

**Review and Evaluation of Clinical Data
NDA #200603**

Applicant:	Sunovion Pharmaceuticals, Inc.
Drug:	Latuda (lurasidone HCl) tablets
Pediatric Indications:	Schizophrenia, bipolar depression
Material Submitted:	PA Labeling Supplement S-035
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I. Background

Lurasidone is an atypical antipsychotic that was first approved as Latuda on October 28, 2010, for the treatment of adults with schizophrenia. It was subsequently approved for the following indications:

- Treatment of adults with major depressive episodes associated with bipolar I disorder (bipolar depression) as monotherapy and adjunctive therapy with lithium or valproate on June 28, 2013 (S-010 and S-011). This approval carried Postmarketing Requirements for a controlled safety and efficacy study in pediatric patients (ages 10 to 17 years) with bipolar depression (2058-1) and a long-term, open-label safety study in this population (PMR 2058-2).
- Treatment of adolescents (ages 13 to 17 years) with schizophrenia on January 27, 2017, based on the safety and efficacy results from Study D1050301 (S-026).
- Monotherapy for children and adolescents (ages 10 to 17 years) with bipolar depression on March 5, 2018, based on safety and efficacy data from Study D1050326 (S-029).

(b) (4)

Study D1050302 was a 104-week open-label study intended to evaluate the long-term safety of lurasidone in pediatric patients with schizophrenia and irritability associated with autistic disorder to meet requirements of a Pediatric Written Request dated April 20, 2012.¹ The original protocol for this trial was submitted on November 13, 2013, under IND 61292. Amendment #1 of this protocol was submitted on January 21, 2014, and expanded the inclusion criteria to include pediatric patients with bipolar depression, which allowed this study to fulfill PMR 2058-2.

The Clinical Study Report (CSR) for Study D1050302 was to be submitted no later than December 30, 2017. A Deferral Extension (DE) was requested because enrollment into the short-term safety and efficacy trial in pediatric patients with bipolar depression was slower than expected and a DE had been requested and granted for that study. A DE was granted on March 14, 2018, and required submission of the CSR by June 30, 2019. The CSR for this trial was submitted on April 30, 2019. The Applicant was subsequently advised that fulfillment of PMR 2058-2 requires submission of a labeling supplement to provide for labeling changes based on findings from Study D1050302. This supplement is intended to satisfy that requirement.

II. Clinical Review of Study D1050302

A. Study Design

This was a multicenter, open-label, 104-week extension study to evaluate the long-term safety of flexible-dose lurasidone (20, 40, 60, or 80 mg/day) in pediatric patients who completed six weeks of treatment in one of three preceding safety and efficacy trials:

- Study D1050301 (patients with schizophrenia).
- Study D1050325 (patients with irritability associated with autistic disorder).
- Study D1050326 (patients with bipolar depression).

This study was conducted at 111 sites in 14 countries: United States, Mexico, Colombia, France, Spain, Bulgaria, Hungary, Poland, Romania, Russia, Ukraine, Korea, Malaysia, and Philippines.

Patients considered to be at imminent risk of suicide and those with moderate or severe movement disorder symptoms, such as dystonia or tardive dyskinesia, were excluded. All subjects were initially treated with lurasidone 40 mg/day for Day 1 to 7. Beginning Day 8, the dose could be decreased to 20 mg/day or

¹ Requirements of the Written Request were felt to be substantially met and Pediatric Exclusivity was granted for Latuda on December 20, 2016.

increased to 60 or 80 mg/day to optimize tolerability and efficacy.² Lurasidone was administered once daily in the evening with food or within 30 minutes of eating. Extension treatment lasted up to 24 months.

Clinical evaluations were conducted every two weeks for the first eight weeks, then every four weeks until Week 104. Baseline evaluations (Day 1) for this extension trial are those at the final visit of the preceding study. For purposes of this review, baseline refers to the open-label baseline unless otherwise indicated. The schedule of assessments is shown in Table 1.

Table 1: Schedule of Assessments

	Study Week								
	6	12	28	40	52	64	76	88	104
BP & Pulse Rate	Every two weeks for the first eight weeks, then every four weeks.								
BARS, SAS, AIMS									
C-SSRS									
CGI-Severity									
Height & Weight	X	X	X	X	X	X	X	X	X
ECG			X		X		X		X
Laboratory Tests		X	X		X		X		X
Tanner Stage			X		X		X		X
Cogstat Battery		X	X		X		X		X
Clinical Status	X	X	X	X	X	X	X	X	X

Source: Extracted from Tables 2, 3, and 4 of the CSR.

Safety assessments included orthostatic blood pressure and pulse rate, movement disorder scales (Barnes Akathisia Rating Scale, Simpson-Angus Scale, and Abnormal Involuntary Movement Scale), and (for patients from the short-term schizophrenia and bipolar depression studies only) the Columbia-Suicide Severity Rating Scale (C-SSRS) and Cogstat Computerized Cognitive Test Battery. Height was measured by stadiometer. Laboratory tests were done under fasted conditions and included a lipid profile, HbA1c value, prolactin, and reproductive hormones (estradiol, testosterone, FSH, and LH). Clinical status of the disorder was monitored using scales specific to the underlying disorder: the Positive and Negative Symptom Scale (PANSS) for patients with schizophrenia, Aberrant Behavior Checklist (ABC) for patients with autistic disorder, and the Children's Depression Rating Scale-Revised (CDRS-R) and Young Mania Rating Scale (YMRS) for patients with bipolar depression.

² The labeled recommended dose range for adolescents with schizophrenia is 40 to 80 mg/day and for pediatric patients with bipolar depression 20 to 80 mg/day.

B. Patient Disposition, Exposure, and Demographics

A total of 702 patients entered this long-term extension study from one of the three preceding trials (271 patients with schizophrenia, 125 patients with autistic disorder, and 306 patients with bipolar depression). The Safety Population (N=701) consists of all patients who received at least one dose of study drug.³ Of patients in the Safety Population, 445 patients (63%) completed 12 months of lurasidone treatment and 378 (54%) received lurasidone for 24 months.

The most common reasons for premature discontinuation were adverse events (AEs) and withdrawal of consent, which led to dropout in 11% (78/701) and 15% (105/701) of all patients, respectively.

The mean duration of exposure to lurasidone in the Safety Population by diagnosis was:

- Schizophrenia 526.8 days
- Autistic Disorder 433.8 days
- Bipolar depression 501.9 days

The overall cumulative exposure in this extension study was 958.4 patient-years. Cumulative exposure by diagnosis was:

- Schizophrenia 390.9 patient-years
- Autistic Disorder 148.5 patient-years
- Bipolar depression 419.1 patient-years

Demographically, there were more males (61%) than females (39%). The mean age was 14.3 years and most patients (76%) were in the 13 to 17 year age range. In terms of race, most were Caucasian (75%). Ethnically, most were not Hispanic or Latino (84%). Patients were almost evenly divided between U.S. and non-U.S. sites (47% and 53%, respectively).

Adverse Event Coding and Data Integrity

I evaluated the accuracy of the coding of reported AE terms to MedDRA Preferred Terms using the AE dataset ADAE.xpt. The coding was reasonably accurate.

Due to the granularity of MedDRA, I combined some closely related AE Preferred Terms into common terms for purposes of computing certain reporting rates, as depicted in Table 2.

³ One patient with bipolar depression entered this extension trial but did not receive lurasidone.

Table 2: Combined MedDRA Preferred Terms

Combined AE Term	Subsumed Preferred Terms
Abdominal pain	Abdominal pain, abdominal discomfort, abdominal distension, abdominal pain upper.
Agitation	Agitation, aggression, irritability, psychomotor hyperactivity, restlessness, violence-related symptom.
Dizziness	Dizziness, dizziness postural, orthostatic hypotension, hypotension, syncope, presyncope.
Dystonia	Dystonia, muscle rigidity, muscle spasms, muscle spasticity, muscle tightness, musculoskeletal stiffness, nuchal rigidity, oculogyric crisis, oromandibular dystonia, torticollis, trismus.
Insomnia	Insomnia, initial insomnia, middle insomnia, terminal insomnia.
Somnolence	Somnolence, sedation, hypersomnia, lethargy, malaise.
Suicidal behavior	Suicidal behavior, suicide attempt, intentional overdose, self-injurious behavior, intentional self-injury

Source: Created by the reviewer from inspection of the dataset ADAE.xpt.

I also audited the consistency of AE documentation in this application by comparing the adverse events listed in the dataset ADAE.xpt, narrative summaries, and case report forms for six randomly selected patients who experienced events that were classified as serious or led to withdrawal of lurasidone.⁴ There was good consistency of AE documentation across these three documents for these patients.

C. Safety Findings

Deaths

There were no deaths in this extension trial.

Serious AEs

AEs were considered serious AEs (SAEs) by the following protocol criteria:

- Resulted in death.

⁴ This represents about 5% of the patients with a serious AE or an AE that led to dropout. The audited patients were (by SUBJID): (b) (6)

- Placed the patient at immediate risk of death.
- Led to inpatient hospitalization or prolonged existing hospitalization.
- Resulted in significant incapacity or substantial disruption of normal life functions.
- Associated with a congenital anomaly or birth defect.
- AEs that may have jeopardized the patient and may have required medical or surgical intervention to prevent one of the above outcomes.
- All cases of bone fracture.

A total of 78 patients experienced a treatment-emergent SAE during this extension trial.

Most SAEs were reported in only one patient. Two of these SAEs, bezoar and hematuria, are unexpected and merit further discussion:

- Patient (b) (6) was a 13 year old female diagnosed with bipolar depression who experienced a bezoar. On Study Day 404, the patient reported pulling her hair out and eating it. There was a history of intermittent trichotillomania over the prior two years, with the current behavior attributed by the patient to increased anxiety over falling grades and bullying at school. On Day 456, she was hospitalized with a bowel obstruction caused by a hair ball. The obstruction passed without intervention and the event was considered resolved on Day 457.
- Patient (b) (6) was a 16 year old male with a diagnosis of schizophrenia who experienced hematuria that was considered serious as well as a fever (104.2 °F) on Study Day 512. He had experienced episodes of fever lasting 24 to 48 hours over the past three months with a weight loss of 6 kg and occasional “urinary problems.” He was hospitalized and found to have an elevated C-reactive protein level (133 mg/L) and white blood cell (WBC) count (15,220/cm³). Laboratory tests during hospitalization were remarkable for hematuria. Serum protein electrophoresis was normal. On Day 518, CT scans of the abdomen, chest, spine, and kidneys; urinalysis; C-reactive protein; and WBC count were normal. He had no somatic complaints and was discharged. A diagnosis of Behcet’s syndrome was considered possible and he was referred for consultation with a rheumatologist. Despite these events, lurasidone treatment was not stopped but was continued for almost a month after hospital discharge.

Reviewer's Comment: In the first case, an etiologic role for lurasidone seems very unlikely given the history of hair pulling and eating prior to lurasidone therapy. In the second case, a causal relationship cannot be entirely ruled out although attribution to lurasidone treatment cannot reasonably be inferred given the onset of fever episodes after one year of lurasidone treatment and resolution of symptoms while continuing treatment.

Several patients sustained bone fractures, which were reported as SAEs per the study protocol. Latuda labeling discusses the risk of reduced bone density and bone mineral content with lurasidone exposure in two sections:

- Section 5.7 (Hyperprolactinemia) states that long-standing hyperprolactinemia, when associated with hypogonadism, may lead to decreased bone density in male and female patients.
- Section 8.4 (Pediatric Use) states that adverse effects in the juvenile animal study included dose-dependent decreases in bone mineral content at two times the maximum recommended human dose (based on mg/m²) in male and female rats.

Decreased bone density increases the risk of fractures. Increased fracture risk could also be associated with falls due to dizziness, orthostatic hypotension, and sedation caused by lurasidone. Eleven patients sustained 12 fractures during this extension trial. The rates of all fractures (per 1000 patient-years) by diagnosis were:

- Schizophrenia 7.7
- Autistic disorder 26.9
- Bipolar depression 9.5

Reviewer's Comment: The background incidence of fractures in the pediatric population (ages 0 to 19 years) has been reported as 9.47 per 1000 children per year.⁵ This rate approximates the rates seen in the patients with schizophrenia and bipolar depression. The elevated reporting rate of fractures in patients with autism may be related to lower bone mineral density in peripubertal boys with autism spectrum disorder compared to typically developing controls.⁶ The four patients with autism who had fractures were all males in the age range 10 to 17 years.

⁵ Naranje SM, et al, 2016, Epidemiology of Pediatric Fractures Presenting to Emergency Departments in the United States, J Pediatr Orthop, 36(4), 45-48.

⁶ Neumeyer AM, et al, 2015, Brief Report: Bone Fractures in Children and Adults with Autism Spectrum Disorders, J Autism Dev Disord, 45(3), 881-887.

Suicidal ideation and behavior were reported as SAEs in this study. The rate of suicidal ideation or suicidal behavior was 38 per 1000 patient-years.

Reviewer's Comment: In placebo-controlled trials of antidepressants, the drug-placebo difference in the number of patients with suicidal thoughts or behavior was 14 patients per 1000 patients under age 18 years.⁷ Given that patients in those trials were likely treated, on average, for considerably less than one year, the rate of suicidal ideation or behavior in this study is probably similar or less than the labeled rate.

The C-SSRS was administered to patients with schizophrenia and bipolar depression. There were no completed suicides during this study. Rates of any suicidal ideation and any suicidal behavior during extension treatment were higher for the patients with bipolar depression than for the patients with schizophrenia, as shown in Table 3 below. A higher proportion of bipolar depression patients than schizophrenic patients made a suicide attempt, as captured by the C-SSRS (2.6% vs. 0.7%). This difference is not surprising given the strong association of suicidal thoughts and behaviors with depressive illness.

Table 3: C-SSRS Rates of Suicidal Ideation and Behavior

	Rate (per 1000 patient-years)	
	Schizophrenia	Bipolar Depression
Any Suicidal Ideation	40.9	105.0
Any Suicidal Behavior	7.7	21.5

Source: Created by the reviewer by analysis of the dataset ADAE.xpt using JMP 11.1.1.

Based on the most severe rating of suicidal ideation on the C-SSRS, the proportion of patients with active ideation with a specific plan and intent was only slightly higher in the bipolar depression group than in the schizophrenia group (1.6% vs. 1.1%).

SAEs related to agitation and aggression were reported in multiple patients. The reporting rates (per 1000 patient-years) for these events were 87, 256, and 62 for patients in the schizophrenia, autistic disorder, and bipolar depression groups, respectively. The much higher rate in patients with autism is not unexpected given that problematic behaviors, such as verbal and physical aggression, are common in children with autism spectrum disorder (ASD).⁸

Several SAEs represented worsening of the underlying illness (bipolar disorder, depression, and psychosis/schizophrenia). Other SAEs met one of the following criteria: 1) the AE is already labeled, 2) the AE is very unlikely to have been

⁷ Information from Section 5.2 of Latuda labeling.

⁸ Farmer CA and Aman MG, 2011, Aggressive behavior in a sample of children with autism spectrum disorders, *Res Autism Spectrum Disorders*, 5(1), 317-323.

caused by lurasidone, or 3) the AE is common in the pediatric population and not unexpected. These events and the number of patients with the event (if more than one) were: abdominal pain, pyrexia, appendicitis (N=3), osteomyelitis, accidental overdose, concussion, contusion, frostbite, peripheral nerve injury, soft tissue injury, Type 1 diabetes mellitus, benign ovarian tumor, akathisia, ataxia, convulsion (N=2), confusional state, intentional drug misuse, and nephrolithiasis.

Reviewer's Comment: In conclusion, the SAEs from this extension trial revealed no new safety findings that can be reasonably linked to lurasidone therapy.

Dropouts Due to Adverse Events

A total of 77 patients dropped out of this extension trial because of a treatment-emergent AE. The proportions were roughly comparable across the three diagnostic groups.

Most of the AEs that led to dropout are either already labeled, reflect worsening of the underlying condition, or are discussed under SAEs above. The following five AEs that led to dropout in one patient each and warrant further discussion:

Neutropenia – Patient (b) (6) was a 13 year old Black female diagnosed with schizophrenia who had an absolute neutrophil count (ANC) of 910/ μ L on Study Day 562. Her baseline ANC was 1,590/ μ L, which was below the lower limit of the reference range (1,820/ μ L). Lurasidone was discontinued and no treatment was given. Three days later, her ANC was 2,350/ μ L, within normal range. The Applicant commented that benign ethnic neutropenia (ANC less than 1,500/ μ L in the absence of other causes) is common among individuals of African descent.

Tourette's disorder – Patient (b) (6) was a 16 year old male diagnosed with schizophrenia who experienced moderate worsening of pre-existing Gilles de la Tourette's syndrome on Study Day 71. The investigator considered this possibly related to study drug and lurasidone was stopped. This AE resolved eight days later.

ALT increased – Patient (b) (6) was a 12 year old male diagnosed with bipolar depression who experienced elevations in ALT to various degrees throughout the extension study. His preceding study baseline ALT was elevated (55 U/L, normal range 5 to 30 U/L) and his extension study baseline ALT was 52 U/L. During extension treatment, his ALT rose to a maximum of 127 U/L on Study Day 409 and was 62 U/L at the last assessment on Day 506, when lurasidone was stopped. AST and GGT levels were also increased during this interval but to a lesser degree. Alkaline phosphatase and total bilirubin levels remained within normal range throughout and there were no gastrointestinal AEs suggestive of clinically significant liver disease in this patient during extension treatment.

Bilirubinuria and proteinuria – Patient (b) (6) was a 16 year old Asian male diagnosed with schizophrenia who had 1+ bilirubin and trace protein on urinalysis on Study Day 83. (This patient had received lurasidone during the preceding short-term trial. At the extension study baseline, urinalysis showed trace protein.) The investigator consulted a pediatric nephrologist who evaluated the patient on Day 100. A urinalysis at that time was within normal limits and the previous findings were considered transient in nature. A kidney/ureter/bladder (KUB) ultrasound revealed a “hyperechoic corticomedullary parenchymal echotexture,” indicating renal parenchymal disease. No solid masses or cysts were seen. The patient had no history of diabetes mellitus or hypertension nor any history of renal disease. The nephrologist recommended that the patient be withdrawn from the trial and lurasidone was stopped on Day 107 (after a total of 150 days of lurasidone exposure across both trials). At no time did the patient experience an elevation in serum creatinine, with his serum creatinine at the double-blind baseline essentially the same as at the end of extension treatment and at the low end of normal range (0.68 and 0.69 ng/mL, respectively). The patient failed to comply with follow-up visits with the study investigator and the consulting nephrologist. Therefore, no further data are available.⁹

Painful erection – Patient (b) (6) was a 10 year old male diagnosed with bipolar depression who experienced a mild but painful erection on Study Day 223 that was considered possibly drug-related by the investigator. Lurasidone was discontinued due to this AE and no treatment was given for the event. However, this AE was ongoing at the time of last evaluation. Painful erection or priapism were not reported by other patients in this database and is not mentioned in Latuda labeling but it has been reported in patients treated with other atypical antipsychotics, such as aripiprazole, olanzapine, quetiapine, and ziprasidone.

Reviewer’s Comment: The case of a prolonged, painful erection is unexpected and should be added to labeling. Otherwise, there is no clear evidence of new safety signals from this trial. In the case of Patient (b) (6) who was diagnosed with renal parenchymal disease, the absence of a pre-lurasidone KUB ultrasound makes it impossible to confirm that this finding was treatment-emergent. In addition, I examined adverse event data listings from three completed long-term trials in adults (Studies D1050234, D1050238, and D1050296) and found no similar events. The hyperechoic area identified on KUB ultrasound seems more likely to represent an incidental finding as opposed to an adverse reaction to lurasidone.

⁹ Information on this patient was obtained from the Narrative Summary as well as the Applicant’s September 20 and October 18, 2019, responses to an Information Request for more detailed clinical information regarding this patient.

Treatment-Emergent Adverse Events

I examined treatment-emergent adverse events that occurred in at least 5% of patients in any diagnostic group during the extension study to identify those that are not already labeled for Latuda as having occurred in at least 2% of lurasidone-treated patients at a rate greater than the placebo rate in either of the short-term, placebo-controlled schizophrenia or bipolar depression pediatric studies.¹⁰ The proportions of patients experiencing these adverse events are displayed by diagnostic group in Table 4.

Table 4: Proportion of Patients with Treatment-Emergent AEs

	Schizophrenia (N=271)	Autism (N=125)	Bipolar Dep (N=305)
Headache	24%	14%	24%
Anxiety	13%	11%	9%
Agitation	13%	30%	9%
Depression	7%	6%	5%
Cough	4%	11%	5%
Toothache	7%	2%	2%
Constipation	5%	3%	2%
Pyrexia	3%	6%	3%

Source: Extracted from CSR Table 39, Latuda labeling, and reviewer's calculation of reporting rates for the combined AE term agitation (as defined above).

Reviewer's Comment: None of these events represent a new safety signal for lurasidone, in my opinion. I also examined all treatment-emergent adverse events listed in the dataset ADAE.xpt to identify any that would be unexpected in this population. Only one such event was identified: painful erection (see the discussion of Patient (b) (6) above).

Laboratory Data

I reviewed the mean change from baseline and shifts from normal to outside normal range during extension treatment for laboratory parameters.¹¹ Changes in the following measures were noteworthy.

Metabolic Parameters

The mean changes from baseline to Week 104 in fasting metabolic parameters are shown in Table 5.

¹⁰ Includes the combined adverse event terms listed in Table 2.

¹¹ This examination consisted of an inspection of the following tables from the CSR: Tables 14.3.4.1.1.90, 14.3.4.1.2.90, 14.3.4.2.1.90, 14.3.4.2.2.90, 14.3.4.3.1.90, 14.3.4.3.2.90, 14.3.4.3.3.90, 14.3.4.3.4.90, 14.3.4.4.1.90, 14.3.4.4.2.90, 14.3.4.5.1.90, and 14.3.4.5.3.90.

Table 5: Mean Changes from OL Baseline to Week 104 in Fasting Metabolic Parameters

Parameter (Units)	N	Mean Change	95% CI of Mean Change
Glucose (mg/dL)	306	+1.90	0.45, 3.34
Total Cholesterol (mg/dL)	307	+2.04	-1.34, 5.41
HDL Cholesterol (mg/dL)	303	-0.76	-2.31, 0.79
LDL Cholesterol (mg/dL)	300	+1.92	-0.84, 4.68
Triglycerides (mg/dL)	305	+7.0	0.6, 13.4

Source: Extracted from CSR Table 14.3.4.2.1.90.

The 95% confidence intervals for the changes in total cholesterol, HDL, and LDL contain the null, suggesting that the population changes in these parameters with long-term lurasidone treatment may be minimal.

The proportions of patients who had a normal value at baseline and who shifted to a value above normal (for fasting glucose, total cholesterol, LDL, and triglycerides) or below normal (for fasting HDL) at endpoint are shown in Table 6.

Table 6: Percentage of Patients with a Shift from Normal to Abnormal Metabolic Values

Parameter (shift direction)	N _{normal at OL BL}	N _{shift at endpoint}	% Shift at Endpoint
Glucose (high)	531	37	7.0%
Total Cholesterol (high)	403	47	11.7%
HDL Cholesterol (low)	432	118	27.3%
LDL Cholesterol (high)	517	15	2.9%
Triglycerides (high)	477	59	12.4%

Source: Extracted from CSR Table 14.3.4.2.2.90

These proportions are high but cannot be fully interpreted in the absence of a control group.

Among all patients with an HbA1C level $\leq 6.1\%$ (the upper limit of normal or ULN) at baseline, 0.8% (5/643) had a level greater than 6.1% at some post-baseline assessment during extension treatment.¹² Among patients with a normal fasting insulin level at baseline, 8.4% (45/537) had a high insulin level at endpoint.

Serum Prolactin and Reproductive Hormones

The median changes from baseline to endpoint in serum prolactin were:

- -0.20 ng/mL (males and females N=641).
- -0.30 ng/mL (females N=255).
- -0.05 ng/mL (males N=386).¹³

¹² Based on the reviewer's analysis of the dataset ADLB.xpt using JMP 11.1.1.

¹³ Ibid.

The proportions of patients who shifted from a normal serum prolactin level at baseline to a high level at any time during extension treatment were 27% (185/692 for all patients), 32% (87/272 females only), and 23% (98/420 males only). The proportions of patients with a markedly high prolactin level (≥ 5 times the ULN) at any time during extension treatment were 2% (12/692 for all patients), 3% (9/272 females), and 1% (3/420 males).¹⁴

Potential prolactin-related AEs among females in this trial included dysmenorrhea (1.0%), amenorrhea (0.7%), irregular menstruation (0.7%), and galactorrhea (0.6%). Among male patients in this study, decreased libido was reported in two patients ($<1\%$) and there were no reports of impotence, gynecomastia, or galactorrhea.¹⁵

The Division of Metabolism and Endocrinology Products (DMEP) was formally consulted to assist with evaluating the effect of lurasidone on reproductive hormones in this trial. A consultative review was completed by Sonia Doi, MD, PhD, Medical Officer in DMEP, on October 17, 2019. Dr. Doi pointed out that, in children, gonadal hormone levels and sex hormone related features vary with the stage of pubertal development. Also, in post-pubertal females, gonadal and pituitary hormones vary with phases of the menstrual cycle. Thus, plasma levels of reproductive hormones must be paired with pubertal stage and, in females, with menstrual cycle phase to be meaningfully interpreted. The pediatric patients in this study were in different stages of pubertal development, both within each diagnostic group and between diagnostic groups, and hormonal analyses were not controlled for age and pubertal stage. Therefore, FSH, LH, testosterone, and estradiol levels in this trial cannot be evaluated in a meaningful fashion. Data from post-pubertal females were not linked to the menstrual cycle phase. Dr. Doi also notes that these females were allowed to use oral contraceptives, which renders serum estradiol, FSH, and LH concentrations in these patients uninterpretable. Nevertheless, because median changes in serum prolactin levels were relatively stable and mostly within normal range throughout this study, Dr. Doi stated that the risk, on average, of prolactin-mediated dysregulation of the hypothalamic-pituitary-gonadal axis with lurasidone treatment is low.

Liver Transaminases

Transient elevations of liver enzymes have been associated with atypical antipsychotics, such as asenapine and olanzapine. In this extension trial, the percentages of patients who had a liver transaminase or bilirubin level within normal range at baseline and who shifted to a value above normal at endpoint are shown in Table 7.

¹⁴ From CSR Table 14.3.4.5.3.90.

¹⁵ Based on the reviewer's search of the dataset ADAE.xpt for these Preferred Terms.

Table 7: Proportion of Patients with a Shift in Transaminase or Bilirubin Levels

Liver Parameter	N _{normal at OL BL}	N _{shift at endpoint}	% Shift to High at Endpoint
AST	606	22	3.6%
ALT	576	36	6.3%
GGT	607	17	2.8%
Total Bilirubin	579	9	1.6%

Source: Extracted from CSR Table 14.3.4.2.2.90

The proportions of patients with an ALT elevation at least twice the ULN or a bilirubin level ≥ 2 mg/dL at any time during extension treatment were 4.6% (32/693) and 1.6% (11/693) for ALT and bilirubin, respectively. No patient experienced jaundice, liver failure, or hepatic necrosis during extension study treatment.¹⁶

Creatine Kinase

Among patients with a normal creatine kinase (CK) level at baseline, 7.2% (41/567) had a shift to a high value at endpoint. A total of 3.7% (25/668) of patients experienced a CK level greater than three times the ULN at some point during extended treatment. An examination of the AEs reported for these 25 patients revealed only one event possibly related to muscle injury (asthenia in two patients). None of these patients reported dystonic reactions or muscle pain. The highest CK level was in Patient (b) (6) (17484 U/L) at Week 104. This patient had no reported adverse events at any time during the trial. The baseline CK in this patient was 104 U/L and subsequent levels prior to endpoint were in the range of 93 to 171 U/L. On follow-up eight days later, the CK value was 256 U/L, suggesting that the extreme level at Week 104 was an error.¹⁷

Atypical antipsychotics have been associated with unexplained elevations in CK.

Serum Creatinine

Changes in serum creatinine were noted in the short-term pediatric trials, per Latuda labeling. In this extension study, the mean change from baseline to Week 104 in serum creatinine was +0.07 mg/dL (N=344) (95% CI 0.008, 0.132). In patients with a normal serum creatinine at baseline, 5.8% (30/521) had a value above normal range at endpoint. This rate is comparable to the rates observed in the short-term pediatric schizophrenia and bipolar depression trials described in Latuda labeling. Patient # (b) (6) had an extremely high serum creatinine at Week 104 of 11.55 mg/dL. The baseline creatinine was 1.01 mg/dL and all values prior to endpoint were within the normal range. This patient had no adverse events reported at the time of this abnormality. On follow-up one week

¹⁶ Based on the reviewer's search of Preferred Terms and Reported Terms in the dataset ADAE.xpt.

¹⁷ Based on the reviewer's analysis of the datasets ADLB.xpt and ADAE.xpt using JMP 11.1.1.

later, this patient's creatinine level was 1.04 mg/dL, suggesting that the extreme value at Week 104 was a laboratory error.

Vital Signs

Blood Pressure/Pulse Rate/Temperature/Respiratory Rate

I examined mean changes from baseline to Week 104 and proportions of patients meeting outlier criteria at endpoint for supine and standing blood pressure and pulse rate, orthostatic changes in blood pressure and pulse rate, body temperature, and respiratory rate.¹⁸ There were no findings that clearly indicate a substantial effect of long-term lurasidone treatment on these measures.

Height/Weight/BMI

Mean changes in observed height, weight, and BMI indices at Weeks 52 and Week 104 are displayed in Table 8.

Table 8: Mean Changes in Observed Height, Weight, and BMI

	Week 52	Week 104
	Mean Δ from OL Baseline (N=453)	Mean Δ from OL Baseline (N=377)
Height		
Actual Height (cm)	2.76	4.94
CDC z-score (SD)	0.02	0.05
CDC Percentile Rank (%)	0.64	1.52
Weight		
Actual Weight (kg)	3.49	5.85
CDC z-score (SD)	-0.01	-0.06
CDC Percentile Rank (%)	-0.37	-2.08
BMI		
Calculated BMI (kg/m ²)	0.63	0.94
CDC z-score (SD)	-0.04	-0.13
CDC Percentile Rank (%)	-1.40	-3.80

Source: Extracted from CSR Table 14.3.6.3.1.90. Z-scores are adjusted for age and gender based on Centers for Disease Control (CDC) growth charts for the U.S. (2000).

Despite increased mean weight at Weeks 52 and 104, z-scores and percentile ranks for weight and BMI decreased slightly. Because these findings are relatively small and probably related to an increase in vertical growth, these findings are not concerning. On average, lurasidone did not appear to substantially affect changes in height, weight, or BMI compared to the general pediatric population.

¹⁸ This examination consisted of an inspection of Tables 14.3.5.1.90 and 14.3.5.2.1.90 from the CSR. Outlier criteria for vital signs are found in Table 11 of the CSR.

Electrocardiograms (ECGs)

I examined mean changes from baseline to all post-baseline assessments in standard ECG parameters, including heart rate, PR interval, QRS duration, QTcB interval, and QTcF interval.¹⁹ None of these changes was remarkable.

Also, my examination of the proportions of patients with an abnormal heart rate, PR interval, and QRS duration suggested no adverse effect on these parameters.²⁰

Lastly, the proportions of patients with abnormal QTcB and QTcF intervals as well as various degrees of QTc prolongation from baseline were examined.²¹ No patient experienced a QTc interval over 500 msec. There was no clear evidence that lurasidone produced appreciable QT prolongation in this trial. This is consistent with the results of a dedicated QT study of lurasidone in patients with schizophrenia or schizoaffective disorder.²²

There were no reports of torsade de pointes. ECG findings that were reported as AEs include QT prolonged, first degree AV block, and second degree AV block, all in Patient # (b) (6), a 13 year old male. Lurasidone was continued and all events except the first degree AV block resolved. ECG-related AEs in other patients were PR shortened, supraventricular extrasystoles, sinus tachycardia, and supraventricular tachycardia (each in one patient).

Tanner Stage

Tanner stage assessment of sexual maturity was rated according to pubic hair development in males and females, genitalia development in males, and breast development in females. An examination of shifts from baseline to endpoint on these four measures revealed only one female who experienced a decrease in Tanner score (Stage IV to Stage III in breast development). An enumeration of patients who had no change from baseline in Tanner stage at Week 104 and those who had an increase in Tanner stage is displayed in Table 9.

Table 9: Enumeration of Patients by Tanner Stage Change from Baseline to Week 104

	Males		Females	
	Pubic Hair	Genitalia	Pubic Hair	Breast
No Change	102	105	80	74
Increase	131	128	64	70

Source: Extracted from CSR Tables 14.3.14.4.90 (males) and 14.3.14.5.90 (females).

¹⁹ Based on examination of the CSR Table 14.3.7.1.90.

²⁰ Based on examination of the CSR Table 14.3.7.3.1.90. Criteria for abnormal values is found in CSR Table 8.

²¹ Based on examination of the CSR Table 14.3.7.5.90.

²² See section 12.2 of Latuda labeling.

More males experienced an increase versus no change in Tanner stage. Among females, more patients had no change versus an increase in Tanner stage. However, these data cannot be interpreted in a meaningful fashion in the absence of an age- and gender-matched control group.

Extrapyramidal Symptoms (EPS)

Movement disorder scales were used during this trial to systematically quantify EPS. Specifically, the Abnormal Involuntary Movement Scale (AIMS) rated dyskinesia, the Simpson-Angus Scale (SAS) rated symptoms of parkinsonism, and the Barnes Akathisia Rating Scale (BARS) rated akathisia. Increased scores in these measures indicate EPS worsening.

Both baseline scores and mean changes from baseline in these scales were small. An enumeration of patients by change from baseline to endpoint is displayed in Table 10.

Table 10: Enumeration of Patients By Change from Baseline in Movement Disorder Scores

	Score Change from Open-Label Baseline to Endpoint		
	Increased (Worse)	Unchanged	Decreased (Improved)
BARS Global Score	18	658	23
AIMS Global Score	6	682	11
SAS Mean Score	38	576	80

Source: Extracted from CSR Tables 14.3.8.3.1.90 (BARS) and 14.3.9.3.1.90 (AIMS). SAS figures were calculated by the reviewer from the dataset ADQSSAS.xpt using JMP 11.1.1.

Most patients experienced either no change or improvement in EPS severity from open-label baseline to endpoint. Four patients experienced treatment-emergent tardive dyskinesia during extension treatment (on Study Days 1, 26, 222, and 328). Two of those cases resolved, one was resolving, and one was not resolved.

Cognitive Effects

Cognitive effects of long-term lurasidone treatment were assessed using the Cogstate Computerized Cognitive Test Battery only for patients who participated in studies D1050301 and D1050326. This battery was comprised of the following tasks:

- Psychomotor speed using a detection task. Subjects must respond as soon as possible to a card being displayed.

- Attention using an identification task. Subjects must identify the color of a card as soon as possible.
- Learning/memory using a one card learning task. Subjects must remember which cards have been shown before in the task.
- Working memory speed and accuracy using a one back task. Subjects must decide if each card is exactly the same as the previous card and must identify the color of the card as quickly as possible.

Scores were standardized based on normative data and age for each task so that positive scores indicated better performance and negative scores indicated worse performance than that of age-matched peers (in standard deviation units). The scoring of each task and the methodology for standardizing the scores are described in Section 2.6.10 of the Statistical Analysis Plan.

The mean scores at open-label baseline and changes from baseline to Week 104 on the above tests are summarized in Table 11.

Table 11: Mean Changes from Baseline to Week 104 in Cogstate Standardized Scores (SD)

Cogstate Domain	N	OL Baseline Mean	Mean Change
Psychomotor speed	309	-1.83	-0.20
Attention (speed)	309	-1.69	-0.24
Learning/Memory (accuracy)	311	-0.21	0.51
Working Memory Speed	310	-0.66	0.09
Working Memory Accuracy	311	-0.47	0.16

Source: Extracted from CSR Table 14.3.11.2.90.

At open-label baseline, on average, patients scored worse than age-matched peers on all domains as indicated by the negative standardized scores. Mean score changes from baseline showed some worsening in cognitive speed but slight to modest improvement on memory tasks. Mean scores were generally comparable between the patients with schizophrenia and patients with bipolar depression.

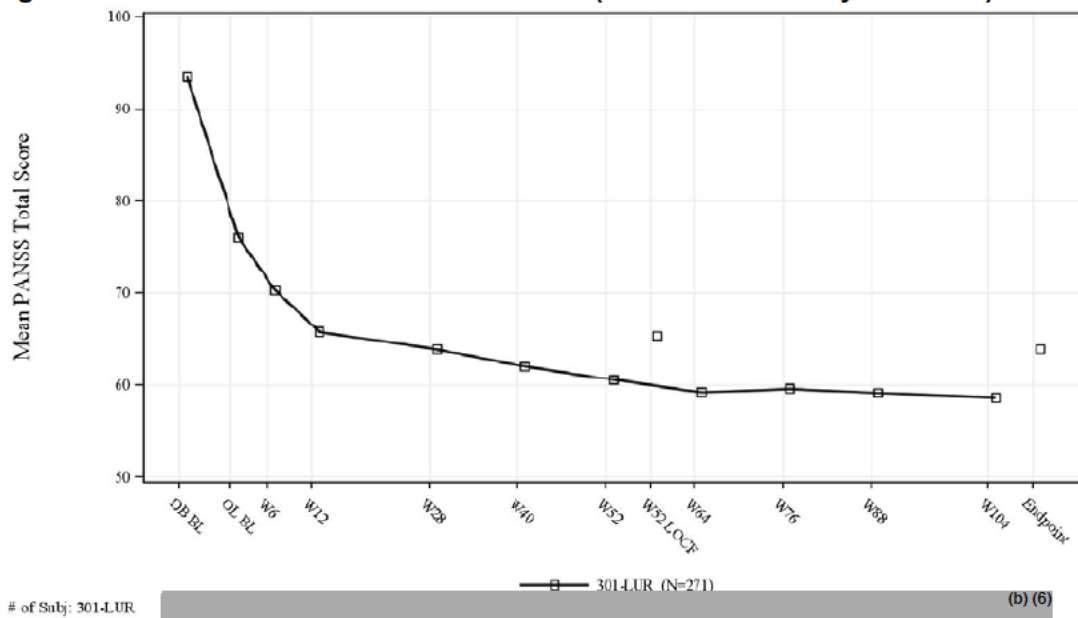
Efficacy

Clinical stability was evaluated by use of diagnosis-appropriate measures of efficacy during extension treatment.

For patients with schizophrenia (from Study D1050301), the mean PANSS total scores over time are depicted in Figure 1 and show clinical improvement from open-label baseline (OL BL). None of the PANSS subscales (positive symptoms, negative symptoms, or general psychopathology) showed clinical deterioration at

any time point during extension therapy. The mean CGI-S scores followed a similar pattern.

Figure 1: Mean PANSS Total Scores Over Time (Patients from Study D1050301)

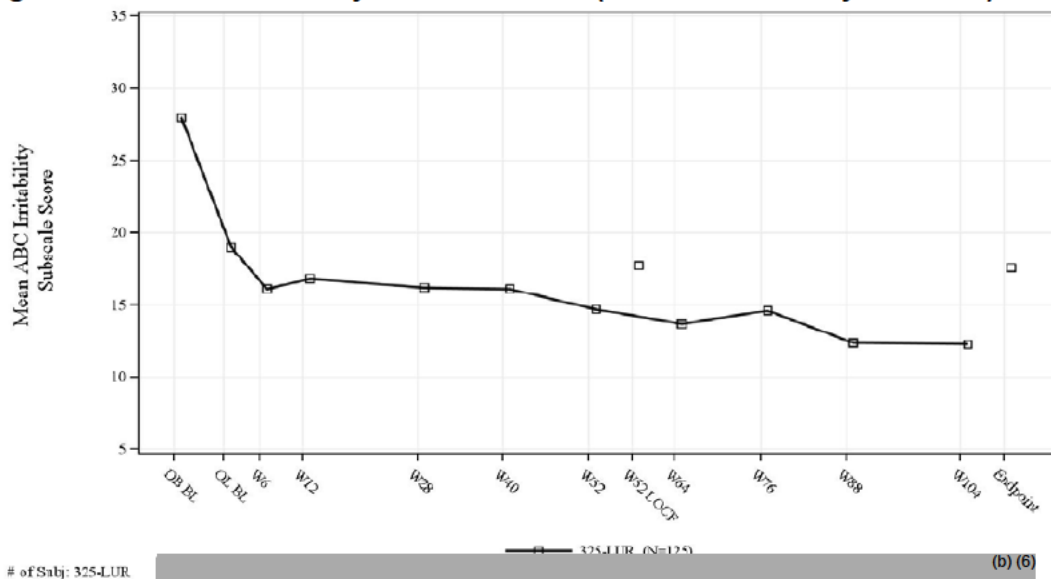


Abbreviations: BL = Baseline; DB = double-blind; LOCF = last observation carried forward; OL = open-label; PANSS = Positive and Negative Syndrome Scale; W = week; 301-LUR = all subjects continued from Study D1050301.

Source: CSR Figure 9.

For patients with autistic disorder from Study D1050325, the mean ABC Irritability subscale scores over time are portrayed in Figure 2. There was some improvement at all time points from open-label baseline. The pattern of improvement on the CGI-S was similar.

Figure 2: Mean ABC Irritability Subscale Scores (Patients from Study D1050325)

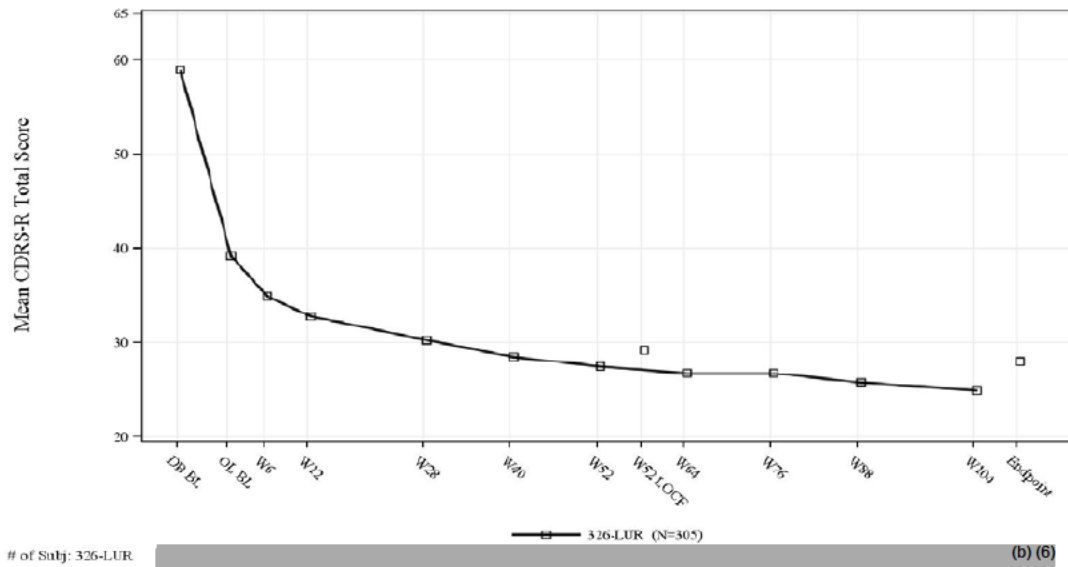


Abbreviations: ABC = aberrant behavior checklist; BL = Baseline; DB = double-blind; LOCF = last observation carried forward; OL = open-label; W = week; 325-LUR = all subjects continued from Study D1050325.

Source: CSR Figure 17.

Figure 3 displays the mean CDRS-R total scores for patients with bipolar depression (from Study D1050326). These data show improvement in depressive symptomatology during extension treatment. Mean CGI-BP-S Depression scores showed a similar pattern of improvement over time.

Figure 3: Mean CDRS-R Total Scores Over Time (Patients from Study D1050326)

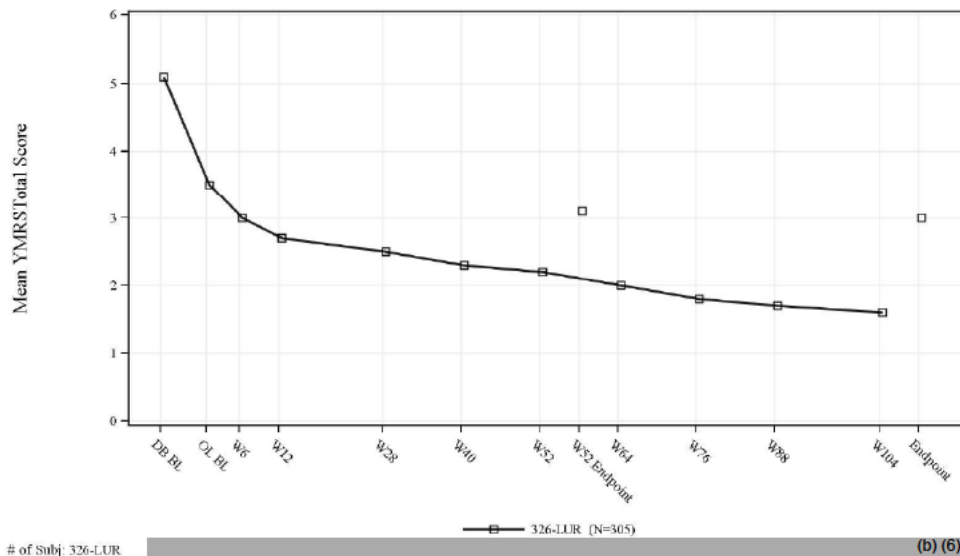


Abbreviations: BL = Baseline; CDRS-R = Children's Depression Rating Scale, Revised; DB = double-blind; LOCF = last observation carried forward; OL = open-label; W = week; 326-LUR = all subjects continued from Study D1050326.

Source: CSR Figure 23.

In addition, patients with bipolar depression experienced, on average, a reduction in manic symptomatology during this study, as shown in the following plot of mean Y-MRS total scores over time (Figure 4).

Figure 4: Mean Y-MRS Scores Over Time (Patients from Study D1050326)



Source: CSR Table 14.20.1.1.96a

A total of 38 of the 701 patients (5.4%) in the safety population discontinued from this study with lack of efficacy as the stated reason for dropout. The proportion of patients who discontinued for this reason was highest in the autistic disorder group (12.8%) and considerably lower for patients with schizophrenia and bipolar depression (4.1% and 1.6%, respectively).²³

Overall, these data suggest that patients, on average, did not experience a decrease in efficacy for their underlying illness during long-term lurasidone treatment.

III. Pediatric Review Committee Comments

The Pediatric Review Committee (PeRC) evaluated the findings from this Pediatric Assessment on November 5, 2019. The PeRC had only one recommendation, that is, that the labeling language that describes changes in weight and height in terms of z-score changes should include text to indicate that the magnitude of these changes did not indicate any clinically significant deviation from the normal growth curves, because prescribers may not be familiar with the proper interpretation of z-score data.

IV. Overall Recommendations for Regulatory Action

This study fulfills PMR 2058-2 under NDA 200603.

No new, substantial safety findings that would preclude use in pediatric patients or require major changes to labeling were seen in this trial.

Nonetheless, I recommend that information from this trial regarding the report of priapism and data relevant to metabolic changes, weight gain, changes in height, elevations in prolactin, and increases in serum creatinine be added to Latuda labeling, as indicated by Track Changes in the labeling attached to this review. I recommend that the Division negotiate these changes with the Applicant.

V. Comments to the Applicant

We have completed our review of labeling supplement S-035, which conveys the Clinical Study Report for Study D1050302 to fulfill PMR 2058-2. Before this supplement may be approved, we request labeling changes to incorporate important safety findings from this trial. Specifically, we request that the report of priapism in Patient (b) (6) and data describing metabolic changes, weight gain, changes in height, elevations in prolactin, and increases in serum creatinine be added to Latuda labeling, as indicated by Track Changes in the attached labeling.

²³ Figures were computed by the reviewer from the dataset ADSL.xpt using JMP 11.1.1.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

GREGORY M DUBITSKY

11/06/2019 12:07:08 PM

Recommend negotiation of labeling changes with the Applicant.

JAVIER A MUNIZ

11/13/2019 03:08:44 PM