for treatment schizophrenia in adults. On January 27, 2017, the indication for treatment of schizophrenia was broadened to include treatment of adolescents (13 to 17 years old).

On June 28, 2013, lurasidone was approved for monotherapy and adjunctive therapy for bipolar depression in adults. In that approval letter, we issued two PREA postmarketing requirements (PMRs) for patients, 10 years and older, with bipolar depression:

- PMR 2058-1, a now completed short-term efficacy and safety study, and
- PMR 2058-2, an ongoing open-label, long-term safety study.

On May 5, 2017, based on the Sunovion's fulfillment of the 6-week safety and efficacy study, the Applicant submitted an efficacy supplement (Supplement 029) to expand the indication to pediatric patients, 10 to 17 years.

## 3.2. Foreign Regulatory Actions and Marketing History

Lurasidone is also approved by the European Medicines Agency and Health Canada. In Asia, lurasidone is approved for adult schizophrenia in Russia, Singapore, Taiwan, and Thailand. The Applicant and their global business partners plan t (b) (4) .

Pediatric indications for lurasidone are not currently approved in foreign countries.

## 3.3. Conclusions on the Substantial Evidence of Effectiveness

As noted in the Executive Summary, I am recommending approval for lurasidone in pediatric patients. Per 21 CFR 314.126, the Applicant's drug development program for demonstrates substantial evidence of effectiveness to support approval for the indication of treatment of depressive episodes associated with bipolar I disorder in pediatric patients 10 to 17 years.

Sunovion conducted one controlled 6-week efficacy and safety trial (Study D1050326) in the target population, age group 10 to 17. The primary and key secondary endpoints showed robust efficacy which occurred on Week 2 and continued through Week 6. Additionally, we can partially extrapolate efficacy from adult trials. Lurasidone is approved in adults for treatment of bipolar I depression using the same efficacy study design.

## 3.4. Application Data Integrity and Submission Quality

**Data Integrity**

The Division of Psychiatry Products filed Sunovion's efficacy supplement on June 27, 2017. From a clinical perspective, the application was written in a straightforward manner and inclusive of the necessary information in the electronic Common Technical Document (eCTD) format. The submission included standard (SDTM) and analysis (ADaM) data. There were no issues uploading the data for my review purposes. The Applicant coded the adverse events using MedDRA 16.0. I agreed with how the Applicant lumped adverse event terms into broader categories of insomnia, somnolence, and extrapyramidal symptoms. However, I did not agree with the coding of "possibly related" or "not related" so I avoided using that category my safety assessment. I did not request additional information from the Applicant.

Around the time of filing the application, the Biostatistics Reviewer requested additional raw efficacy data from Study D1050326 from the Applicant. He then could adequately review the

data.

**Compliance with Good Clinical Practices**

The Applicant attests that the studies, which include foreign clinical sites, were conducted in accordance with good clinical practice.

**Financial Disclosure**

Overall, there are no conflicts of interest that affect the integrity of Supplement 029.

Study D1050326 had 391 total investigators. Seventy-four were principal investigators and 317 were sub-investigators. At clinical site 041, one sub-investigator, Richard Jackson, MD, declared financial compensation from Sunovion in excess of $25,000 since 1999. Dr. Jackson declared that he received honoraria and expense reimbursement totaling (b) (6) between 2011 and 2015 from Sunovion for speaking engagements and speaker training.

The Applicant explained that Dr. Jackson's amount of compensation had not exceeded $25,000 in 2013, when he became a sub-investigator for Study D1050326. The Applicant chose not to include clinical site 041 in the analysis data. Therefore, there is not a conflict of interest.

# 4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

## 4.1. Office of Scientific Investigations (OSI)

At the time of filing this application, the team decided not to request an OSI audit.

## 4.2. Product Quality

No CMC information was submitted in Supplement 029.

## 4.3. Clinical Microbiology

No clinical microbiology information was submitted in Supplement 029.

## 4.4. Nonclinical Pharmacology/Toxicology

No nonclinical information was submitted in Supplement 029.

## 4.5. Clinical Pharmacology

The lurasidone efficacy Supplement 029 contains clinical pharmacology data. One clinical pharmacology study (Study D1050300) was conducted in support of this submission. Study D1050300 was an open-label, multicenter, single and multiple ascending dose study to evaluate the pharmacokinetics (PK), safety, and tolerability of lurasidone at doses of 20 mg, 40 mg, 80 mg, 120, and 160 mg in 105 subjects aged 6 to 17 years with schizophrenia spectrum, bipolar spectrum, autistic spectrum disorder, or other psychiatric disorders. Lurasidone doses were taken with a 350 kilocalorie meal.

The PK study enrolled 6 to 9 year olds, but were the PREA PMR for pediatric bipolar I disorder, dated June 28, 2013, required ages 10 to 17 years because study of bipolar disorder in children younger than 10 years is highly impractical.

**Results of Study D1050300**

The pharmacokinetic and pharmacodynamic (PD) parameter findings were consistent with the existing labeling, including dose adjustments (e.g., hepatic or renal impairment, drug-drug interactions via CYP3A4).

The clinically relevant PK and PD results in pediatric patients were:

- Lurasidone exposure (i.e., steady-state Cmax and AUC) in children and adolescent patients (10 to 17 years of age) was generally similar to adults across the dose range from 40 to 160 mg, without adjusting for body weight.
- Older subjects (13-15 and 16-17 years) appeared to have higher oral clearance than younger subjects (6-9 years and 10-12 years) and adults.

The pharmacology study evaluated tolerability of lurasidone at doses of 20 mg, 40 mg, 80 mg, 120 mg, and 160 mg in 105 subjects aged 6 to 17 years. The subjects in the 6 to 9 year age group experienced tolerability difficulties (moderate or severe vomiting, sedation, and somnolence) during the 120 mg dosing scheme. Doses greater than 120 mg were therefore not evaluated in the 6 to 9 year age group. Further, the subjects in the 10 to 17 year age group reported most treatment emergent adverse events (TEAEs) in the 120 mg and 160 mg dosing schemes. The most frequently reported TEAEs were somnolence, sedation, vomiting, nausea, upper abdominal pain, and dystonia.

Presumably, based on the tolerability results, the age range and dose range for the planned 6-week efficacy study were modified. The age range increased to 10 to 17 years and the dose range decreased to 20 mg, 40 mg, 60 mg, and up to 80 mg.

There are no clinical safety issues stemming from the Study D1050300 that preclude approval.

Refer to the Clinical Pharmacology Reviewer's review for more detail.

# 5. Sources of Clinical Data and Review Strategy

## 5.1. Review Strategy

The Applicant submitted three sources of clinical data in Supplement 029 as described in Table 2. There is a clinical pharmacology study, a short-term efficacy study in the pediatric (10 to 17 years) bipolar I disorder population, and an ongoing long-term extension safety study.

My review strategy for lurasidone in the treatment of bipolar I depression in pediatric patients includes analysis of multiple sources:

- The review of efficacy stems from review of Study D1050326 efficacy data and our Biostatistical Reviewer's review.
- The review of safety is derived from the raw safety data of the short-term and long-term (up to cut-off date) studies, the 120-Day Safety Report, dated September 5, 2017, and the Division of Pharmacovigilance's review of postmarket adverse events of lurasidone in patients <18 years old.
- I used JMP Clinical 6.0 to analyze safety data and demographics from Study D1050326 and the long-term safety study (D1050302). I reviewed adverse events among age sub-groups and the breakdown of dose by age. Additionally, I assessed if the Applicant correctly combined similar MedDRA terms, such as insomnia.
- Lastly, I used DARRTS and Drugs@FDA to find background information.

## 5.2. Table of Clinical Studies

The following Table 2 describes the clinical studies of lurasidone in pediatric patients. The two completed pediatric trials submitted in Supplement 029 are a designated pharmacokinetic study and a 6-week safety and efficacy study (Study D1050326).

Study D1050326 was a six-week, double-blind, randomized, placebo-controlled study. It was conducted at 64 sites in 11 countries (Bulgaria, Colombia, France, Hungary, Mexico, Philippines, Poland, Russia, South Korea, Ukraine, and United States).

Table 2 also describes the ongoing long-term safety extension study (Study D1050302) including pediatric patients with different psychiatric diagnoses. Data from this study, up to a cut-off point (October 2016), was submitted with Supplement 029. Further results from the ongoing safety study were submitted in the 120-day safety update.

**Table 2: Clinical Studies of Lurasidone in Supplement 029**

| Study Type | Study Identifier | Objective(s) of the Study | Study Design and Type of Control | Lurasidone Dosage Regimen | Number of Subjects Entered/ Completed | Diagnosis of Pts | Duration of Treatment with Lurasidone | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| PK Study | D1050300 | To characterize the PK and assess safety of single and multiple oral doses of lurasidone in pediatrics; To characterize the PK of lurasidone metabolites | Open-label, Multicenter, SAD/MAD | lurasidone 20, 40, 80, 120, or 160 mg/day; qd; single dose; ;multiple dose; po | 105/90 | Schiz; Bipolar; Autism; ADHD in subjects aged 6-17 years | 10 to 12 days | Completed; Full report |
| Phase 3 Efficacy and Safety | D1050326 PMR 2058-1 | To evaluate the efficacy of lurasidone *vs.* placebo in children and adolescent subjects with bipolar I as measured by the change from baseline on CDRS-R, CGI-BP-S, and safety assessments | Double-blind, randomized, placebo-controlled, multi-center, fixed dose study | lurasidone 20 to 80 mg/day; qd; po | 350/318 | Bipolar I in subjects aged 10-17 years | 6 weeks | Completed; Full report |
| Long-term Safety | D1050302 | To evaluation the long-term safety of lurasidone in children and adolescent subjects with bipolar I | Open-label, extension | Lurasidone flexible dose 20 to 80 mg/day | 305 entered by 5/5/17 cut-off date | Schiz; Bipolar; Autism in subjects aged 10-17 years | 104-weeks | Ongoing; interim report in 120-day safety update |

(Source: Reviewer created)

# 6. Review of Relevant Individual Trials Used to Support Efficacy

## 6.1. Study D1050326- 6-week, randomized, double-blind, placebo-controlled study of efficacy and safety of lurasidone in children and adolescent subjects with bipolar I depression

### 6.1.1. Study Design

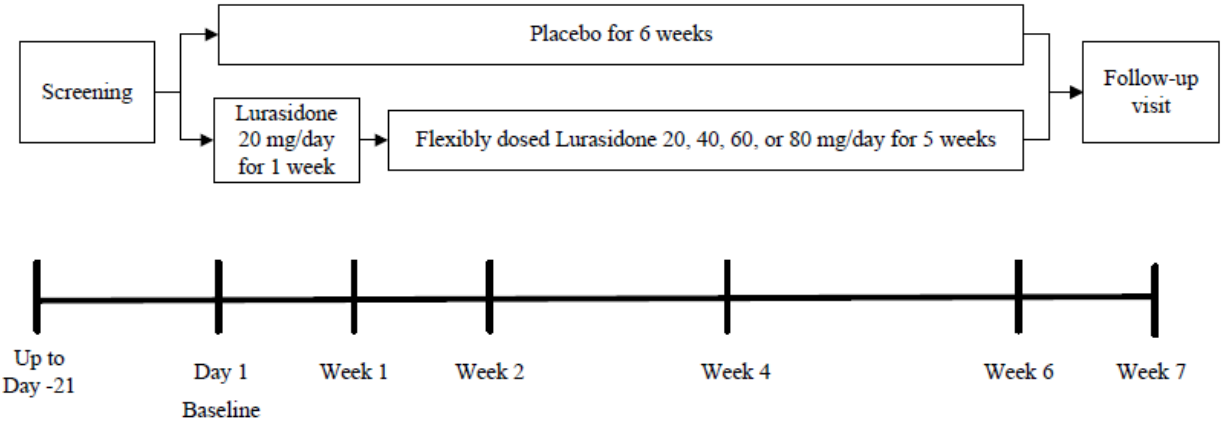
**Overview and Objective**

Study D1050326 was a 6-week, randomized, double-blind, placebo-controlled, flexible dose, parallel-group study to evaluate the efficacy and safety of lurasidone 20 to 80 mg/day in children and adolescent patients with depression associated with bipolar I disorder.

**Trial Design**

Study D1050326 had three periods of the trial: screening, treatment phase, and follow-up. During the 21-day screening period, eligible subjects were tapered off all psychotropic medications except those permitted in the protocol. Following the screening period, subjects who continued to meet entry criteria were randomly assigned in a 1:1 ratio to either lurasidone (20 to 80 mg/day, flexibly dosed) or placebo. The double-blind treatment period was 6-weeks. See the schematic diagram of study design in Figure 1. Subjects who completed the study were eligible to participate in a separate 104-week open-label extension study (D1050302).

**Figure 1: Study Design Schematic of D1050326**




(Source: Figure 1 on page 26 of clinical study report dated 4/28/17.)

**Subjects**

Study D1050326 evaluated 350 male or female patients 10 to 17 years with a DSM-5 diagnosis of bipolar I disorder, the most recent episode depressed, with or without rapid cycling disease course (≥4 episodes of mood disturbance but < 8 episodes in the previous 12 months) and without psychotic features. Patients could have been inpatient, outpatient, or partially hospitalized and could have been attending therapeutic day programs, other supported rehabilitation programs, or school.

Enrolled patients also were relatively healthy and their guardian consented to attend study visits with the patient. Patients weight was within the 3rd to 97th percentile for gender-specific body mass index (BMI)-for-age growth charts from the World Health Organization (WHO).

Exclusion criteria include:

- Primary psychiatric diagnosis other than bipolar I disorder (e.g. Axis I or Axis II diagnosis, psychosis).
- Neurological disorder including intellectual disability, autism spectrum disorder, severe head trauma, chromosomal disorder with developmental impairment, or chronic organic disease of the central nervous system (CNS).
- Subjects were excluded if they had a Children's Depression Rating Scale, Revised (CDRS-R) total score > 85 at screening or baseline, a decrease of ≥ 25% in the CDRS-R adjusted total score between screening and baseline, or a CDRS-R total score < 45 at baseline.
- Moderate or severe extrapyramidal symptoms, dystonia, tardive dyskinesia, or any other severe movement disorder.
- History of electroconvulsive therapy.
- Treatment-resistance to antipsychotics or antidepressants.
- Imminent risk of suicide or injury to self, others, or property during the study, as judged by the Investigator.

Medications:

Prohibited medications were antidepressants (including monoamine oxidase inhibitors), mood stabilizers (e.g., lithium, divalproex/valproic acid, carbamazepine), and additional antipsychotic medications (except for lurasidone).

Allowed medications were benzodiazepines, anticholinergics, medications for somatic illness (e.g. antacids), and sleeping medications.

**Dosing**

Three hundred fifty patients (350) were randomized to lurasidone or placebo. The lurasidone group enrolled 176 patients and there were 174 patients in the placebo group.

The patients who were randomized to lurasidone were dosed at 20 mg for seven days (Day 1 to Day 7). Flexible dosing (20 to 80 mg/day) of study drug was permitted after seven days (i.e., beginning on Day 8), based on Investigator's judgment, to optimize efficacy and tolerability. Dose adjustments, when necessary, were to occur at weekly visits. However, dose reductions for tolerability or safety purposes were permitted any time and could be more than one dose level (i.e. 20 mg) at a time (maximum of two dose levels at a time), beginning at Day 8.

Subjects randomized to the placebo arm received matching placebo from Day 1 to Week 6. The study drug was administered orally once daily, in the evening, with a meal of at least 350 calories or within 30 minutes after eating.

**Study Efficacy Endpoints**

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 based on the adult Hamilton Depression Rating Scale and was originally developed as a rating scale for children aged 6–12 years. 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), weeks 1, 2, 4, and 6. A follow-up visit was scheduled for Week 7.

Other secondary endpoints were:

- Change in anxiety symptoms as measured by the Pediatric Anxiety Rating Scale (PARS);
- Change in quality of life as measured by the Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q);
- Change in social and psychiatric functioning as measured by the Clinician-rated Children's Global Assessment Scale (CGAS);

- Treatment response, defined as ≥ 50% reduction from baseline in CDRS-R adjusted total score;
- Symptom remission, defined as CDRS-R total score ≤ 28 and Young Mania Rating Scale (YMRS) total score ≤ 8 and CGI-BP-S depression score ≤ 3 at Endpoint; and
- Change in attention deficit hyperactivity symptoms as measured by the Attention Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS) score.

I particularly liked the use of two secondary endpoints. The Young Mania Rating Scale (YMRS) was used to evaluate if lurasidone may trigger a manic episode or hypomania, which is a concern in the treatment of depressive episodes in bipolar disorder. The ADHD-RS was important because differential diagnosis between bipolar I disorder and ADHD could be difficult in younger pediatric patients. There can be symptom overlap or comorbidity, so the ADHD-RS could assess if the lurasidone affected the severity of ADHD.

**Safety Assessment**

The safety assessments in Study D1050326 include:

- Baseline physical examination;
- Weight, body mass index (BMI), and waist circumference;
- Monitoring of adverse events;
- Laboratory measurements;
- Vital signs and electrocardiogram (ECG) measurements;
- Treatment-emergent mania, defined as YMRS score of ≥ 20 on any two consecutive visits or at the final assessment;
- Suicidal ideation using the Columbia Suicide Severity Rating Scale (C-SSRS);
- Movement disorders assessed by the Barnes Akathisia Rating Scale (BARS), the Abnormal Involuntary Movement Scale (AIMS), and the Simpson-Angus Scale (SAS); and
- Pregnancy testing, Tanner staging, and menstrual cyclicity in female subjects).

A Data and Safety Monitoring Board (DSMB) reviewed the safety and clinical outcome data, including data on adverse events and (AEs) and serious AEs (SAEs), at regular intervals. The DSMB was independent of the Applicant, contract research organization (CRO), and the Investigators and was empowered to recommend stopping the study due to safety concerns, but not for efficacy or futility.

For long-term safety assessment, patients who completed the study were eligible to participate in a separate 104-week open-label extension study (D1050302).

**Statistical Analysis Plan**

The Applicant conducted a blinded interim analysis after 90% of patients enrolled; no sample size adjustment was necessary. All efficacy analyses were conducted using the Intent-to-Treat (ITT) population. The ITT population (N=343) consisted of all randomized subjects who received at least one dose of lurasidone. The primary analysis was a Mixed-effect Model Repeat Measurement (MMRM) analysis for both the primary and key secondary endpoints' change in scores from baseline to week 6. Refer to the Biostatistics Reviewer's review for more detail.

### 6.1.2. Study Results

**Efficacy Results**

The well-designed 6-week efficacy study, Study D1050326, of lurasidone in pediatric patients (10 to 17 years) demonstrated efficacy. The study design matched Sunovion's 6-week adult study for treatment of depressive episodes associated with bipolar I disorder. Study D1050326 used an age-appropriate scale, the CDRS-R, as the primary endpoint, instead of the Montgomery-Asberg Depression Rating Scale as in the adult study.

Study D1050326 demonstrated robust efficacy on the primary and key secondary endpoints of CDRS-Rand CGI-BP-S, respectively. The change from baseline to six weeks on both endpoints showed statistical significance with a p-value of <0.0001. See Table 3 for the effect size and confidence intervals, which also supported efficacy of lurasidone over placebo. Duration of effect over six weeks was demonstrated by statistical significance between lurasidone and placebo from Week 2 to end of the study.

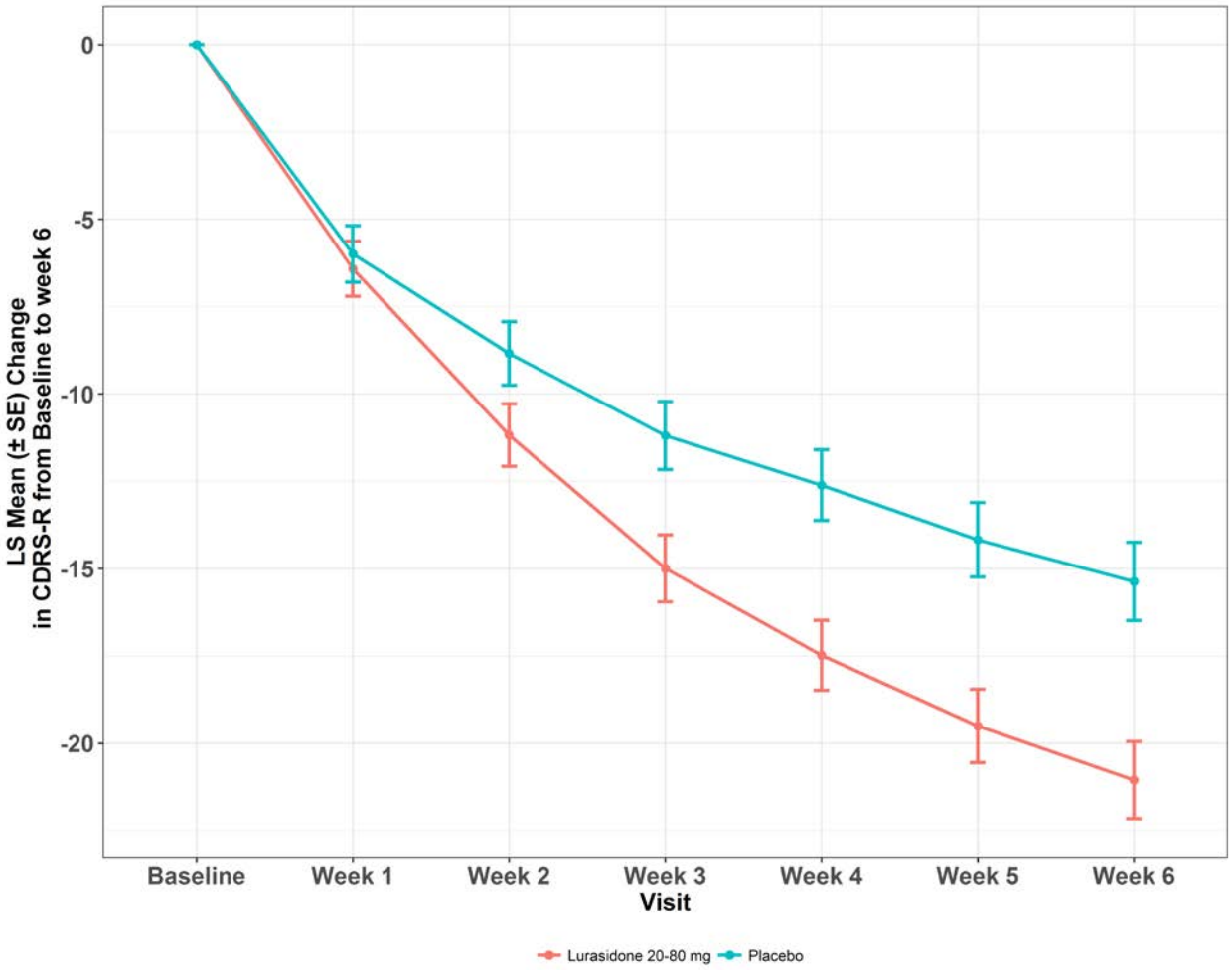
**Table 3: CDRS-R Total Score and CGI-S-BP Depression Score at Six Weeks (ITT population)**

| **PRIMARY ENDPOINT**<br>**CDRS-R Total Score**<br>**Week 6** | **Placebo**<br>**(N=170)** | **Lurasidone 20 to 80 mg/day (N=173)** |
|---|---|---|
| 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 | - | −8.4, −3.0 |
| Effect Size (vs Placebo) [b] | - | 0.45 |
| p-value (vs Placebo) | - | <0.0001 |
| **KEY SECONDARY ENDPOINT**<br>**CGI-BP-S Depression Score** | **Placebo (N=170)** | **Lurasidone 20 to 80 mg/day (N=173)** |
| n | 157 | 162 |
| LS Mean (SE) | −1.05 (0.087) | −1.49 (0.085) |
| Difference of LS Mean (SE) (vs Placebo) | - | −0.44 (0.112) |
| 95% CI of Difference | - | −0.66, −0.22 |
| Effect Size (vs Placebo) | - | 0.44 |
| p-value (vs Placebo) | - | <0.0001 |

(Source: Modified Applicant's tables 14.2.1.1.1 and 14.2.2.1.1)

After one week of treatment, the lurasidone and placebo treatments groups started to separate, indicating change in CDRS-R from baseline, in Figure 2. The lurasidone group had significantly greater reduction in depressive symptoms on the CDRS-R than placebo beginning at Week 2 and continuing through Week 6.

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




(Source: Biostatistics Reviewer's review)

Using the Applicant's efficacy endpoint dataset, the Biostatistics Reviewer, Andrew Potter, replicated the robust efficacy findings from changes from baseline in the primary and key secondary endpoints. Refer to his review for more detail on analysis of the efficacy data.

Study D1050326 was a global trial in 11 countries (Bulgaria, Colombia, France, Hungary, Mexico, Philippines, Poland, Russia, South Korea, Ukraine, and United States). We analyzed the foreign data, finding that efficacy data from some countries differed from the treatment effect in U.S. subjects. Within the non-U.S. subjects, there was country-to-country variability in the treatment effect. Most likely, the variability was related to data collection technique or cultural differences in treatment of bipolar I disorder in southeast Asia. Specifically, the greatest treatment effect occurred in the Ukraine and Russia. In three countries, Bulgaria, Korea, and

the Philippines, the lurasidone arm worsened compared to placebo. However, the sample size was small in those regions. The efficacy sub-analysis conducted by Dr. Potter did not affect efficacy of lurasidone in U.S. subjects.

**Patient Disposition**

Study D1050326 enrolled 350 patients. Of those, 174 subjects were randomized to placebo and 176 subjects were randomized to lurasidone. Three subjects were randomized but not dosed, yielding 347 subjects in the safety population.

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 phase for reasons of lack of efficacy or treatment emergent adverse events (AEs). The adverse events will be discussed in the Review of Safety Section 8.0. Refer to the Biostatistical Reviewer's review for more detail and a tabular description of all randomized subjects' disposition.

**Protocol Violations**

Three protocol violations occurred during the Study D1050326. Two protocol violations in the placebo arm and one in the lurasidone arm. The violations were lack of post baseline CDRS-R assessment. The small number of protocol violations did not impact analysis of efficacy.

**Demographic Characteristics**

The population of Study D1050326 can be generalized to U.S. bipolar I disorder pediatric patients. The ITT population was balanced by sex, with half the subjects 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 by age with strata 10-14 years and 15-17 years in an attempt to balance the numbers of subject in age subgroups. The age groups were not balanced between 75 children (10 to 12 years) and 268 adolescents (13 to 17 years). The smaller numbers of 10 to 12 year-olds could be explained by lack of bipolar I disorder diagnosis in younger patients.

The majority of subjects were white (74.9%), 10.4% of subjects were black or African American, and 14.8% of subjects were Asian or other. More than half of subjects were from outside the United States (US) (56.8% Non-US vs. 43.9% US).

The racial and ethnicity percentages of the study population appear to represent the population of the United States (U.S.), despite the population containing more non-U.S.

patients (56.8%) than U.S. patients (43.9%). This finding does not impact the efficacy results because the global study population is from most included countries with similar culture as the U.S.

See Table 4 for demographics of sex, age, race, and geographical regions of the study population.

**Table 4: Demographic Characteristics (ITT Population)**

| Characteristic | Placebo (N=170) | Lurasidone 20-80 mg (N=173) | Total (N=343) |
|---|---|---|---|
| **Sex, 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, 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 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) |

(Source: Study D1050326 Table 14.1.2.1 Modified by reviewer)

**Other Baseline Characteristics**

The Applicant accounted for facets of the study population to make the efficacy results more generalizable to the U.S. bipolar depression patients.

**Rapid cycling in bipolar I disorder**

In Study D1050326, the subjects were stratified into treatment groups based on their history of rapid cycling. Rapid cycling may be a predeterminant of switching from a depressive episode into a manic episode. The patients were evenly randomized by history of rapid cycling to avoid impact to either treatment group. About 25% of the bipolar patients had a history of rapid cycling, which roughly represents the occurrence in bipolar I disorder. See Table 5 for the stratification numbers by treatment group.

**Table 5: Study D1050326: Course of Illness for ITT population**

| Course of Illness | Statistic | Placebo (N=170) | Lurasidone 20 to 80 mg/day |
|---|---|---|---|
| Without rapid cycling (0 to 3 cycles within past 12 months) | n (%) | 145 (85.3) | 147 (85.0) |
| With rapid cycling (4 to 7 cycles within past 12 months) | n (%) | 24 (14.1) | 26 (15.0) |
| With rapid cycling (8 or more cycles within past 12 months) | n (%) | 1 (0.6) | 0 (0.0) |

(Source: Modified from Applicant's Table 7, page 27)

**Concomitant Medications**

Capturing data on concomitant medication use in Study D1050326 represented a reasonable generalization for multiple medication use, including psychotropics, taken by bipolar I patients in the postmarket setting. In Table 6, the two treatment groups were comparable with about 50% patients in the treatment groups receiving concomitant medications, including somatic medications such as acne treatment or antibiotics.

**Table 6: Number of subjects with concomitant medication by treatment group**

| Number of subjects | Placebo Group [n (%)] N=170 | Lurasidone Group [n (%)] N=173 | Total [n (%)] N=343 |
|---|---|---|---|
| With any concomitant medication | 84 (49.4) | 91 (52.6) | 175 (51.0) |

(Source: Reviewer created from Table 14.1.7.2.1)

Concomitant use of benzodiazepines, as a rescue medication, was balanced between placebo and lurasidone arms. The placebo group had 10% benzodiazepine usage (N=17) and the lurasidone group had 12.1% usage (N=21). Lorazepam was by far the most commonly prescribed benzodiazepine at 79% of the total usage (30 lorazepam/38 patients with concomitant benzodiazepines).

See Table 7 for the percentages of concomitant medications used during the Study D1050326. Antidepressants and antipsychotics were on the prohibited list of medications in the protocol. However, they are listed in the concomitant medications and not explained by the Applicant.

**Table 7: Concomitant psychiatric-related medications among treatment groups**

| Concomitant Medication | Placebo Group [n (%)] N=170 | Lurasidone Group [n (%)] N=173 |
|---|---|---|
| Benzodiazepines | 17 (10) | 21 (12.1) |
| Stimulants (for ADHD) | 12.4 | 10.4 |
| Anticholinergics | 1 (0.6) | 2 (1.2) |
| Sedative hypnotics | 21 (12.4) | 19 (11.0) |
| Antidepressant (fluvoxamine) | - | 1 (0.6) |
| Antipsychotic (risperidone) | - | 1 (0.6) |
| Antiepileptics | 1 (0.6) | 4 (2.3) |

(Source: Reviewer created)

**Dose**

Study D1050326 evaluated 20, 40, 60, or 80 mg/day doses of lurasidone. Based on the robust efficacy findings stated above and the percentages of subjects taking each dose, lurasidone appears to be effective at lower doses. At Week 6, 67% of patients were receiving lower lurasidone doses (i.e., 20 or 40 mg/day).

The mean of the average total daily dose for lurasidone subjects during the double-blind period was 32.6 mg overall, with a predominant dose of 20 mg (51.8%), followed by 40 mg (26.5%). At baseline, the mean total daily dose for lurasidone subjects was 19.91 mg; this mean dose increased at each visit through Week 5, at which point the mean dose was 42.02 mg. Similar trends were seen in each age group (10 to 12 years old and 13 to 17 years old). See Table 8.

**Table 8: Mean Lurasidone dose by age group during double-blind period of Study D1050326**

| | Lurasidone mg per day (10 to 12 years) n=38 | Lurasidone mg per day (13 to 17 years) n=130 |
|---|---|---|
| Mean (SD) | 30.2 (11.2) | 33.1 (13.1) |
| Median | 28.1 | 31.4 |
| Min | 18 | 18 |
| Max | 60 | 64 |

(Source: Modified Applicant's table 14.1.6.4.1)

As explained in the study design, doses were increased on a weekly timeframe based on efficacy and tolerability. A higher percentage of patients taking lurasidone were receiving lower (e.g. 20 and 40 mg/day) doses at the end of the double-blind period (Week 6) than in the placebo group. One patient in the 10 to 12 year age group and fourteen in the 13 to 17 years group received 80 mg per day (Table 9). Additionally, the placebo group's average weekly dose was higher at Week 6, compared to lurasidone group. This could be explained by investigators increasing the dose of blinded placebo due to lower efficacy. See Table 9.

**Table 9: Average weekly dose of lurasidone or placebo at Week 6 of N=322 completers**

| Dose | Lurasidone arm (% pts) | Placebo arm (% pts) |
|---|---|---|
| 20 and 40 mg/day | 67 | 53 |
| 20 mg/day | - | 30 |
| 40 mg/day | - | 23 |
| 60 mg/day | 19 | 19 |

| | | |
|---|---|---|
| 80 mg/day | 14 | 28 |

(Source: Reviewer created using Biostatistics Reviewer data)

# 7. Integrated Review of Effectiveness

## 7.1. Assessment of Efficacy Across Trials

Section 7.1 is not applicable to this clinical review because there is one efficacy study.

## 7.2. Integrated Assessment of Effectiveness

Lurasidone is effective for treatment of depressive episodes in pediatric patients age 10 to 17 years diagnosed with bipolar I disorder. The following reasons support my conclusion:

1. The positive efficacy findings of the 6-week, randomized, placebo-controlled, efficacy study support lurasidone for the indication of treatment of bipolar depression in pediatric patients.
2. The Applicant has submitted substantial evidence of effectiveness: robust statistical significance was met on acceptable primary and secondary endpoints.
3. The biostatistician replicated the Applicant's efficacy findings.
4. The study was of similar design as other studies the Agency has accepted for the proposed indication (i.e., bipolar I depression).
5. The demographics are generalizable to the U.S. bipolar I population. Further analysis showed that removal of the subjects from Russia, Ukraine, Bulgaria, and Philippines still resulted in statistical significance.
6. The study population characteristics of concomitant medication use and rapid cycling are also generalizable to the U.S. bipolar I population.
7. Both age groups (10 to 12 years and 13 to 17 years) demonstrated response to similar mean doses, which were the lower doses.

# 8. Review of Safety

## 8.1. Safety Review Approach

My approach to the safety review was to focus on Study D1050326, the efficacy trial. Then I expanded my analysis to include the safety information submitted thus far for the ongoing 104-

week long-term safety study, D1050302.

I took the following steps for my approach to the safety review of Supplement 029:

1. First, I reviewed the Applicant's written explanation of safety, entitled Clinical Safety in eCTD 2.7.4.
2. Second, I analyzed the safety datasets for Study D1050326 and the ongoing long-term safety study, D1050302, using the tools JMP 13.0 and JMP Clinical 6.0. The ADaM and STDM files were located under eCTD 5.3.5.1 and 5.3.5.2.
3. Third, I reviewed the 120-day Safety Update.

## 8.2. Review of the Safety Database

### 8.2.1. Overall Exposure

Lurasidone was approved in 2010 and has a relatively well-known safety profile. The current lurasidone label says that adult trial exposure totals 1250.9 patient-years, including exposure data on 326 adolescents (13 to 17 years) with schizophrenia and additional data in younger patients with autism disorder (6 to 17 years).

Lurasidone exposure in pediatric patients (10 to 17 years) diagnosed with bipolar I depression was 334.0 subject-years, as of the May 5, 2017, the cut-off date for the 120-day Safety Update. The 334.0 subject-years includes exposure from both Study D1050326 and the long-term safety study (Study D1050302).

Although the Sunovion provided exposure data by 7-day increments for both the trials, it is more meaningful to view the age and number of patients exposed to lurasidone in 6-month increments. See Table 10. After completion of the ongoing Study D1050302, the number of subject-years will increase.

**Table 10: Exposure to lurasidone by age and 6-month or 12-month timepoints**

| Indication | Age Range | Any Exposure, n (%) | Exposure ≥ 26 Weeks, n (%) | Exposure ≥ 52 Weeks, n (%) |
|---|---|---|---|---|
| Bipolar Depression | 10-12 | 68 (100) | 50 (73.5) | 36 (52.9) |
| | 13-17 | 256 (100) | 195 (76.2) | 117 (45.7) |
| **Total** | **10-17** | **324 (100)** | **245 (75.6)** | **153 (47.2)** |

(Source: Modified from Applicant's 120-day Safety Update- 9/5/17)

### 8.2.2. Adequacy and characteristics of the safety population:

**Safety Database**

The size of the safety database is acceptable. In addition to the number of patients in lurasidone efficacy and long-term safety trial, there is extensive adult experience with the drug, the off-label use in pediatric patients, and data from the lurasidone schizophrenia trial in adolescents.

Lurasidone exposure in pediatric patients (10 to 17 years) for 52 weeks or more was n= 153. That number exceeds the minimum ICH E1A guidelines for size of a safety database for non-life-threatening conditions. The E1A guidelines say "100 patients exposed for a minimum of one-year is considered to be acceptable to include as part of the safety database".

The number of pediatric patients (10 to 17 years) with bipolar I disorder was adequate to access safety. The size of the safety database in Study D1050326 is 347 for 6-weeks. There were 172 patients in the placebo arm and 175 in the lurasidone arm, totaling 347. Three hundred five (305) patients from the 6-week efficacy study continued in the long-term safety study (D1050302), all receiving lurasidone.

By the cut-off date for this application (October 2016), Study D1050302 enrolled a total of 619 pediatric patients, 305 bipolar I disorder plus 314 from Sunovion's other pediatric lurasidone trials. Again, the size of the Applicant's safety database was adequate to assess both short and long-term safety.

**Demographics of safety database**

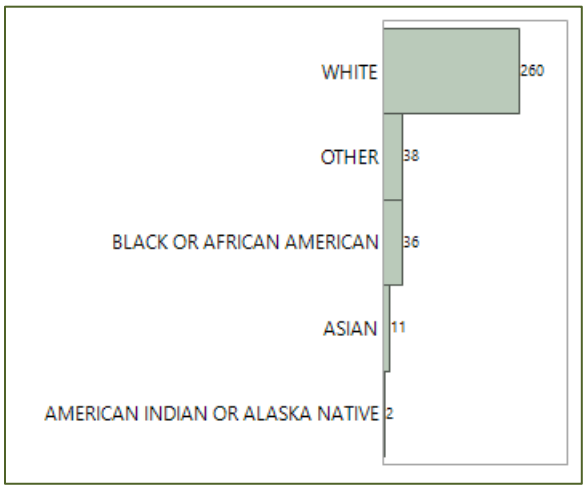
**Study D1050326**

The safety database from Study D1050326 (N=347) included three subjects more than the Intent to Treat population (N=343). The demographics and relevance to U.S. bipolar patients were discussed in Section 6.1.2, table of demographics. Therefore, I only included the highlights of my analysis in this section.

The bipolar population in Study D1050326 was balanced in each treatment arm by gender, race, concomitant medication use, and history of rapid cycling. Overall, the study population is applicable to the U.S. population and known racial and age-group prevalence of bipolar I disorder in the United States.

The racial distribution in Study D1050326 is generalizable to the U.S. population, with Whites being the majority and African-Americans and those subjects identifying with Latino ethnicity being the next prevalent groups. In the global study, most of the patients were White (74.9%) and did not identify with Hispanic or Latino ethnicity (81.3%). There were 10.3 % African-Americans (36/347) and 10.9% Other. See Figure 3. Based on my analysis of population by study site, the Other category was generally patients from Colombia (n=14) and Mexico (n=33), which make up 13.5 % (47/347) of the study population. Hence, the study also has African-Americans and people from Latin America as the next prevalent groups after white patients.

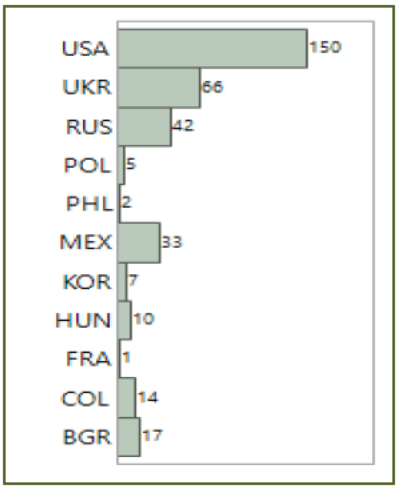
**Figure 3: Distribution of race in Study D1050326 (N=347)**




(Source: Reviewer created)

The Figure 4 of clinical site distribution by country also supports that the population in Study D1050326 is generalizable to U.S. patients. About half (43.9%) of the patients in the study were from the U.S., compared to all the other countries added together to make 56.8% non-U.S. subjects. Although the non-U.S. patients are more than half of safety population, the countries are culturally similar to the U.S. population.

**Figure 4: Number of subjects per country in Study D1050326**




(Source: Reviewer created)

In the Study D1050326 safety database, age groups were 10 to 12 years and 13 to 17 years. The younger patients (10 to 12 years) were only 21.6% of the pediatric population. See Table 11 and Figure 5. This finding is most likely because diagnosis of bipolar I disorder usually occurs between 15 and 30 years. There were twice as many males (n=50) compared to females (n=25) among the younger patients (10 to 12 years). This finding may also be explained by diagnosis patterns. Young males present with ADHD more than females and ADHD and bipolar disorder have overlapping symptoms.

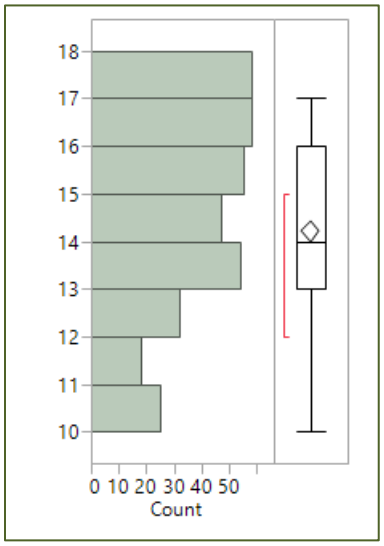
**Table 11: Treatment by age group in Study D1050326**

| | Lurasidone 20-80 mg | | Placebo | | | |
|---|---|---|---|---|---|---|
| **Age Group** | **Count** | **Column %** | **Count** | **Column %** | **Count** | **% of Total** |
| age >=6 and age <=12 | 38 | 21.7% | 37 | 21.5% | 75 | 21.61% |
| age >=13 and age <=17 | 137 | 78.3% | 135 | 78.5% | 272 | 78.39% |
| All | 175 | 100.0% | 172 | 100.0% | 347 | 100.00% |

(Source: Reviewer created)

Study D1050326 enrolled patients 10 to 17 years; the mean age was 14.2 years. See Figure 5 for the age distribution.

**Figure 5: Age distribution in Study D1050326**

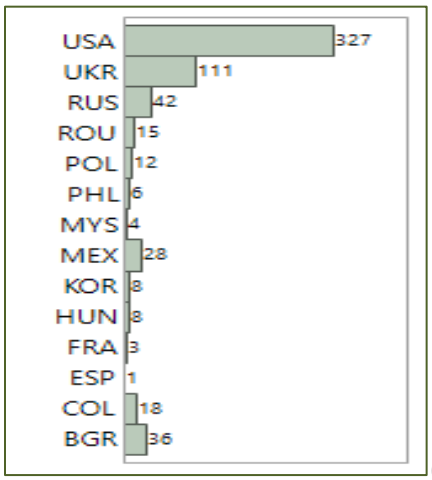



(Source: Reviewer created)

**Study D1050302 demographics**

The Applicant provided data for the long-term safety study (D1050302) in the initial Supplement 029 submission. The demographic data showed enrollment of 619 patients taking lurasidone 20 mg to 80 mg. As viewed in Figure 6, 52.8% (327/619) of patients are from the United States, thus providing relevance to the U.S. population.

**Figure 6: Number of patients per country in Study D1050302**




(Source: Reviewer created)

In the long-term safety study, the population contains 63% males and 38% females. See Table 12. The difference in sex is not applicable to the U.S. or to bipolar I disorder, which are both about 50:50, male to female ratio. However, the study is currently ongoing so the population sex distribution may be an artifact of the order and timing of the Applicant's other psychiatric efficacy trials (i.e. schizophrenia and autism are more prevalent in males) rolling into the long-term safety study.

**Table 12: Sex distribution in Study D1050302**

| | LURASIDONE-FLEX (20MG,40MG,60MG,80MG) | | | |
|---|---|---|---|---|
| **Sex** | **Count** | **Column %** | **Count** | **% of Total** |
| F | 233 | 37.6% | 233 | 37.64% |
| M | 386 | 62.4% | 386 | 62.36% |
| All | 619 | 100.0% | 619 | 100.00% |

For Study D1050302, I did not analyze additional demographic data, such as mean dose. I focused the safety review of this study on reported adverse events.

In summary, considering the efficacy study and the long-term study, the Applicant's safety data is generalizable to U.S. pediatric bipolar I depression patients.

## 8.3. Safety Results

My analysis of the safety data mirrors the Applicant's assessment of safety. I analyzed the efficacy trial safety data, long-term safety study data (up to the cutoff date October 2016), and reviewed the 120-day Safety Update (data cutoff date of May 5, 2017).

The safety data provided in the application indicate that lurasidone is relatively well-tolerated. The safety profile of lurasidone in pediatric bipolar I disorder is comparable to the safety data in the lurasidone label.

### 8.3.1. Deaths

No deaths in the lurasidone bipolar I depression pediatric clinical development program are reported through the data cutoff date of the 120-day Safety Update, May 5, 2017.

### 8.3.2. Serious Adverse Events

Based on my analysis of the safety data in Study D1050326, there were six serious adverse events (SAEs) reported. Four (2.3%) were in the placebo arm and two (1.1%) were in the lurasidone treatment arm. The serious adverse events reported in the lurasidone arm were bipolar disorder and humerus fracture. In the placebo arm, the SAEs were psychotic disorder, depression, , and spontaneous abortion. The psychiatric-related serious adverse events may represent an exacerbation of the underlying psychiatric condition or may be related to lack of efficacy of study drug, although the investigators did not all report them as related. Two of the SAEs occurred in the 10 to 12 year age group and the other four were in the older age group (13 to 17 years).

No additional treatment-emergent serious adverse events were reported in the 120-day safety update of Study D1050326.

**Narratives were created by reviewer using JMP Clinical:**

1. Actual Arm: LURASIDONE 20-80 MG; Dose 20 mg/day

Serious Adverse Event (coded term [reported term]): BIPOLAR I DISORDER [BIPOLAR MIXED EPISODE]

Subject D1050326-0005-00003 was a 14-year-old African American male. His medical history included agitation (2013), indigestion (2013), initial onset of bipolar I disorder (2012), insomnia (2012), irritability (2012), headaches (2011), 314.01 ADHD (2006), and initial behavioral disturbance (2005).

The subject discontinued the trial on August 27, 2014, (Day 8) due to symptoms worsened. On Day 9 the subject experienced a bipolar I disorder [bipolar mixed episode] (moderate) which was considered a serious adverse event (SAE). Though the event was considered serious, no reasons were provided on the case report form.

Concomitant medications taken at the onset of the SAE included: acetaminophen, lorazepam, risperidone, and valproic acid.

The investigator considered the AE to be unlikely related to study medication. The event ended on September 9, 2014, (Day 21) with a final outcome of recovered/resolved.

*Reviewer's Comment: The bipolar mixed episode may have been due to the cyclical nature of bipolar I disorder.*

2. Actual Arm: LURASIDONE 20-80 MG

Serious Adverse Event (coded term [reported term]): HUMERUS FRACTURE [LEFT HUMERAL CONDYLE FRACTURE]

Subject D1050326-0352-00007 was a 10-year-old other male. His medical history included initial onset of bipolar I disorder (2014), 314.01 attention deficit and hyperactivity disorder (2010), and initial behavioral disturbance (2010). The subject completed the trial on October 29, 2015 (Day 43).

On Day 26 the subject experienced a humerus fracture [left humeral condyle fracture] (mild) which was considered a serious adverse event (SAE). Trial medication had an action of "dose not changed" as a result of the event. Adverse events that occurred within a +/- 3-day window of the onset of the SAE included fall (mild).

The investigator considered the AE to be not related to study medication.

*Reviewer's Comment: I agree with investigator that the broken arm is not related to study drug.*

**Study D1050302, Ongoing long-term study**

The applicant submitted safety data from the cutoff point, October 2016, from Study D1050302. The most serious adverse events were reported in Psychiatric Disorder (8.1%) and Injury System Organ Classes (2.7%), (n=619). The most prevalent serious adverse events are expected based on the underlying disease in the population: bipolar I disorder (1.3%), schizophrenia (1.5%), suicidal ideation (2.1%), suicide attempt (1.1%). There is one case of Type 1 diabetes reported in a White male.

**Significant Adverse Events**

The significant adverse events of suicidality and mania were not reported as serious adverse events in Study D1050326. That was probably because the SAEs did not result in hospitalization.

There was one significant AE related to suicidality and self-injury reported as a treatment emergent AE in the placebo group; No reports were in the lurasidone group.

For mania, there were three (1.7%) subjects in the lurasidone group and four (2.3%) subjects in the placebo group who experienced treatment-emergent mania, indicating a similar rate between placebo and lurasidone over six weeks.. Treatment-emergent mania was defined as a YMRS total score ≥ 20 at any two consecutive visits or at the final assessment, or a recorded adverse event of mania or hypomania. The likely reasons for mania reported in this trial could be drug-related, lack of efficacy-related, or bipolar I disorder-related.

### 8.3.3. Discontinuations Due to Adverse Effects

Overall, there were few discontinuations due to AEs during the 6-week efficacy study.

Notably, most of the discontinuations in the long-term safety study are psychiatrically-related. Lurasidone appears better tolerated in the older age group (13 to 17 years) because there were fewer discontinuations. However, there is not enough data to assess if the psychiatric events leading to discontinuation are induced by lurasidone, caused by lack of lurasidone efficacy long-term, or the cyclical nature of bipolar I disorder.

**Study D1050326**

There were three (1.7%) discontinuations from Study D1050326 in each treatment arm due to adverse events. The adverse events (AEs) leading to discontinuation of from the study are presented in Table 13. None of the AEs leading to treatment discontinuation were reported in more than one subject in either group. All three of the AEs leading to treatment discontinuation in the placebo group were classified as Psychiatric Disorders (depression, mania, and psychotic disorder), whereas only one of the AEs in the lurasidone group related to Psychiatric Disorders (bipolar I disorder). The remaining AEs resulting in discontinuation in the lurasidone group were fatigue and restless legs syndrome.

**Table 13: Adverse events leading to study discontinuation -Study D1050326**

| TEAE leading to discontinuation | Lurasidone n= 175 | Placebo n=172 |
|---|---|---|
| Depression | - | 1 |
| Mania | - | 1 |
| Psychotic disorder | - | 1 |
| Bipolar I disorder | 1 | - |
| Fatigue | 1 | - |
| Restless leg syndrome | 1 | - |

(Source: Reviewer created)

**Study D1050302**

As of the cutoff date, May 5, 2017, for the 120-day safety update, a total of 9.2% (28/305) bipolar I disorder subjects discontinued from the long-term safety study due to AEs. Many discontinuations were reported as Psychiatric Disorders SOC (21/28). At the preferred term level, the only AEs leading to study discontinuation for subjects in the open-label extension that were reported in more than three subjects were suicidal ideation and suicide attempt (each with five subjects, 1.6%), depression (four subjects, 1.3%), and akathisia, bipolar I disorder, and mania (each with three subjects, 1.0%). All other AEs leading to treatment discontinuation occurred in only one subject.

Table 14 shows a higher incidence of AEs leading to discontinuation was seen in subjects aged 10 to 12 years (16.1%) versus 7.4% in subjects in the 13 to 17 years age group. The age groups are divided into the actual treatment groups from the efficacy study. Again, there were 305 (62 + 243) bipolar I subjects rolled in to the long-term open-label study.

**Table 14: Adverse events leading to discontinuation in Study D1050302 by age group**

| | Age group: 10-12 years old | | | Age group: ≥ 13 years old | | |
|---|---|---|---|---|---|---|
| Subjects with at least one TEAE | PBO-LUR (N=29) n (%) | LUR-LUR (N=33) n (%) | 326-LUR (N=62) n (%) | PBO-LUR (N=120) n (%) | LUR-LUR (N=123) n (%) | 326-LUR (N=243) n (%) |
| Adverse Events Leading to Discontinuation | 2 (6.9) | 8 (24.2) | 10 (16.1) | 8 (6.7) | 10 (8.1) | 18 (7.4) |

(Source: Reviewer created from Table 9 of 120-day safety update)

### 8.3.4. Treatment Emergent Adverse Events and Adverse Reactions

**Study D1050326**

Subgroup analysis of lurasidone dose by age group (10 to 12, 13 to 17 years) showed that higher doses (60 and 80mg) of lurasidone are less tolerated than lower doses (20 and 40 mg). As expected, most adverse events were reported in the lurasidone arm and by the younger age group, 10 to 12 years. However, the two treatment arms and age groups were within about ten points of each other. Of the 175 lurasidone-treated subjects, 112 (64.0%) reported one or more treatment-emergent adverse events (TEAEs). Of the 172 placebo-treated subjects, 89 (51.7%) reported one or more TEAEs. The proportion of lurasidone-treated subjects with one or

more TEAEs within the two age groupings included 27/38 subjects (71.1%) in the 10 to 12- year age group, and 85/137 subjects (62.0%) in the 13 to 17 years age group.

Adverse events reported greater or equal to two percent (≥2%) are in Table 15 and Figure 8. The table presents the distribution between treatment groups. The most commonly reported are adverse events that occur twice as much as placebo are nausea, vomiting, abdominal pain, diarrhea, somnolence, fatigue, weight increased, decreased appetite, dizziness, insomnia, and oropharyngeal pain. The analysis included all adverse events, not just the events tagged as treatment-emergent by the Applicant.

In the lurasidone label, the adult bipolar I disorder patients most commonly reported akathisia, extrapyramidal symptoms, somnolence, nausea, vomiting, diarrhea, and anxiety. There was overlap of most commonly reported adverse events in the pediatric bipolar I patients: somnolence, nausea, and vomiting. The pediatric patients taking lurasidone did not report unexpected adverse events.

Regarding somnolence, the Applicant combined the terms hypersomnia, hypersomnolence, sedation, and somnolence. Their numbers for both lurasidone (11%) and placebo (6%) arms were higher than mine. Using JMP Clinical's standard approach, my numbers are 9.1% for lurasidone and 4.7% for placebo in Table 15. In the label, I kept the Applicant's higher numbers.

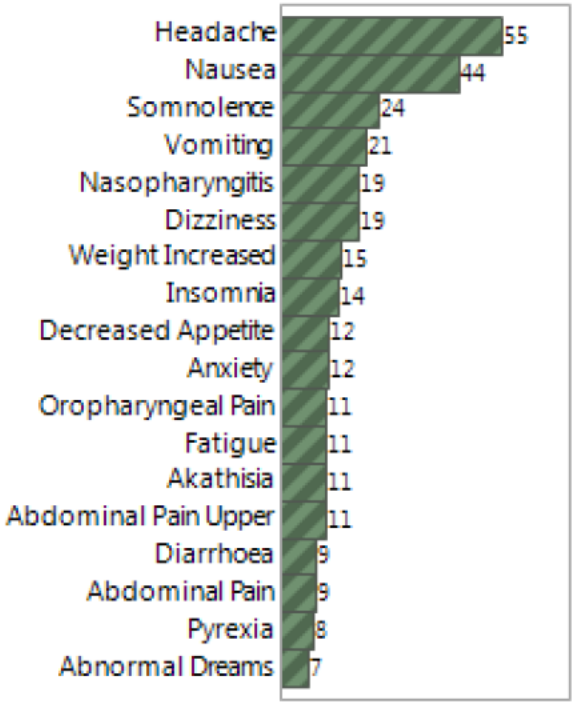
**Table 15: Adverse events in Study D1050326 ≥ 2%**

| | | Lurasidone 20-80 mg | | Placebo | | |
|---|---|---|---|---|---|---|
| **Body System or Organ Class** | **Dictionary-Derived Term** | **Count** | **%** | **Count** | **%** | **Total** |
| Nervous System Disorders | Headache | 27 | 15.4% | 28 | 16.3% | 55 |
| | Somnolence | 16 | 9.1% | 8 | 4.7% | 24 |
| | Dizziness | 11 | 6.3% | 8 | 4.7% | 19 |
| | Akathisia | 5 | 2.9% | 6 | 3.5% | 11 |
| Gastrointestinal Disorders | Nausea | 33 | 18.9% | 11 | 6.4% | 44 |
| | Vomiting | 14 | 8.0% | 7 | 4.1% | 21 |
| | Abdominal Pain Upper | 7 | 4.0% | 4 | 2.3% | 11 |
| | Abdominal Pain | 7 | 4.0% | 2 | 1.2% | 9 |
| | Diarrhea | 6 | 3.4% | 3 | 1.7% | 9 |
| Psychiatric Disorders | Insomnia | 10 | 5.7% | 4 | 2.3% | 14 |
| | Anxiety | 5 | 2.9% | 7 | 4.1% | 12 |
| | Abnormal Dreams | 4 | 2.3% | 3 | 1.7% | 7 |
| General Disorders | Fatigue | 6 | 3.4% | 5 | 2.9% | 11 |
| | Pyrexia | 4 | 2.3% | 4 | 2.3% | 8 |
| Infections and Infestations | Nasopharyngitis | 8 | 4.6% | 11 | 6.4% | 19 |
| Investigations | Weight Increased | 12 | 6.9% | 3 | 1.7% | 15 |

| | | Lurasidone 20-80 mg | | Placebo | | |
|---|---|---|---|---|---|---|
| **Body System or Organ Class** | **Dictionary-Derived Term** | **Count** | **%** | **Count** | **%** | **Total** |
| Metabolism and Nutrition Disorders | Decreased Appetite | 8 | 4.6% | 4 | 2.3% | 12 |
| Respiratory, Thoracic and Mediastinal Disorders | Oropharyngeal Pain | 7 | 4.0% | 4 | 2.3% | 11 |

(Source: Reviewer created using JMP Clinical)

**Figure 7: Number of subjects reporting adverse events ≥ 2%, both groups, Study D1050326**




(Source: Reviewer created using JMP Clinical)

**Atypical antipsychotic class adverse events**

In Study D1050326, the incidence of metabolic adverse events was higher in the lurasidone group (n=16, 9.1%) than in the placebo group (n=5, 2.9%), with the most common metabolic event being weight increased (6.9% and 1.7%, respectively).

In my analysis of metabolic adverse events in the ongoing long-term safety study (N=305 bipolar I), decreased appetite (6/305, 2.0%) and increased appetite (7/305, 2.3%) were

reported at nearly even rates. A future analysis of weight gain over time would be prudent when the long-term study is completed.

The incidence of extrapyramidal symptoms (EPS)-related TEAEs was comparable between the lurasidone and placebo groups (eight subjects [4.6%] receiving lurasidone and seven subjects [4.1%] receiving placebo). Akathisia was the most common EPS-related AE, also reported at similar frequency between the lurasidone and placebo subjects (2.9% and 3.5%, respectively). See Table 15, Adverse Events.

**Psychiatric adverse events**

Treatment-emergent mania was defined as a YMRS total score ≥ 20 at any two consecutive visits or at the final assessment, or an adverse event of mania or hypomania. There were three (1.7%) subjects in the lurasidone group and four (2.3%) subjects in the placebo group who experienced treatment-emergent mania; the treatment groups were comparable.

**Hypersensitivity events**

The incidence of TEAEs related to hypersensitivity was similar in the lurasidone and placebo groups (2.9% versus 2.3%, respectively). No hypersensitivity related TEAE was reported by more than one subject. In the safety data from Study D1050326, there is one case of rash and one case of rash pruritic. The numbers are too small to be valuable because the cases each had an incidence as risk difference of 0.005 and 0.5 -log10 (raw p-value). See Section 8.5.1 for more information on rash.

**Study D0105302, Ongoing**

In Study D1050302, as in the 6-week efficacy Study D1050326, the younger age group reported more adverse events than the 13 to 17 year age group. See Table 16:

**Table 16: Summary of Treatment-Emergent Adverse Events by Age Group: Study D1050302 Safety Population, through May 5, 2017**

| | Age group: 10-12 years old | | | Age group: ≥ 13 years old | | |
|---|---|---|---|---|---|---|
| **Subjects with at least one TEAE of following types** | **PBO-LUR (N=29) n (%)** | **LUR-LUR (N=33) n (%)** | **326-LUR (N=62) n (%)** | **PBO-LUR (N=120) n (%)** | **LUR-LUR (N=123) n (%)** | **326-LUR (N=243) n (%)** |
| Any Adverse Events | 21 (72.4) | 27 (81.8) | 48 (77.4) | 91 (75.8) | 92 (74.8) | 183 (75.3) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Adverse Events Related to Study Drug | 13 (44.8) | 18 (54.5) | 31 (50.0) | 61 (50.8) | 61 (49.6) | 122 (50.2) |
| Serious Adverse Events | 2 (6.9) | 8 (24.2) | 10 (16.1) | 11 (9.2) | 11 (8.9) | 22 (9.1) |

Abbreviations: PBO-LUR: Subjects randomized to placebo in Study D1050326; LUR-LUR: Subjects randomized to lurasidone in Study D1050326; 326-LUR: All subjects who continued from Study D1050326

(Source: Modified Applicant's Table 9 from 120-day safety update)

As expected, the safety data from the long-term safety study (reported > 2%) aligned with adverse events reported in the Study D1050326. The most commonly reported adverse reactions were insomnia, anxiety, somnolence, and weight increased. There were not meaningful sex-related differences in the number of adverse events. It appears there is more weight gain than loss over time. See Table 17.

**Table 17: Weight parameters by sex in Study D1050302, cutoff date May 5, 2017**

| | Sex | | |
|---|---|---|---|
| | F | M | Total |
| | Count (%) | Count (%) | Count (%) |
| Total | N=233 | N=386 | N=619 |
| Weight decreased | 6 (2.6) | 12 (3.1) | 18 (2.9) |
| Weight increased | 30 (12.9) | 36 (9.3) | 66 (10.7) |

(Source: Reviewer created using JMP Clinical)

### 8.3.5. Laboratory Findings

Study D1050326 captured laboratory findings at baseline and at Week 6. Table 18 lists the criteria for defining potentially markedly abnormal laboratory findings described in this section of the review. I included the laboratory findings relevant to atypical antipsychotic metabolic adverse events, hyperprolactinemia, and liver function enzymes. Other laboratory findings were unremarkable.

**Table 18: Criteria for Potentially Markedly Abnormal Post-Baseline Laboratory Values for Children and Adolescent Subjects**

| Category | Lab Parameter (unit) | Sex | High |
|---|---|---|---|
| Chemistry | Alkaline phosphatase (U/L) | | >=3 x ULN |

| | | | |
|---|---|---|---|
| | Alanine Aminotransferase (U/L) | | >=2 x ULN |
| | Aspartate Aminotransferase (U/L) | | >=2 x ULN |
| | Bilirubin (mg/dL) | | >=2 |
| | Albumin (g/dL) | | Low <50% LLN |
| | Creatinine (U/L) | | >=2.0 |
| | Glucose (mg/dL) overall | | >200 |
| | Prolactin (mg/mL) | | >=1 x ULN |
| Lipid Panel | Cholesterol (mg/dL) | | >=240 |
| | Triglycerides (mg/dL) | Female | >=170 |
| | | Male | >=200 |
| | Cholesterol/HDL cholesterol (mg/Dl) | | <=40 LLN |
| | LDL cholesterol | | >=160 |

ULN- Upper limit of the normal range.
LLN- lower limit of the normal range.
(Source: Created from Table 14.3.4.5.0, page 1225.)

The mean change from baseline to end of study for the metabolic adverse events from the 6-week Study D1050326 are in Table 19. The mean changes from lipid panels are comparable between lurasidone and placebo arms. Study D1050326 was a short-term study and because weight gain was greater in the lurasidone arm, long-term analysis of the metabolic adverse events is necessary.

**Table 19: Mean change from baseline to Week 6 and Endpoint for lipid parameters**

| Parameter (Units) | Visit | Placebo N/mean (SD) | Lurasidone 20 to 80mg N/mean (SD) |
|---|---|---|---|
| Cholesterol, fasting (mg/dL) | Baseline | 164/ 158.0 (34.72) | 165/ 159.2 (31.87) |
| | Week 6 | 138/ -1.5 (21.03) | 139/ -6.0 (26.49) |
| | Endpoint | 145/ -1.4 (20.81) | 144/ -6.3 (26.43) |
| HDL Cholesterol, fasting (mg/dL) | Baseline | 164/ 53.2 (14.54) | 165/ 52.8 (13.22) |
| | Week 6 | 136/ -3.0 (11.34) | 138/ -0.4 (9.19 |
| | Endpoint | 143/ -2.8 (11.13) | 143/ -0.5 (9.36) |
| LDL Direct, fasting (mg/dL) | Baseline | 164/ 86.3 (28.91) | 165/ 88.0 (27.89) |
| | Week 6 | 136/ 0.9 (18.60) | 138/ -4.7 (21.36) |
| | Endpoint | 143/ 1.0 (18.27) | 143/ -4.9 (21.14) |
| Triglycerides, fasting (mg/dL) | Baseline | 164/ 93.8 (49.26) | 165/ 97.1 (53.65) |
| | Week 6 | 138/ 6.9 (58.04) | 139/ -7.8 (58.39) |
| | Endpoint | 145/ 5.9(57.24) | 144/ -7.6 (57.42) |
| Glucose, fasting (mg/dL) | Baseline | 164/ 90.6 (9.41) | 165/ 90.0 (10.04) |
| | Week 6 | 138/ -0.6 (10.81) | 139/ 1.3 (12.57) |
| | Endpoint | 145/ -0.5 (10.64) | 145/ 1.6 (12.64) |

(Source: Reviewer created from Table 14.3.4.2.1, pages 1085-93.)

**Hyperprolactinemia**

As with other antipsychotics, blood prolactin levels of patients taking lurasidone were increased. During Study D1050326, serum prolactin was measured at baseline and Week 6. Females had greater increases in blood prolactin than males. Figure 9 shows outliers taking lurasidone. Patient D1050326-0852-00012 was an outlier with extremely high prolactin levels at screening, baseline, and end of study (1874, 2262, 2096 mIU/L, respectively.) Another outlier, Patient D1050326-0687-00006, had prolactin level of 83 mIU/L at baseline, 4228 mIU/L at visit

two, but the prolactin decreased to 153 mIU/L at visit eight. Table 20 shows blood prolactin levels increased in less than three percent of pediatric patients with bipolar I disorder from either treatment group (1.3, 2.6%).

**Figure 8: Females; Bivariate Fit of Prolactin Serum Log2 (Trial Mean/ULN) by Log2 (Trial Mean/ULN)**

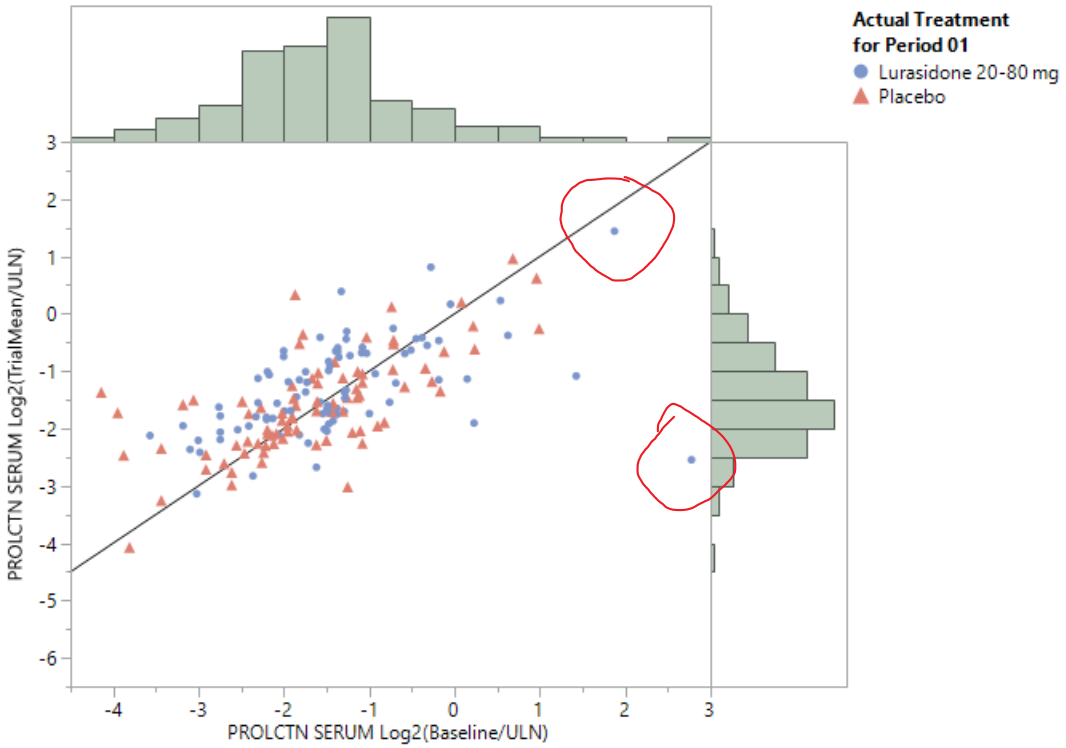



**Table 20: Number of patients with increased blood prolactin in the long-term safety study from D1050326.**

| Preferred term | PBO-LUR (N=149) n (%) | LUR-LUR (N=156) n (%) | 326-LUR (N=305) n (%) |
|---|---|---|---|
| Blood prolactin increased | 2 (1.3) | 4 (2.6) | 6 (2.0) |

(Source: Modified from Table 14.3.1.2.1.46 in 120-day safety update)

**Liver Function Tests**

The liver function tests from Study D1050326 were unremarkable. My analysis of potential cases of Hy's Law using JMP Clinical were negative. In Table 21, there were no notable differences between groups in the incidence of Potentially Markedly Abnormal Laboratory Values (PMALVs) for alkaline phosphatase, ALT, AST, bilirubin, or albumin.

**Table 21: Number and Percentage of subjects with potentially markedly abnormal liver function tests**

| | Placebo (N=172) | Lurasidone 20 – 80 mg (N=175) |
|---|---|---|
| Alkaline Phosphatase (U/L) | | |
| Any Post-Baseline DB Visit | 154 | 162 |
| >=3 x ULN | 0 | 0 |
| Alanine Aminotransferase (U/L) | | |
| Any Post-Baseline DB Visit | 155 | 163 |
| >=2 x ULN | 3 (1.9) | 3 (1.8) |
| Aspartate Aminotransferase (U/L) | | |
| Any Post-Baseline DB Visit | 155 | 161 |
| >=2 x ULN | 1 (0.6) | 2 (1.2) |
| Bilirubin (mg/dL) | | |
| Any Post-Baseline DB Visit | 153 | 162 |
| >=2 | 2 (1.3) | 1 (0.6) |
| Albumin (g/dL) | | |
| Any Post-Baseline DB Visit | 155 | 163 |
| <50% LLN | 0 | 0 |

(Source: Modified from Table 14.3.4.5.1, page 1227.)

None of the laboratory findings of mean change for liver enzymes were clinically significant from baseline to Week 6 and end of the study. These values are listed in Table 22.

**Table 22: Mean change over time for liver function test in Study D1050326**

| | Placebo (N=172) | | Lurasidone 20-80 mg (N=175) | |
|---|---|---|---|---|
| Visit | Actual | Change from Baseline | Actual | Change from Baseline |
| Aspartate Aminotransferase (U/L) | | | | |
| Baseline | | | | |
| N | 172 | | 175 | |
| Mean (SD) | 20.3 (6.71) | | 21.5 (9.18) | |
| Week 6 n | 147 | 147 | 151 | 151 |
| Mean (SD) | 20.4 (8.23) | -0.1 (6.23) | 22.0 (10.09) | 0.5 (10.80) |
| Endpoint n | 155 | 155 | 161 | 161 |
| Mean (SD) | 20.3 (8.07) | -0.1 (6.08) | 21.9 (9.87) | 0.4 (10.54) |
| Alanine Aminotransferase (U/L) | | | | |
| Baseline | | | | |
| n | 172 | | 175 | |
| Mean (SD) | 15.5 (9.92) | | 18.8 (17.15) | |
| Week 6 | | | | |
| n | 147 | 147 | 154 | 154 |
| Mean (SD) | 15.9 (11.49) | 0.4 (6.96) | 18.9 (16.04) | -0.2 (17.21) |
| Endpoint | | | | |
| n | 155 | 155 | 163 | 163 |
| Mean (SD) | 15.8 (11.23) | 0.3 (6.83) | 18.8 (15.65) | -0.3 (16.78) |
| Albumin (g/dL) | | | | |
| Baseline | | | | |
| n | 172 | | 175 | |
| Mean (SD) | 4.67 (0.291) | | 4.62 (0.297) | |
| Week 6 n | 147 | 147 | 154 | 154 |
| Mean (SD) | 4.63 (0.311) | -0.03 (0.266) | 4.67 (0.326) | 0.04 (0.280) |
| Endpoint n | 155 | 155 | 163 | 163 |
| Mean (SD) | 4.63 (0.308) | -0.03 (0.267) | 4.66 (0.324) | 0.03 (0.292) |
| Alkaline Phosphatase (U/L) | | | | |

| | | | | |
|---|---|---|---|---|
| Baseline | | | | |
| n | 172 | | 175 | |
| Mean (SD) | 155.6 (97.79) | | 164.0 (106.47) | |
| Week 6 n | 146 | 146 | 153 | 153 |
| Mean (SD) | 155.9 (101.13) | 0.1 (32.68) | 156.3 (103.83) | -2.6 (30.60) |
| Endpoint n | 154 | 154 | 162 | 162 |
| Mean (SD) | 155.4 (100.13) | 0.4 (32.14) | 160.0 (105.99) | -3.2 (30.26) |

(Source: Table 14.3.4.2.1, page 1068-1070.)

The 120-day safety update listed abnormal liver function tests (LFTs) but no subject discontinued study due to an abnormality in liver function.

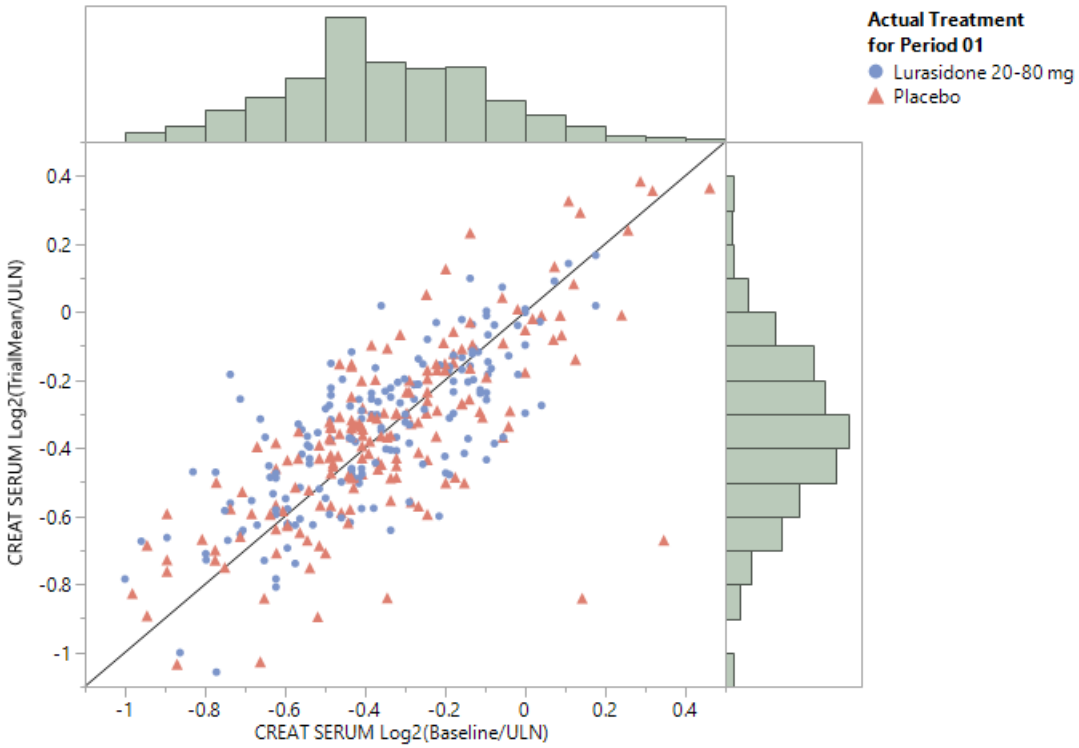
- In Study D1050326, total protein increased by 0.05 ± 0.430 g/dL from baseline to Week 6 in the lurasidone group, compared to a decrease (-0.02 ± 0.439 g/dL) in the placebo group
- GGT increased at Endpoint by 1.0 ± 9.50 U/L (Study D1050326) and 1.5 ± 8.76 U/L (Study D1050302).
- Potentially Markedly Abnormal Laboratory Value of high ALT occurred in 6 (2.8%) subjects in Study D1050302
- A TEAE of alanine aminotransferase increased occurred in one (0.4%) subject in Study D1050302

**Serum Creatinine**

The Applicant proposed updating the lurasidone label with serum creatinine values from Study D1050326 to align with the other studies in the label. The label was updated to say that the mean change from baseline in serum creatinine was +0.021 mg/dL for patients taking lurasidone compared to +0.009 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 6.7% (11/163) of patients taking lurasidone and 4.5% (7/155) on placebo.

Although a greater change in mean serum creatinine occurred in the lurasidone arm, my analysis of the shift plot in Figure 11 indicate that most of the outliers are placebo and that the lurasidone subjects are not remarkable. Additionally, the Applicant's Table 14.3.4.5.1 says zero cases of serum creatinine above the upper limits of normal.

**Figure 9: Bivariate Fit of CREAT SERUM Log2(Trial Mean/ULN) By CREAT SERUM Log2(Baseline/ULN)**




### 8.3.6. Vital Signs

Analysis of the Applicant's vital signs data did not identify safety issues.

### 8.3.7. Cardiovascular: Electrocardiograms (ECGs) and QT

Electrocardiograms (ECG) were conducted at baseline and Week 6 for Study D1050326 using the standard 12-lead ECG, including HR, PR interval, QRS interval, RR interval, QTc, QTc interval corrected for HR – Bazett's formula (QTcB), and QTc interval corrected for HR – Fridericia's formula (QTcF). All ECGs were centrally read using a core laboratory.

Based on unremarkable findings, no label changes are necessary regarding pediatric patients (10 to 17 years).

## 8.4. Safety Analyses by Demographic Subgroups

This section is not applicable because I discussed any clinically meaningful differences in safety by age group earlier in the review.

### 8.4.1. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Lurasidone is an atypical antipsychotic and not subject to abuse.

## 8.5. Safety in the Postmarket Setting

### 8.5.1. Safety Concerns Identified Through Postmarket Experience

In support of this application, the Division of Pharmacovigilance (DPV) in the Office of Surveillance and Epidemiology conducted a review of the lurasidone cases in the FDA Adverse Event Reporting System (FAERS) and the medical literature to provide an overall safety profile in pediatric patients less than 18 years of age.

No new safety signal was identified from two fatal cases in pediatric patients taking lurasidone. Of the 53 non-fatal cases, the majority reported either labeled adverse events or unlabeled adverse events that were confounded by a concomitant medication, medical history, or the cases contained insufficient information for assessment.

DPV identified four adverse events of interest (serotonin syndrome, arthralgia/joint swelling, and Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis [SJS/TEN]), but there were only single cases of each event in this pediatric case series. No clear patterns or trends suggested a new safety signal associated with the remainder of the reported adverse events in the pediatric case series.

After receipt of DPV's consult, I analyzed the Study D1050326 safety database for Stevens-Johnson Syndrome (SJS) and found no reports. The Applicant's submission had a line listing of all postmarket events reported globally to Sunovion. There were six SJS events listed, but the listings did not specify pediatrics or adults. DPV and I discussed this and decided there was not enough concern at this time to add SJS to the label.

I reviewed other hypersensitivity reactions in the Applicant's list of global postmarket reported events. Rash was reported the most for hypersensitivity reactions. See Section 8.3.4 for analysis on hypersensitivity.

The postmarketing experience section of the lurasidone label currently says Hypersensitivity Reactions: Urticaria, throat swelling, tongue swelling, and dyspnea. I recommend adding rash.

### 8.5.2. Expectations on Safety in the Postmarket Setting

The Division of Pharmacovigilance (DPV) in the Office of Surveillance and Epidemiology will monitor reported adverse events using FAERS. The DPV reviewers should especially monitor for hypersensitivity reactions (SJS and rash) and elevations in serum creatinine.

## 8.6. Integrated Assessment of Safety

Lurasidone was demonstrated to be reasonably safe and relatively well-tolerated at doses 20 to 80 mg daily for treatment of depressive episodes in pediatric patients age 10 to 17 years diagnosed with bipolar I disorder. The following reasons support my conclusion:

1. My review of safety for lurasidone in pediatric patients (10 to 17 years) indicate that lurasidone is relatively well-tolerated. The most common adverse reactions compared to placebo were nausea (16%), somnolence (9%), weight gain (7%), and vomiting (6%).
2. Lurasidone has been shown to have no clinically relevant effects on vital signs or ECG assessments at the doses studied.
3. The safety profile of lurasidone in children and adolescent subjects with bipolar depression is consistent with that seen in the adult population.
4. No deaths occurred during the 6-week efficacy trial or the ongoing long-term safety study.
5. No serious adverse events were reported from the ongoing long-term safety study.
6. The low incidence of serious adverse events in the lurasidone arm (e.g. bipolar mixed episode, humerus fracture) may be explained by other factors than lurasidone treatment.
7. The usual class adverse events for atypical antipsychotics of EPS and metabolic syndrome were relatively low lurasidone treatment group, although weight gain in lurasidone was greater than placebo.
8. The long-term data submitted thus far show that 10.7% of pediatric patients experience weight gain versus 2.9% weight decreased.
9. No new safety signals were identified in the interim long-term data and 120-day safety update. The psychiatric disorders SOC listed adverse events (e.g. bipolar, depression, schizophrenia, suicidal ideation) that may be attributable to the underlying diseases and not lurasidone.

# 9. Advisory Committee Meeting and Other External Consultations

The NDA 200603 Supplement 029 was not subject to an Advisory Committee because the study design, efficacy and safety study results, and indication in the study population did not pose questions requiring advice. The efficacy was robustly positive and the safety profile expected.

# 10. Labeling Recommendations

## 10.1. Prescription Drug Labeling

The Applicant proposed draft labeling to update the lurasidone label for the indication of treatment of depressive disorder in pediatric patients (10 to 17 years) with bipolar I disorder. The proposed dosing information was "(b) (4) " That language was too general to explain the dosing results of Study D1050326. The label should explain the mean dose for Study D1050326 was 40 mg per day and more adverse events were reported in younger patients, indicating that lower doses (e.g. 20 and 40 mg) may be beneficial and do not increase the dose without addressing efficacy and adverse reactions, especially in 10 to 12 year olds. Those points were removed during labeling negotiations.

In the draft label, I updated the numbers in the table of adverse events ≥ 2% and commonly reported adverse reactions ≥ 5% in Section 6.1 to reflect my analysis where my numbers were higher than the Applicant's. The Applicant disagreed so I reanalyzed my safety data to understand why I had different results. My original analysis used all reported adverse events. When I reanalyzed the dataset using treatment-emergent tagged adverse events, my numbers matched the Applicant's proposed counts in Section 6.1 of the label.

# 11. Risk Evaluation and Mitigation Strategies (REMS)

This section is not applicable to Supplement 029.

# 12. Postmarketing Requirements and Commitments

This section is not applicable to Supplement 029 because the efficacy supplement was submitted in response to PREA postmarketing requirements. Study of pediatric patients zero to nine years old will be waived.

# 13. Appendices

## 13.1. Patient Experience Data

The study design for Study D1050326 and the additional information included in the Applicant's Supplement 029 do not include patient experience data because the requirement for patient experience data went into effect after submission of this efficacy supplement on May 5, 2017.

NDA applications submitted on or after June 12, 2017, should contain patient experience data. In accordance with the 21st Century Cures Act, FDA is required to "make public a brief statement regarding the patient experience data and related information, if any, submitted and reviewed as part of the application for all NDAs submitted.

Patient Experience Data Relevant to this Application (check all that apply)

| | | |
|---|---|---|
| □ | The patient experience data that was submitted as part of the application include: | Section where discussed, if applicable |
| | □ Clinical outcome assessment (COA) data, such as | [e.g., Sec 6.1 Study endpoints] |
| | □ Patient reported outcome (PRO) | |
| | □ Observer reported outcome (ObsRO) | |
| | □ Clinician reported outcome (ClinRO) | |
| | □ Performance outcome (PerfO) | |
| | □ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) | |
| | □ Patient-focused drug development or other stakeholder meeting summary reports | [e.g., Sec 2.1 Analysis of Condition] |
| | □ Observational survey studies designed to capture patient experience data | |
| | □ Natural history studies | |
| | □ Patient preference studies (e.g., submitted studies or scientific publications) | |
| | □ Other: (Please specify) | |
| □ | Patient experience data that were not submitted in the application, but were considered in this review: | |
| | □ Input informed from participation in meetings with patient stakeholders | |

| | | |
|---|---|---|
| | □ Patient-focused drug development or other stakeholder meeting summary reports | [e.g., Current Treatment Options] |
| | □ Observational survey studies designed to capture patient experience data | |
| | □ Other: (Please specify) | |
| X | Patient experience data was not submitted as part of this application. | |

## 13.2. Financial Disclosure

Financial disclosure checklist filled below. One conflict of interest is described in Section 3.4 Application Data Integrity and Submission Quality.

**Covered Clinical Study (Name and/or Number): Study D1050326**

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 391 | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0<br>Significant payments of other sorts: 1<br>Proprietary interest in the product tested held by investigator: 0<br>Significant equity interest held by investigator in Sponsor: 0<br>Sponsor of covered study: 0 | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☒ | No ☐ (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☒ | No ☐ (Request information from Applicant) |

| | | |
|---|---|---|
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0 | | |
| Is an attachment provided with the reason: | Yes ☒ | No ☐ (Request explanation from Applicant) |

APPEARS THIS WAY ON ORIGINAL

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

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/s/

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NANCY C DICKINSON
03/05/2018

JAVIER A MUNIZ
03/05/2018

MITCHELL V Mathis
03/05/2018