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Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Latuda

lurasidone

Procedure no: EMEA/H/C/002713/P46/008

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

The 12th December 2017, the MAH submitted a completed paediatric study for Latuda, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study D1050326 is a standalone study.

Latuda was approved for the treatment of schizophrenia in adults in EU on 21st March 2014.

Currently Latuda has no paediatric indication. The MAH stated that the submitted paediatric study does not influence the benefit risk for Latuda and that there is no consequential regulatory action.

This is the first paediatric study submitted for the treatment of bipolar depression with lurasidone. There is no agreed Paediatric Investigation Plan (PIP) for the treatment of bipolar depression.

According to the PIP (P/0214/2016) for schizophrenia, the studies in the paediatric clinical program for schizophrenia are according to below (see also Annex 1).

Study 1

Open-label, multicentre, single and multiple fixed ascending dose study to evaluate pharmacokinetics, safety, and tolerability of lurasidone in the paediatric population (D1050300). Completed, submitted and assessed.

Study 2

Randomised, parallel, double-blind, placebo-controlled, fixed-dose regimen, multicentre, study to evaluate the efficacy and safety of lurasidone in adolescent patients with schizophrenia (D1050301). Completed, submitted and assessed.

Study 3

A 104-week, flexible-dose, open-label multicentre extension study to evaluate the long-term safety and effectiveness of lurasidone in adolescent patients with schizophrenia (D1050302). Date of completion (last patient, last visit): By April 2018.

Study 4

Randomised, double-blind, active-controlled, non-inferiority, flexible dose study to evaluate the maintenance of the efficacy of lurasidone compared to aripiprazole in the treatment of adolescent patients with schizophrenia (5474). Date of completion (last patient, last visit): By April 2018.

CHMP comment

According to the CSR provided by the MAH, subjects in Study D1050326, ie on bipolar depression, who completed the study were eligible to participate in the separate 104-week open-label extension Study D1050302 in adolescent patients with schizophrenia. However, in the Clinical overview provided by the MAH, the title of Study Long-term D1050302 is as follows: "A 2-year, open-label extension to D1050301, multicenter, flexible-dose clinical study to evaluate the long-term safety and efficacy of

lurasidone in children and adolescent subjects (6 to <18 years old)."

2.2. Information on the pharmaceutical formulation used in the study

The investigational product was film-coated lurasidone 20 mg active tablets, 40 mg active tablets, 20 mg placebo tablets, and 40 mg placebo tablets. The study drug was packaged as 20 mg, 40 mg, or placebo tablets in Aluminum-Aluminum blister cards. Study drug was labeled with the clinical trial number and all appropriate investigational labeling requirements

2.3. Clinical aspects

For complete information, see Lurasidone D1050326 clinical study report (CSR) provided by the MAH.

2.3.1. Introduction

Lurasidone is a novel compound synthesized by Sumitomo Dainippon Pharma Co., Ltd. with high affinities for dopamine D2 and serotonin 5-hydroxytryptamine (5-HT) 2A and 5-HT7 receptors, moderate affinity for serotonin 5-HT1A and noradrenaline α2C and α2A receptors, and little or no affinity for histamine H1 and muscarinic M1 receptors. It has been postulated that one of the potential antidepressant mechanisms exhibited by lurasidone is related to its high affinity to the 5-HT7 receptor (Stahl, 2013).

As of 27 Oct 2016, lurasidone has been approved for the treatment of adult patients with schizophrenia in Australia, Canada, the European Union (EU), the Russian Federation, Singapore, Switzerland, Taiwan, Thailand, and the United States (US). Within the EU, lurasidone is marketed for the treatment of adult patients with schizophrenia in Denmark, Finland, Norway, the Netherlands, Sweden, and the United Kingdom. In addition, lurasidone has been approved for the treatment of major depressive episodes associated with bipolar I disorder (bipolar depression) as monotherapy and as adjunctive therapy with lithium and valproate in adult patients in Canada and the US.

Lurasidone has been evaluated both as monotherapy and adjunctive therapy (to lithium or valproate) in two 6-week trials in adults with bipolar depression, and has received the US Food and Drug Administration (FDA) approval for monotherapy and adjunctive treatment in this disorder. The pharmacologic profile and demonstrated efficacy and safety in adult patients with bipolar depression suggests that lurasidone, as monotherapy, may be an effective treatment in the pediatric bipolar depression population.

To date, there have been 3 completed clinical studies of lurasidone in children and/or adolescents. One study (D1050300) evaluated the safety, tolerability, and pharmacokinetics (PK) of single and multiple doses of lurasidone in adolescents (12 to 17 years of age) and children (6 to 11 years of age) with schizophrenia spectrum, bipolar spectrum, autistic spectrum disorder, and other psychiatric disorders. A second study (D1050325) evaluated the efficacy and safety of 2 doses of lurasidone in children and adolescents with irritability associated with autistic disorder. The third study (D1050301) evaluated the efficacy and safety of 2 doses of lurasidone in adolescents (13 to 17 years of age) with schizophrenia.

Adult bipolar disorder is a chronic and often disabling condition with a lifetime prevalence of approximately 4.4% (Merikangas, 2007) The treatment of bipolar disorder is a challenging clinical endeavor, in part due to its symptomatic complexity involving both relatively distinct, as well as, at times, overlapping manic and depressive phases (mania, mixed mania, and depression).

Although standard antidepressants are widely used in bipolar depression, their use remains controversial in part due to their tendency to induce switching into hypomania or mania and induce cycle acceleration (APA, 2002). Clearly, new effective and safe treatments are needed for the treatment of depressive states in bipolar disorder, especially since these represent the most common conditions experienced over the illness course (Judd, 2002; Judd, 2003).

It is now recognized that pediatric bipolar disorder is a prevalent and morbid disorder and represents a significant public health concern. Approximately 14% to 28% of patients with bipolar disorder experience onset of illness before age 13 and 50% to 67% experience onset before age 19 (Leverich, 2007). These children comprise a complex psychopathologic patient population who are characterized by poor functioning, high rates of hospitalization, and elevated need for special education services. Earlier age of onset has been associated with a more difficult and complicated course of illness, including faster cycling, more days depressed, greater frequency of lifetime manic and depressive episodes, increased risk of substance abuse and other comorbidities, as well as a higher lifetime risk of suicide attempts (Leverich, 2007).

Compared with adults, children and adolescents show a greater sensitivity to a range of antipsychotic-related adverse events (AEs) with second generation antipsychotics (Ratzoni, 2002; Correll, 2011). Treatment with atypical antipsychotics can be associated with significant weight gain and metabolic abnormalities, a profile which may differ across atypical antipsychotic agents.

The MAH submitted a final report(s) for study D1050326, assessed in the sections below.

2.3.2. Clinical study

D1050326 - A RANDOMIZED, 6-WEEK, DOUBLE-BLIND, PLACEBO-CONTROLLED, FLEXIBLE DOSE, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF LURASIDONE IN CHILDREN AND ADOLESCENT SUBJECTS WITH BIPOLAR I DEPRESSION

Description

The efficacy of lurasidone for the treatment of children and adolescent subjects (10-17 years) with bipolar depression was demonstrated in a randomized, parallel-group, double-blind, placebo-controlled, flexibly dosed, 6-week multi-centre study.

Methods

Objectives

Primary Objective

The primary objective of this study was to evaluate the efficacy of lurasidone (20 to 80 mg/day flexibly dosed) compared with placebo in children and adolescent subjects with bipolar I disorder, most recent episode depressed, with or without rapid cycling disease course, and without psychotic features (diagnosed by Diagnostic and Statistical Manual of Mental Disorders, 5th Ed. [DSM-5] criteria) as measured by the change from Baseline in the Children's Depression Rating Scale, Revised (CDRS-R) total score.

Key Secondary Objective

The key secondary objective of this study was to evaluate the efficacy of lurasidone

(20 to 80 mg/day flexibly dosed) compared with placebo as measured by the Clinical Global Impression-Bipolar Version, Severity of Illness (CGI-BP-S) score (depression).

Other Secondary Objectives

The other secondary objectives of this study 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
- Change in attention deficit/hyperactivity symptoms as measured by the Attention Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS) score
- Safety and tolerability of lurasidone 20 to 80 mg/day flexibly dosed as measured by AEs, laboratory measurements, and physical examination
- Treatment-emergent mania, defined as YMRS score of ≥ 20 on any 2 consecutive visits or at the final assessment, or an AE of mania or hypomania

Study design

This was a randomized, parallel, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of flexibly dosed lurasidone (20 to 80 mg/day) for 6 weeks compared with placebo in children and adolescent subjects with depression associated with Bipolar I Disorder (bipolar depression).

Subjects could have been inpatient, outpatient, or partially hospitalized and could have been attending therapeutic day programs, other supported rehabilitation programs, or school. Subjects could have been hospitalized at the discretion of the Investigator for up to 14 days without prior approval of the Medical Monitor. For hospitalization beyond the first 14 days, prior approval by the Medical Monitor was required on a weekly basis (7 days), and was allowed up to the entire study period. For hospitalized subjects, they must have been clinically stable, in the judgment of the Investigator, to warrant discharge to the appropriate living environment. In making a discharge determination, Investigators should also have considered the following additional factors: appropriateness for outpatient treatment; a stable residence with adequate caregiver support; and the ability of the subject to be compliant with study drug and study visits.

If a subject discontinued during the treatment period and was clinically unstable, additional hospitalization (beyond the original 14 days allowed) could have been allowed on a case-by-case basis with pre-approval of the Medical Monitor.

For both outpatient and inpatient subjects, a reliable informant (eg, parent, legal guardian, or caregiver) of the subject was to accompany the subject at each visit.

Subjects were evaluated for eligibility during a screening period of up to 21 days, during which they were tapered off all psychotropic medications (except for those explicitly permitted per protocol [PP]) in a manner that is consistent with labeling recommendations and conventional medical practice.

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.

Subjects who received lurasidone were dosed at 20 mg for 7 days (Day 1 to Day 7). Flexible dosing (20 to 80 mg/day) of study drug was permitted after 7 days (ie, beginning on Day 8), based on investigator judgment, to optimize efficacy and tolerability. Dose changes to optimize efficacy (including increases and decreases), when necessary, were to occur at weekly visits. In general, dose adjustments were to occur at least 1 week apart and 1 dose level at a time to allow for adequate evaluation of clinical efficacy. However, dose reductions for tolerability or safety purposes were permitted to occur more frequently than at weekly intervals and more than 1 dose level at a time (maximum of 2 dose levels at a time), beginning at Day 8. If dose reductions were required between regular study visits, the subject returned to the study site for an unscheduled visit to receive new medication kits and return all used/unused medication kits at the time of dose adjustment.

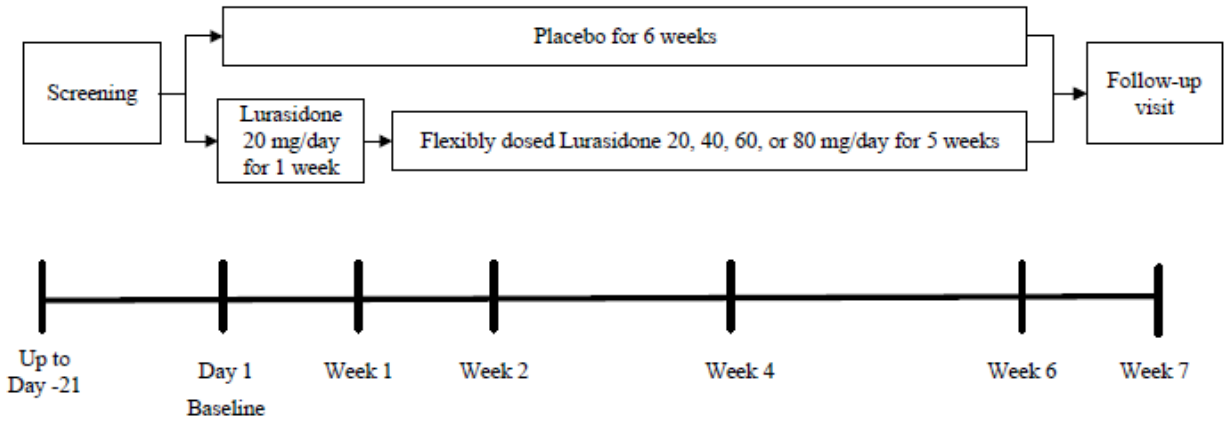
Safety and efficacy assessments were conducted at scheduled visits during the study. A follow up visit occurred 7 ± 2 days after the last dose of study drug.

Subjects who completed the study were eligible to participate in a separate 104-week open-label extension study (D1050302).

A Data and Safety Monitoring Board (DSMB) reviewed the safety and clinical outcome data, including data on AEs and SAEs, at regular intervals. The DSMB was independent of the Sponsor, 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. The DSMB could have reviewed blinded, unblinded, or partially unblinded data, but the Sponsor (with the exception of the authorized members of the Pharmacovigilance and Risk Management department who were independent from the core study team and were responsible for reporting suspected unexpected serious adverse reactions), CROs, and the Investigators were to remain blinded until the official unblinding of the database. The membership of the DSMB and its mandate are described in the DSMB charter (Appendix 16.1.9.3).

A study schematic is presented below in Figure 1 of the CSR. Details of study assessments and other procedures to be performed at each visit are presented in Table 2 of the CSR, Schedule of Assessments.

Study schematic



Schedule of Assessments

Study Visit Number Study Visit Type	Visit 1 Screening[a]	Visit 2 Baseline	Visit 3 Week 1	Visit 4 Week 2	Visit 5 Week 3	Visit 6 Week 4	Visit 7 Week 5	Visit 8[b] Week 6	Visit 9 Follow-up Week 7[c]
Study Visit Day (± 2 days)	**-21 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**
Obtain informed consent/assent	X								
Inclusion/exclusion criteria	X	X							
Randomize to treatment		X							
Interactive Voice/Web Response System (IXRS) subject registry/visit	X	X	X	X	X	X	X	X	X
Dispense study drug		X	X	X	X	X	X		
Study drug accountability/assess compliance			X	X	X	X	X	X	
Clinical and Laboratory Evaluations:									
Prior/concomitant medication review	X	X	X	X	X	X	X	X	X
Adverse event monitoring	X	X	X	X	X	X	X	X	X
Medical history	X								
Psychiatric history/mental status	X								
Schedule for Affective Disorders and Schizophrenia for School-age Children (K-SADS-PL)	X								
Physical examination	X							X	
Vital signs[d]	X	X	X	X	X	X	X	X	X
Height as measured by stadiometer	X							X	
Weight	X	X	X	X	X	X	X	X	X
Waist circumference measurement		X						X	
Tanner staging	X							X	
Menstrual cyclicity (female subjects)		X						X	
Electrocardiogram (ECG)	X	X						X	
Hematology, chemistry, and urinalysis	X	X						X	
Hormonal Parameters [e]	X	X						X	
Blood sample for lurasidone concentration [f]								X	
Serum prolactin [g]	X	X						X	
Glycosylated hemoglobin (HbA_{1c})	X	X						X	
Glucose and lipid panel	X	X[h]						X	
Serum insulin and C-reactive protein		X						X	
Serum beta subunit of human chorionic gonadotropin (β-hCG) (females only) [i]	X								
Urine drug screen	X	X			X			X	
Urine β-hCG [i, j]		X			X			X	X
Barnes Akathisia Rating Scale (BARS)		X	X	X	X	X	X	X	X
Abnormal Involuntary Movement Scale (AIMS)		X	X	X	X	X	X	X	X
Simpson-Angus Scale (SAS)		X	X	X	X	X	X	X	X
Children's Depression Rating Scale, Revised (CDRS-R)	X	X	X	X	X	X	X	X	

Study Visit Number Study Visit Type	Visit 1 Screening[a]	Visit 2 Baseline	Visit 3 Week 1	Visit 4 Week 2	Visit 5 Week 3	Visit 6 Week 4	Visit 7 Week 5	Visit 8[b] Week 6	Visit 9 Follow-up Week 7[c]
Study Visit Day (± 2 days)	**-21 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**
Cogstate Computerized Cognitive Test Battery	X	X						X	
Clinical Global Impression-Bipolar Version, Severity of Illness (CGI BP-S)	X	X	X	X	X	X	X	X	
Children's Global Assessment Scale (CGAS)		X			X			X	
Young Mania Rating Scale (YMRS)	X	X	X	X	X	X	X	X	
Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)		X			X			X	
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X	X	X	X	X	X	X	X
Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU)		X			X			X	
Pediatric Anxiety Rating Scale (PARS)		X			X			X	
Attention Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS)		X						X	

[a] Screening period could occur over more than 1 day.
[b] If a subject discontinued from the study, all Visit 8 procedures were to be performed at the discontinuation visit, within 48 hours of the last dose of study drug. Subjects who continued in the extension study (D1050302) received extension phase medication at Visit 8. The extension study (D1050302) began at the end of Week 6 (Visit 8).
[c] Visit 9 was only for subjects not entering the extension study (D1050302).
[d] Vital sign measurements included orthostatic changes in blood pressure and heart rate (HR).
[e] Hormonal Parameters included follicle stimulating hormone, luteinizing hormone, testosterone (male subjects only), and estradiol (female subjects only).
[f] Time and date of the 3 previous doses of study drug and the time of the blood sampling were to be recorded.
[g] Prolactin levels were blinded, except at screening and Baseline visits. The Investigator was to be notified if prolactin concentrations were more than 200 ng/mL.
[h] Subjects fasted for lipids and glucose laboratory tests only. These visits were to be scheduled in the morning, and blood work was to be done first.
[i] Required only for female subjects ≥ 11 years of age.
[j] Any positive urine β-hCG test was to be confirmed by serum β-hCG.

Study population /Sample size

Inclusion criteria

Male or female subjects 10 to 17 years of age, inclusive, with a DSM-5 diagnosis of bipolar I disorder, 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, confirmed by a trained clinician by means of the Schedule for Affective Disorders and Schizophrenia for School-age Children [K-SADS-PL]). Eligible subjects must have had a lifetime history of at least 1 manic episode, a current major depressive episode ≥ 4 weeks and < 12 weeks, a CDSR-R score ≥ 45 and a YMRS score ≤ 15 (with YMRS Item 1 [elevated mood] score ≤ 2) at screening and Baseline, and have been 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

Subjects with Axis I or Axis II diagnosis (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition [DSM-IV]) or any DSM-5 diagnosis other than bipolar I disorder that had been the primary focus of treatment within 3 months of screening, intellectual disability, autism spectrum disorder, neurologic 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 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. Subjects were also excluded if they had moderate or severe extrapyramidal symptoms, dystonia, tardive dyskinesia, or any other severe movement disorder; a lifetime history of electroconvulsive therapy; resistance to

antipsychotic treatment or history of non-response to antidepressants; or if they were considered by the Investigator to be at imminent risk of suicide or injury to self, others, or property during the study.

Treatments

The study drug was lurasidone 20 mg tablets, 40 mg tablets, and matching placebo.

Double-blind study drug was packaged in uniquely identifiable 7-day (plus 2 days) blister cards. Each blister card contained 3 columns and 9 rows. Each row contained 3 tablets of study drug. Depending on treatment assignment, each tablet contained lurasidone 20 mg, lurasidone 40 mg, or matching placebo. Subjects were required to take 3 tablets (1 row) each day, according to dosing instructions. All study drug was to be taken once daily in the evening by mouth with food (at least 350 calories) or within 30 minutes after eating.

Flexibly dosed lurasidone 20 to 80 mg/day doses were selected based on the following:

- The PK data from Study D1050300 demonstrated similar exposure (eg, maximum plasma concentration and area under the concentration-time curve) between the pediatric and adult populations.
- Doses up to 80 mg were safe and well tolerated in Study D1050300.
- Doses up to 120 mg per day flexibly dosed have demonstrated efficacy and safety in the adult

See also page 7 of this report.

Method of Assigning Subjects to Treatment Groups

Subjects who meet eligibility criteria were randomly assigned to receive either lurasidone 20 to 80 mg/day, flexibly dosed, or matching placebo in a double-blind fashion (1:1).

To avoid a potential imbalance in treatment allocation between younger and older subjects and between those treated with ADHD stimulant medications versus not treated, randomization within a country was balanced using permuted blocks with 2 stratification criteria applied: 1) age group (10 to 14 years old at screening and 15 to 17 years old at screening); and, 2) stimulant usage status. Stratification by age group and ADHD stimulant usage status was employed as a conservative measure in light of literature that suggested imbalances in age of diagnosis (Marchand, 2006) and the comorbidity of ADHD (Butler, 1995) with pediatric bipolar disorder.

Outcomes/endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint was the change in the CDRS-R total score compared with placebo from double-blind Baseline to Week 6.

Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint was the change in CGI-BP-S score (depression) compared with placebo from double-blind Baseline to Week 6.

Other Secondary Efficacy Endpoints

The other secondary efficacy endpoints of this study were:

- Change from Baseline in PARS score compared with placebo
- Change from Baseline in PQ-LES-Q score compared with placebo

- Change from Baseline in CGAS score compared with placebo
- Proportion of responders, where response is defined as ≥ 50% reduction from Baseline in adjusted CDRS-R total score at last observation carried forward (LOCF) Endpoint compared with placebo
- Proportion of subjects achieving remission, where remission is defined as post-Baseline CDRS-R total score ≤ 28, YMRS total score ≤ 8, and CGI-BP-S depression score ≤ 3
- Change from Baseline in ADHD-RS score compared with placebo

Safety Endpoints

Safety measurements included the following:

- Proportions of subjects with AEs, discontinuations due to AEs, and serious AEs (SAEs)
- Frequency and severity of suicidality using the Columbia Suicide Severity Rating Scale (C-SSRS)
- Vital signs and electrocardiogram (ECG) measurements
- Movement disorders assessed by the Barnes Akathisia Rating Scale (BARS), the Abnormal Involuntary Movement Scale (AIMS), and the Simpson-Angus Scale (SAS)
- Weight, body mass index (BMI), and waist circumference
- Laboratory measurements (including hormonal parameters), Tanner staging, menstrual cyclicity (female subjects), and physical examinations
- Cogstate Computerized Cognitive Test Battery
- Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU)
- Proportion of subjects with treatment-emergent mania, defined as a YMRS score of ⩾20 on any 2 consecutive visits or at the final assessment, or an AE of mania or hypomania

CHMP comment

Primary and key secondary endpoints and treatment duration were in line with EMA Guidelines on depression.

Statistical Methods

All statistical tests were interpreted at a 2-sided significance level of 5% and all confidence intervals (CIs) were presented at a 2-sided confidence level of 95%. The overall type I error rate for testing lurasidone 20 to 80 mg/day versus placebo was strongly controlled at the 5% level across the primary and key secondary endpoints using a sequential testing procedure. The primary efficacy outcome was to be tested first, and if the result was found to be statistically significant at a 5% level, then the key secondary efficacy outcome was to be tested. Otherwise, the testing procedure would stop. This closed testing procedure did not require an alpha spending adjustment. There were no adjustments for multiplicity for secondary efficacy analyses or safety analyses.

Analysis Population

The primary analysis population for all efficacy analyses was the Intent-to-Treat (ITT) population. The ITT Population included all randomized subjects who received at least 1 dose of study drug and had at least 1 post-Baseline assessment in any efficacy variable. The PP Population included all ITT subjects who had no important protocol deviations that could have impacted the efficacy analysis. The Safety Population included all randomized subjects who received at least 1 dose of study drug and was used for all safety data analyses. Subjects were analyzed for efficacy according to the treatment group to which they were randomized. Subjects were analyzed for safety according to the predominant treatment actually received, defined as the treatment to which the subject was exposed for the greatest duration. In the event of a tie, the treatment closest to the last day of study drug was selected as the predominant treatment. Predominant treatment was generally the same as the randomized treatment, unless the subject received incorrect therapy during the entire study.

Age Group versus Age Strata

The stratification variable at randomization (ie, in IXRS), age stratum ("10 to 14 years" or "15 to 17 years" at screening), was used in all efficacy analyses.

Two additional age groupings (defined below) were used to support age-related safety analyses selected efficacy data summaries, and a limited number of descriptive analyses for Baseline and demographic characteristics:

• Age group at screening: "10 to 12 years" or "13 to 17 years"

• Age group at screening: "10 to 12 years", "13 to 15 years", or "16 to 17 years"

The primary efficacy endpoint

The primary efficacy endpoint was the change in CDRS-R total score from Baseline at Week 6. The CDRS-R is a semi-structured, clinician-rated instrument designed for use with children and adolescents between the ages of 6 and 17 years. The CDRS-R was administered separately to the subject and caregiver, and it contained 17 ordinally-scaled items that evaluated the presence and severity of symptoms commonly associated with depression in childhood:

• Fourteen items were based on separate interviews with the child and parent and assessed impaired schoolwork, difficulty having fun, social withdrawal, sleep disturbance, appetite disturbance, excessive fatigue, physical complaints, irritability, excessive guilt, low self-esteem, depressed feelings, morbid ideation, suicidal ideation, and excessive weeping. The 14 items were rated on a 1 (no psychopathology) to 7 (most psychopathology) scale, where a rating of 3 represented mild psychopathology.

• Three items were based solely on the rater's observation of the child (ie, no questions). These 3 items assessed sleep disturbance, appetite disturbance, and listless speech, and were rated on a 1 (no pathology) to 5 (most pathology) scale.

The CDRS-R total score ranges from 17 to 113. In general, higher values of the CDRS-R total score represent a greater severity of illness.

Mixed Model for Repeated Measures

The primary efficacy endpoint (the change from Baseline in the CDRS-R total score at Week 6) was analyzed using a likelihood-based mixed model for repeated measures (MMRM). The response (dependent) variable was the change from Baseline in CDRS-R total score assessed weekly (Weeks 1 to 6). The MMRM model included fixed effects terms for treatment, visit (as a categorical variable),

pooled country, age stratum, CDRS-R total score at Baseline, and treatment-by-visit interaction. An unstructured covariance model was fit using restricted maximum likelihood estimation. Denominator degrees of freedom were computed with the Kenward-Rogers method. The likelihood based mixed effects model could accommodate incomplete data under the missing-at-random assumption. If the model did not converge, a robust sandwich estimator of the standard error (SE) of the fixed effects and a spatial exponential covariance pattern model was used.

The treatment difference (lurasidone group minus placebo) in least squares (LS) mean, its 2-sided 95% CI, and the associated p-value based on the MMRM model were presented. In addition, descriptive statistics (mean, SD, and 95% CI) were provided for the CDRS-R total score and change from Baseline by study visit for each treatment group.

The primary efficacy analysis was repeated for the PP Population to examine the impact of premature dropouts and/or protocol deviations.

Supportive Analysis

As a supportive analysis of the primary efficacy outcome, the change from Baseline in CDRS-R total score at Week 6 was analyzed in the ITT Population with an analysis of covariance (ANCOVA) model that included fixed effects for treatment, pooled country, age stratum, and the Baseline CDRS-R score as covariate using the LOCF approach. The LS mean of the treatment difference (lurasidone minus placebo), the 2-sided 95% CI, and the associated p-value were presented.

Sensitivity Analysis

The robustness of the MMRM results for the primary efficacy outcome in the ITT Population were explored in a sensitivity analysis using a pattern mixture model (PMM) with placebo-based multiple imputation (Attachment 4.3.1 of the SAP). This method was based on a method proposed by Ratitch and O'Kelly (Ratitch, 2011). The assumption that efficacy profiles of dropouts after discontinuation were similar to those of placebo subjects is very conservative because it tends to minimize the difference between lurasidone and placebo groups. To corroborate the robustness of the MMRM result, the primary efficacy outcome was analyzed with the random effects PMM to assess the impact of dropout pattern (Attachment 4.3.2 of the SAP) (Hedeker, 1997) in the ITT Population. Since roughly 86% of subjects were completers, the subjects were classified into 2 categories: completers and dropouts.

Supplemental/Additional Analyses

As pre-specified in the protocol, a supplemental MMRM model was performed using the same predictor terms described above for primary efficacy analysis plus 2 additional terms: ADHD stimulant usage (stratification factor) and treatment-by-ADHD stimulant usage interaction as a fixed effect to evaluate the impact of this factor on treatment effect. Additional analyses of the primary efficacy outcome were performed to assess the consistency of the treatment effect across countries and age group by adding the following interaction terms to the primary MMRM model: treatment-by-pooled country and treatment-by-age group. The p-value of each interaction term (ie, treatment-by-stimulant usage, treatment-by-pooled country interaction and treatment-by-age group) was presented. If the interaction term appeared to be significant ($p < 0.10$), further exploration was done to further determine the nature of the interaction. This was performed for the ITT Population.

Effect Size

Effect size for within-group and between-group was presented at each post-Baseline visit for all efficacy endpoints in MMRM and ANCOVA-based output. Within-group effect size was calculated as

mean change from Baseline divided by the SD. Based on the MMRM, the between-group effect size at a visit was calculated as the LS mean difference from placebo divided by the model estimate of the pooled SD at the visit, which was obtained from the square root of the diagonal element, associated at the visit, from the covariance matrix; based on the ANCOVA model, between-group effect size was calculated as the LS mean difference from placebo divided by the model estimate of the pooled SD, which was calculated as the SE of the LS mean difference divided by the square root of the sum of inverse treatment group sample sizes.

Subgroup Analysis

The primary efficacy variable (change from Baseline in CDRS-R total score at Week 6) and the key secondary variable (change from Baseline in CGI-BP-S depression score at Week 6) were examined to explore the consistency of the treatment effect across the subgroups listed below (if there were at least 30 subjects in the subgroup) with an LOCF approach based on the ITT Population:

• Gender: Male, female

• Race group: White, non-white

• Age stratum (stratification variable): 10 to 14 years, 15 to 17 years at screening

• Age group: 10 to 12 years, 13 to 17 years at screening

• Country: US, non-US

• ADHD stimulant usage stratum: Yes, no

• Ethnicity: Hispanic, non-Hispanic

• BMI (kg/m2) at screening: < 25th, 25th to 85th, > 85th percentile

Key secondary efficacy outcome

The key secondary efficacy outcome was the change from Baseline at Week 6 in CGI-BP-S depression score. The CGI-BP-S is a 3-question clinician-rated assessment of the subject's current illness state (depression, mania, and overall) using a 7-point scale that ranges from 1 (normal, not ill) to 7 (very severely ill) for each question. A higher score is associated with greater illness severity.

The change from Baseline in CGI-BP-S depression score at Week 6, for treatment comparisons of lurasidone 20 to 80 mg/day versus placebo, was analyzed using a MMRM model that was similar to the one described for the primary variable (ie, with fixed effects terms for treatment, visit as a categorical variable, pooled country, age stratum [stratification factor], CGI-BP-S depression score at Baseline, and treatment-by-visit interaction).

The secondary efficacy endpoint was also analyzed using sensitivity analyses, supportive analyses, supplemental and additional analyses, and subgroup analyses similar to those used for the primary variable.

Safety Analysis

All safety summaries were based on the Safety Population. Safety reports included all safety data collected during the 6-week double-blind period, as well as all safety data collected post-treatment if a subject did not enter the extension study.

To provide better interpretation for safety data related to age, for all safety assessments and in a limited number of descriptive analyses, data was presented based on the following age groups at screening:

- “10 to 12 years” and “13 to 17 years”
- “10 to 12 years”, “13 to 15 years”, and “16 to 17 years”

Unless otherwise specified, for all safety data based on statistical analyses (eg, MMRM, ANCOVA, rank ANCOVA, etc), when “similar model to the efficacy analysis” is stated, it should be interpreted as that age group (“10 to 12 years”, “13 to 17 years” at screening) was uniformly used (ie, age stratum is replaced and no longer a model term) in the corresponding statistical model while no other change of model terms was made.

There was no imputation of missing values for clinical laboratory test results, vital sign measurements, and ECG evaluations in the by-visit analyses.

Results

Recruitment / Number analysed

Of the 450 subjects screened, 350 (77.8%) subjects were randomized to receive study treatment. A total of 100 (22.2%) subjects were screen failures, including 71 (15.8%) subjects who failed to meet inclusion criteria, 18 (4.0%) subjects who withdrew their consent, 5 (1.1%) subjects who were lost to follow-up, 5 (1.1%) subjects who were withdrawn by the Investigator, and 1 (0.2%) subject who was withdrawn by the Sponsor..

Thirty two (9.1%) randomized subjects discontinued from the study. The number of discontinuations and the primary reason for each discontinuation was similar in both treatment groups. The most common reason for discontinuation was withdrawal of informed consent (9 [2.6%] subjects), followed by lack of efficacy, adverse event, and lost to follow-up (6 [1.7%] subjects each). There were 3 (0.9%) subjects who discontinued due to a protocol violation (see table below). A Kaplan-Meier plot of time to discontinuation is presented in the figure below.

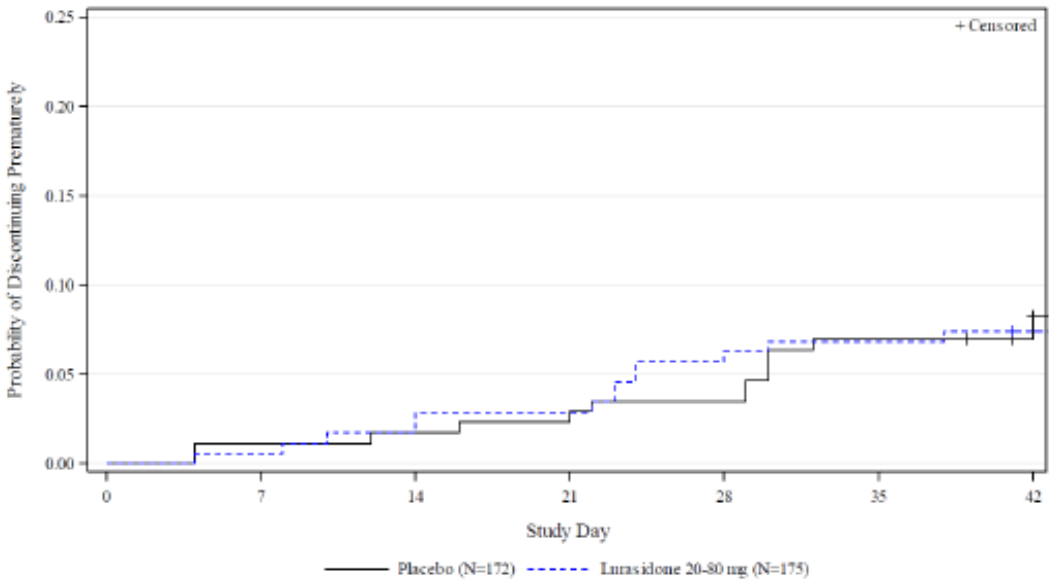
A total of 318 (90.9%) subjects completed the 6-week double-blind period of the study, and 306 (87.4%) subjects entered the open-label extension study (D1050302).

Subject Disposition (All Randomized Subjects)

	Placebo (N = 174) n (%)	Lurasidone 20 to 80 mg (N = 176) n (%)	Total (N = 350) n (%)
Number randomized	174 (100.0)	176 (100.0)	350 (100.0)
Number randomized, but not dosed	2 (1.1)	1 (0.6)	3 (0.9)
Number who completed the 6-week double-blind period	156 (89.7)	162 (92.0)	318 (90.9)
Number who completed the 6-week double-blind period and entered into the open-label extension Study D1050302	150 (86.2)	156 (88.6)	306 (87.4)
Number who discontinued during the double-blind period by primary reason for discontinuation	18 (10.3)	14 (8.0)	32 (9.1)
Lack of efficacy	3 (1.7)	3 (1.7)	6 (1.7)
Adverse event	3 (1.7)	3 (1.7)	6 (1.7)
Lost To follow-up	3 (1.7)	3 (1.7)	6 (1.7)
Protocol violation	2 (1.1)	1 (0.6)	3 (0.9)
Withdrawal of consent	6 (3.4)	3 (1.7)	9 (2.6)
Other	1 (0.6)	1 (0.6)	2 (0.6)

Abbreviations: ITT = Intent-to-Treat; PP = Per Protocol.
Note: Percentages are relative to the number of subjects randomized per treatment group.
Source: Table 14.1.1.3.

Kaplan-Meier Plot of Time to Discontinuation (Safety Population)



Note: Subjects who completed the study were censored at the day of study completion. The day of discontinuation for subjects who were lost to follow-up was the imputed last day of dosing as described in the statistical analysis plan.
Source: Figure 14.1.1.1.

Analysis Populations

The ITT Population consisted of 343 (98.0%) randomized subjects who received at least 1 dose of study drug and had at least 1 post-Baseline assessment in any efficacy variable. The PP Population consisted of 301 (86.0%) randomized subjects who had no important protocol deviations that could

have impacted the efficacy analysis. The Safety Population consisted of 347 (99.1%) randomized subjects who received at least 1 dose of study drug.

Baseline data

The Safety Population was comprised of similar numbers of male (51.0%) and female (49.0%) subjects. The mean age was 14.2 ± 2.11 years. There were approximately equal numbers of subjects in the 10- to 14-year-old age stratum and the 15- to 17-year-old age stratum (50.7% and 49.3%, respectively). The majority of subjects (78.4%) were in the 13- to 17-years-old age group, and 21.6% of subjects were in the 10- to 12-years-old age group. Overall, 74.9% of subjects were White and 81.3% of subjects were not Hispanic or Latino. There were approximately equal numbers of subjects located in the US and Europe (43.2% and 40.6%, respectively), with an additional 13.5% of subjects located in South America and 2.6% located in Asia .

The overall mean screening BMI was 21.44 ± 3.405 kg/m2 and the screening BMI Z-score was 1.48±1.027, with no imbalance between treatment groups. At screening, 31.7% of the study population was overweight and 3.7% was obese.

Baseline demographic characteristics were similar for the Safety Population (see Table 14.1.2.3 of the CSR) and the PP Population (Table 14.1.2.2).

Demographic Characteristics (Safety Population) – *Part of the table is shown*

Characteristic	Placebo (N = 172)	Lurasidone 20 to 80 mg (N = 175)	Total (N = 347)
Gender, n (%)	**172**	**175**	**347**
Male	89 (51.7)	88 (50.3)	177 (51.0)
Female	83 (48.3)	87 (49.7)	170 (49.0)
Age (years)			
n	172	175	347
Mean (SD)	14.3 (2.04)	14.2 (2.18)	14.2 (2.11)
Median	14.0	14.0	14.0
Min, Max	10, 17	10, 17	10, 17
Age Stratum[a], n (%)	172	175	347
10 to 14 years old	87 (50.6)	89 (50.9)	176 (50.7)
15 to 17 years old	85 (49.4)	86 (49.1)	171 (49.3)
Age Group 1[b], n (%)	172	175	347
10 to 12 years old	37 (21.5)	38 (21.7)	75 (21.6)
13 to 17 years old	135 (78.5)	137 (78.3)	272 (78.4)

Abbreviations: BMI = body mass index; IXRS = Interactive Voice/Web Response System; SD = standard deviation.
[a] As per IXRS.
[b] As per RAVE age at screening.
Note: For each parameter, percentages are relative to the number of subjects per treatment group with non-missing data for that parameter.
Source: Table 14.1.2.3.

Baseline Psychiatric History

The mean age at onset of the initial behavioral disturbance was 10.59 ± 3.481 years, and the mean duration from onset to informed consent was 4.13 ± 2.999 years. The mean age at onset of bipolar I disorder was 12.31 ± 2.738 years, the mean age at onset of the last manic episode of bipolar I disorder was 13.51 ± 2.335 years, and the mean age of onset of the current depression episode of bipolar I disorder was 14.49 ± 2.152 years. The mean duration from onset of the current depression episode of bipolar I disorder to informed consent was 0.23 ± 0.174 years (Table 14.1.3.1).

The majority (85.1%) of subjects had a history of bipolar I disorder without rapid cycling (0 to 3 cycles within the past 12 months), 14.6% of subjects had a history of rapid cycling (4 to 7 cycles with the past 12 months), and 1 subject reported 8 or more cycles within past 12 months (Table 14.1.3.1).

The majority (72.9%) of subjects had no prior hospitalizations for bipolar I depression, 16.3% of subjects had 1 prior hospitalization, 6.4% of subjects had 2 prior hospitalizations, 2.0% of subjects had 3 prior hospitalizations, and 2.3% of subjects had 4 or more prior hospitalizations (Table 14.1.3.1).

A total of 31.8% of subjects in the ITT Population had other psychiatric disorders present. The most common other current psychiatric diagnoses were ADHD (DSM-5 314.01, 15.7%; DSM-5 314.00, 4.4%; DSM-5 314.0, 1.2%; DSM-5 314.9, 0.9%; and DSM-5 314, 0.6%) and oppositional defiant disorder (DSM-5 313.81, 6.1%) (Table 14.1.3.4). No other current psychiatric diagnosis was present in ≥5% of subjects.

The Baseline mean CDRS-R total score and CGI-BP-S Depression score for all subjects in the ITT Population was 58.9 ± 8.24 and 4.5 ± 0.61, respectively, and there was no imbalance between treatment groups.

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

Characteristic	Placebo (N = 170)	Lurasidone 20 to 80 mg (N = 173)	Total (N = 343)
Baseline CDRS-R Total Score			
n	170	173	343
Mean (SD)	58.6 (8.26)	59.2 (8.24)	58.9 (8.24)
Median	57.5	59.0	58.0
Min, Max	45, 82	44, 80	44, 82
Baseline CGI-BP-S Depression			
n	170	173	343
Mean (SD)	4.5 (0.57)	4.6 (0.65)	4.5 (0.61)
Median	4.0	5.0	4.0
Min, Max	4, 6	3, 6	3, 6

Abbreviations: CDRS-R = Children's Depression Rating Scale, Revised; CGI-BP-S = Clinical Global Impression-Bipolar Version, Severity of Illness; ITT = Intent-to-Treat; SD = standard deviation.
Note: For each parameter, percentages are relative to the number of subjects per treatment group with non-missing data for that parameter.
Source: Table 14.1.2.1.

CHMP comment

It was noted that baseline psychiatric history was similar in the two treatment groups.

Baseline Medical History

A total of 182 (52.4%) subjects in the Safety Population reported 1 or more pre-existing medical condition. Pre-existing medical conditions by preferred term that were reported by ≥ 10% of subjects overall were seasonal allergy (11.8%), headache (10.4%), and insomnia (10.1%). Overall, pre-existing medical conditions were balanced between treatment groups. The only pre-existing medical condition that was reported with an incidence of more than 5% higher in the lurasidone group compared with the placebo group was anxiety (6.3% vs. 1.2%, respectively).

CHMP comment

It was noted that baseline medical history was rather similar in the two treatment groups. However, the frequency for anxiety *was higher in the lurasidone group compared with the placebo group (6.3% vs. 1.2%, respectively).*

Duration of Treatment and Measurement of Exposure

The mean duration of exposure to study drug in the Safety Population was 40.3 ± 7.16 days in the lurasidone group and 40.4 ± 6.75 days in the placebo group. Overall, the majority (84.7%) of subjects received study drug for at least 41 days (see table below).

Duration of Exposure to Study Drug (Safety Population)

	Placebo (N = 172)	Lurasidone 20 to 80 mg (N = 175)	Total (N = 347)
Total Duration (Days)			
n	172	175	347
Mean (SD)	40.4 (6.75)	40.3 (7.16)	40.4 (6.95)
Median	42.0	42.0	42.0
Min, Max	4, 46	2, 48	2, 48
Category, n (%)			
≥ 7 days	170 (98.8)	174 (99.4)	344 (99.1)
≥ 14 days	168 (97.7)	169 (96.6)	337 (97.1)
≥ 21 days	166 (96.5)	168 (96.0)	334 (96.3)
≥ 28 days	163 (94.8)	163 (93.1)	326 (93.9)
≥ 35 days	160 (93.0)	163 (93.1)	323 (93.1)
≥ 41 days	147 (85.5)	147 (84.0)	294 (84.7)
Category, n (%)			
1 to 6 days	2 (1.2)	1 (0.6)	3 (0.9)
7 to 13 days	2 (1.2)	5 (2.9)	7 (2.0)
14 to 20 days	2 (1.2)	1 (0.6)	3 (0.9)
21 to 27 days	3 (1.7)	5 (2.9)	8 (2.3)
28 to 34 days	3 (1.7)	0	3 (0.9)
35 to 40 days	13 (7.6)	16 (9.1)	29 (8.4)
≥ 41 days	147 (85.5)	147 (84.0)	294 (84.7)

Overall Exposure (subject years)	**19.0**	**19.3**	**38.4**

Abbreviation: SD = standard deviation.
Note: Total duration = last dose date – first dose date + 1.
Note: Percentages are relative to the number of subjects per treatment group.
Note: For subjects who were lost to follow-up, last dose day was imputed was imputed as described in the statistical analysis plan.
Source: Table 14.1.6.2.

CHMP comment

It was noted that, the overall rate of discontinuation was 9%, with slightly fewer subjects discontinuing in the lurasidone group (8%) compared with placebo group (10%).

It was noted that, the mean duration of exposure to study drug (40.3 ± 7.16 days in the lurasidone group and 40.4 ± 6.75 days in the placebo group) were similar in the two treatment groups. Overall, the majority (84.7%) of subjects received study drug for at least 41 days.

Efficacy results

Primary Endpoint

CDRS-R Total Score

The mean (± SD) CDRS-R total score at Baseline was 59.2 ± 8.24 for the lurasidone group and 58.6 ± 8.26 for the placebo group .

The LS mean change (± SE) from Baseline to Week 6 for the CDRS-R total score based on an MMRM model was -21.0 ± 1.06 for the lurasidone group and -15.3 ± 1.08 for the placebo group. The placebo-adjusted LS mean change from Baseline to Week 6 in CDRS-R total score for the lurasidone group (-5.7 ± 1.39) was significantly different from placebo (95% CI: -8.4, -3.0; $p < 0.0001$; adjusted $p<0.0001$) .

The change from Baseline in CDRS-R total score over time using an MMRM model is summarized in the table below and presented graphically in the figure below. The LS mean decrease in the CDRS-R total score in the lurasidone group was significantly greater than placebo beginning at Week 2 and continuing through Week 6.

CDRS-R Total Score: Change from Baseline over Time - Mixed Model for Repeated Measures (ITT Population)

CDRS-R Total Score	Placebo (N = 170)	Lurasidone 20 to 80 mg (N = 173)
Week 1		
n	170	173
LS Mean (SE)	-5.9 (0.74)	-6.3 (0.72)
Difference of LS Mean (SE) (vs. Placebo)	-	-0.5 (0.85)
95% CI of Difference[a]	-	(-2.1, 1.2)
Effect Size (vs. Placebo)[b]	-	0.06
p-value (vs. Placebo)[a]	-	0.5926
Week 2		
n	169	171
LS Mean (SE)	-8.7 (0.86)	-11.1 (0.84)
Difference of LS Mean (SE) (vs. Placebo)	-	-2.4 (1.04)
95% CI of Difference[a]	-	(-4.4, -0.3)
Effect Size (vs. Placebo)[b]	-	0.25
p-value (vs. Placebo)[a]	-	0.0238
Week 3		
n	167	167
LS Mean (SE)	-11.1 (0.92)	-14.9 (0.90)
Difference of LS Mean (SE) (vs. Placebo)	-	-3.8 (1.14)
95% CI of Difference[a]	-	(-6.1, -1.6)
Effect Size (vs. Placebo)[b]	-	0.36
p-value (vs. Placebo)[a]	-	0.0009
Week 4		
n	165	161
LS Mean (SE)	-12.5 (0.96)	-17.4 (0.95)
Difference of LS Mean (SE) (vs. Placebo)	-	-4.9 (1.22)
95% CI of Difference[a]	-	(-7.3, -2.5)
Effect Size (vs. Placebo)[b]	-	0.44
p-value (vs. Placebo)[a]	-	< 0.0001

CDRS-R Total Score	Placebo (N = 170)	Lurasidone 20 to 80 mg (N = 173)
Week 5		
n	159	161
LS Mean (SE)	-14.1 (1.02)	-19.4 (1.00)
Difference of LS Mean (SE) (vs. Placebo)	-	-5.3 (1.30)
95% CI of Difference[a]	-	(-7.9, -2.8)
Effect Size (vs. Placebo)[b]	-	0.45
p-value (vs. Placebo)[a]	-	< 0.0001
Week 6		
n	157	161
LS Mean (SE)	-15.3 (1.08)	-21.0 (1.06)
Difference of LS Mean (SE) (vs. Placebo)	-	-5.7 (1.39)
95% CI of Difference[a]	-	(-8.4, -3.0)
Effect Size (vs. Placebo)[b]	-	0.45
p-value (vs. Placebo)[a]	-	< 0.0001
Adjusted p-value (vs. Placebo)[c]	-	< 0.0001

Abbreviations: CDRS-R = Children's Depression Rating Scale, Revised; CI = confidence interval; ITT = Intent-to-Treat; LS = least-squares; MMRM = mixed model for repeated measures; SD = standard deviation; SE = standard error.

[a] LS Mean, LS mean difference, and the associated 95% CI and p-value for change from Baseline are based on MMRM with fixed effects terms for treatment, visit (as a categorical variable), pooled country, age stratum, CDRS-R total score at Baseline, and treatment-by-visit interaction.

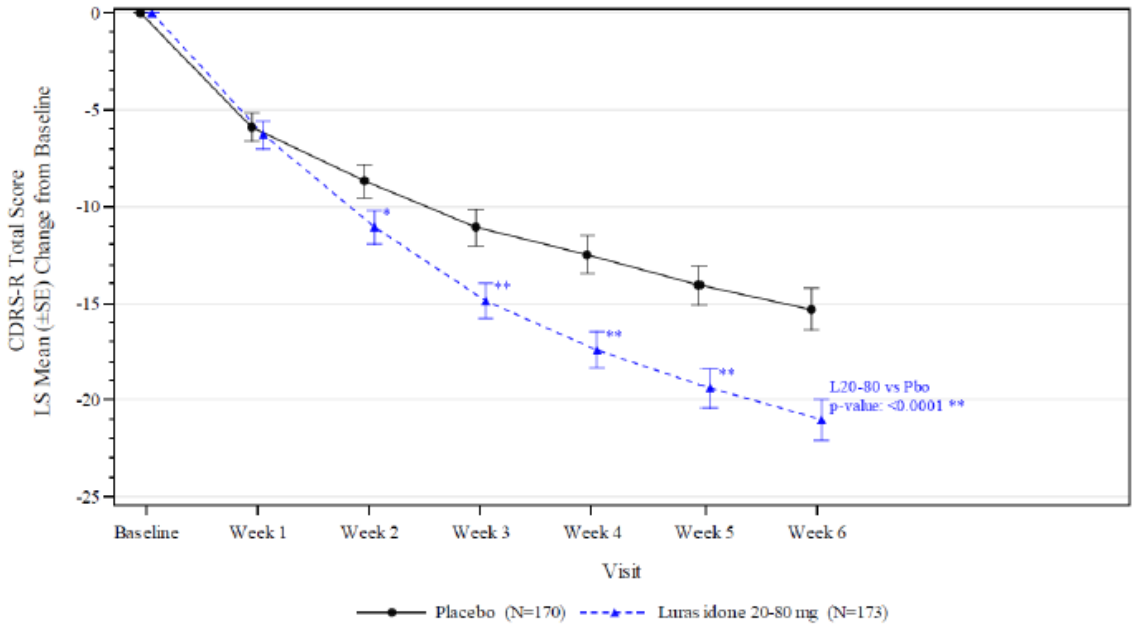
[b] Between-group effect size is calculated as the absolute value of LS mean difference divided by the model estimate of the pooled SD, obtained from the square root of the diagonal element, associated with that week, from the covariance matrix.

[c] The adjusted p-value is equal to the corresponding raw p-value.

Note: Higher values of CDRS-R total score represent greater severity of illness.

Source: Table 14.2.1.0.0 and Table 14.2.1.1.1.

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



Abbreviations: CDRS-R = Children's Depression Rating Scale, Revised; ITT = Intent-to-Treat; L20-80 = lurasidone 20 to 80 mg/day; LS = least squares; Pbo = placebo; SE = standard error.
Note: * $p \leq 0.05$; ** $p \leq 0.01$.
Source: Figure 14.2.2.1.

The primary efficacy analysis was repeated for the PP Population to examine the potential impact premature discontinuations and protocol deviations may have had on the efficacy results. Results were similar to those observed in the ITT Population. The LS mean change (± SE) from Baseline to Week 6 for the CDRS-R total score was -20.7 ± 1.14 for the lurasidone group and -14.7 ± 1.16 for the placebo group. The placebo-adjusted LS mean change from Baseline to Week 6 in CDRS-R total score for the lurasidone group (-6.0 ± 1.49) was significantly different from placebo (95% CI: -8.9, -3.1; p<0.0001). As was observed in the ITT Population, the change from Baseline in CDRS-R total score over time in the PP Population was significantly greater than placebo beginning at Week 2 and continuing through Week 6 (Table 14.2.1.1.3 and Figure 14.2.2.2).

As a supportive analysis of the primary efficacy analysis, the change from Baseline to Week 6 in CDRS--R total score was analyzed in the ITT Population using ANCOVA with an LOCF approach. The ANCOVA results were similar to the primary analysis that used the MMRM. The placebo-adjusted LS mean change from Baseline was significantly different from placebo at Week 6 (observed) (-5.5 ± 1.37; 95% CI: -8.2, -2.8; p < 0.0001) and Week 6 LOCF (-5.2 ± 1.38; 95% CI: -7.9, -2.5; p = 0.0002) (Table 14.2.1.1.2 and Figure 14.2.2.3).

A supplemental analysis tested for treatment-by-pooled-country, treatment-by-age-group, and treatment-by-ADHD stimulant-usage interactions on the change from Baseline in CDRS-R total score using an MMRM in the ITT Population. There were no significant treatment-by-group interactions (Table 14.2.1.1.6).

CDRS-R Responders

The proportion of responders at Week 6, defined as a ≥ 50% reduction from Baseline in adjusted CDRS-R total score, is presented in the table below.

At Week 6 LOCF, 103 (59.5%) subjects in the lurasidone group were CDRS-R responders compared with 62 (36.5%) subjects in the placebo group. The odds ratio (95% CI) comparing the CDRS-R response rate of the lurasidone group with the placebo group was2.617 (95% CI: 1.684, 4.065), which was statistically significant (p < 0.0001). Results were similar for the completer analysis at Week 6 (Table 25 of the CSR). Results of the CDRS-R responder analysis using the PP Population were similar to that of the ITT Population (Table 14.2.1.4.2).

CDRS-R Responder Analysis (ITT Population, Observed and LOCF)

Response Criteria Visit	Placebo (N = 170)	Lurasidone 20 to 80 mg (N = 173)
Week 6		
n*[a]	157	161
Response, n (%)[b]	58 (36.9)	102 (63.4)
NNT (95% CI)[c]	-	4 (2 , 7)
Effect Size[d]	-	0.60
Odds Ratio[e]	-	3.104 (1.948, 4.946)
p-value[e]	-	< 0.0001
Week 6 (LOCF)		
n*[a]	170	173
Response, n (%)[b]	62 (36.5)	103 (59.5)
NNT (95% CI)[c]	-	5 (2 , 8)
Effect Size[d]	-	0.52
Odds Ratio[e]	-	2.617 (1.684, 4.065)
p-value[e]	-	< 0.0001

Abbreviations: CDRS-R = Children's Depression Rating Scale, Revised; CI = confidence interval; ITT = Intent-to-Treat; LOCF = last observation carried forward; NNT = number needed to treat; US = United States.

[a] n* is the number of subjects per treatment group and visit with both Baseline and post Baseline CDRS-R total score.

[b] Percentages are relative to n*.

[c] NNT = 1/(lurasidone response rate – placebo response rate). The 95% CI of NNT is not displayed when the lower bound is ≤ 0.

[d] Effect Size (vs. placebo) = log (odds ratio) × sqrt (3)/pi; odds ratio from 2 × 2 contingency table.

[e] Odds ratio, CI, and the associated p-value versus placebo are from logistic regression model with terms for treatment, age stratum, pooled country (US vs. Non-US), and Baseline CDRS-R total score.

Note: Response defined as reduction from Baseline of ≥ 50% in adjusted CDRS-R total score at Week 6/Endpoint (see statistical analysis plan for details).

Source: Table 14.2.1.4.1.

Subgroup Analyses

The change from Baseline to Week 6 in the CDRS-R total score was further examined to explore the consistency of the treatment effect across various predefined subgroups using an LOCF approach. The following subgroups were analyzed:

- Age stratum (Table 14.2.1.3.1 of the CSR)
- Gender (Table 14.2.1.3.2)
- Race group (Table 14.2.1.3.3)
- Ethnicity (Table 14.2.1.3.4)

- BMI (Table 14.2.1.3.5)
- ADHD stimulant usage stratum (Table 14.2.1.3.6)
- Country (US vs. non-US) (Table 14.2.1.3.7).
- Rapid cycling versus non-rapid cycling (Table 14.2.1.3.8)
- Age group (Table 14.2.1.3.9)

Age stratum was the only treatment-subgroup interaction (defined as p < 0.10) that was identified (screening age 10 to 14 years old vs. 15 to 17 years old; p = 0.0134).

The placebo-adjusted LS mean change from Baseline to Week 6 LOCF in CDRS-R total score for the lurasidone group was -1.8 (-5.6, 2.0) for subjects in the 10- to 14-year-old age stratum and was -8.6 (-12.4, -4.8) for subjects in the 15- to 17-year-old age stratum (Table 14.2.1.3.1). The placebo-adjusted LS mean change from Baseline at Week 6 LOCF in the CDRS-R total score is presented for each subgroup in the figure below.

Table 14.2.1.3.1 - CDRS-R Total Score: Subgroup Analysis of Change from Baseline to Week 6 by Age Stratum (10-14 years old, 15 to 17 years old) (ITT, LOCF)

Table 14.2.1.3.1
CDRS-R Total Score: Subgroup Analysis of Change from Baseline to Week 6 by Age Stratum (10-14 years old, 15 to 17 years old) (ITT, LOCF)

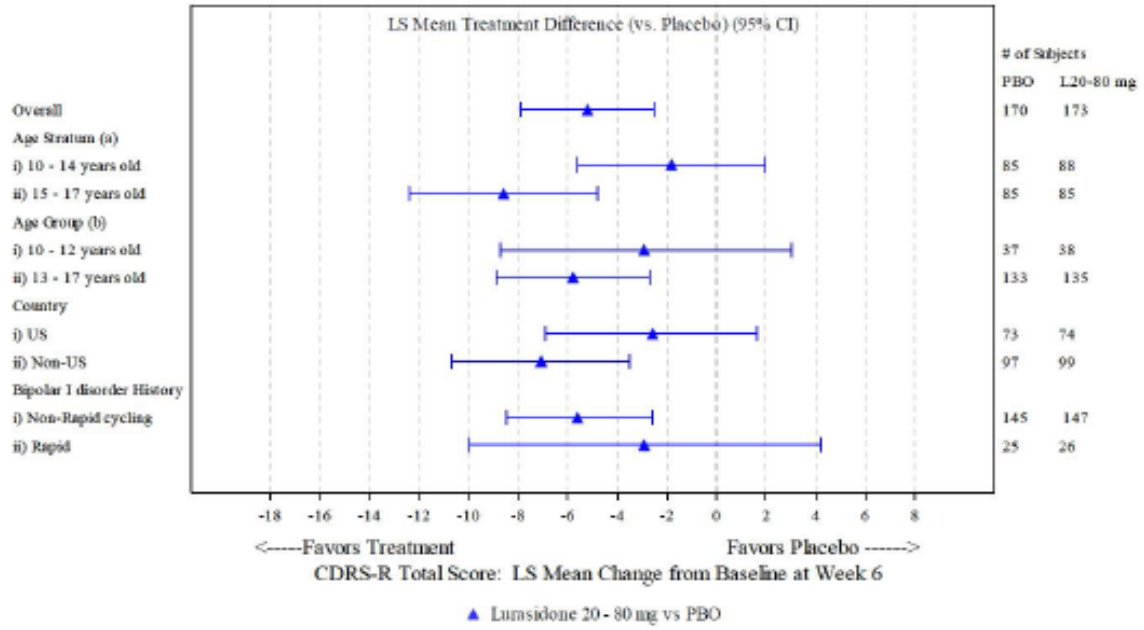
CDRS-R Total Score	Placebo (N=170)	Lurasidone 20-80 mg (N=173)
Screening age 10-14 years old		
n	85	88
Mean (SD) at Baseline	57.8 (7.73)	58.9 (7.98)
Mean (SD) at Week 6 LOCF	40.5 (14.25)	39.1 (13.78)
Change from Baseline		
Mean (SD)	-17.3 (12.99)	-19.8 (13.06)
LS Mean (SE) (a)	-17.0 (1.58)	-18.8 (1.55)
LS Mean Diff (95% CI) (vs. Placebo) (a)		-1.8 (-5.6, 2.0)
Screening age 15-17 years old		
n	85	85
Mean (SD) at Baseline	59.4 (8.73)	59.6 (8.53)
Mean (SD) at Week 6 LOCF	44.7 (14.81)	36.4 (12.12)
Change from Baseline		
Mean (SD)	-14.7 (14.43)	-23.2 (12.88)
LS Mean (SE) (a)	-14.3 (1.54)	-22.9 (1.51)
LS Mean Diff (95% CI) (vs. Placebo) (a)		-8.6 (-12.4, -4.8)
p-value Treatment*Subgroup Interaction		0.0134

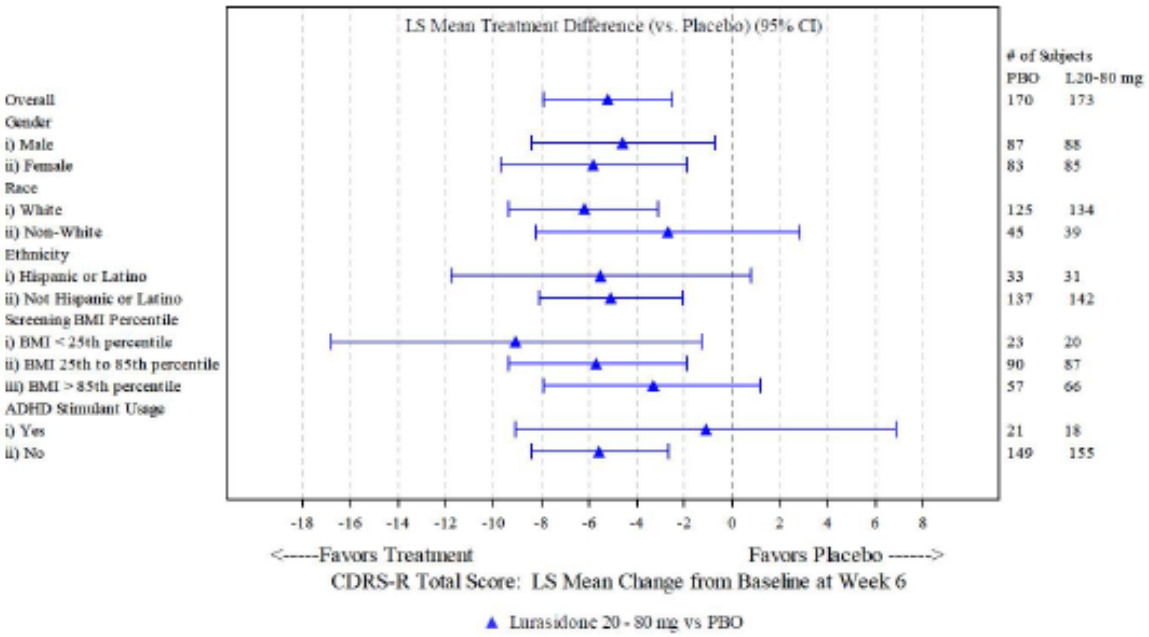
Note: (a) LS Means, LS Mean Difference, associated 95% CI and p-value are based on an ANCOVA model with treatment, pooled country, age stratum, treatment-by-age stratum interaction as fixed factors, and baseline CDRS-R total score as a covariate.
Cross reference: Listing 16.1.7.1, 16.2.6.1
Source: \\galton\data\ftl_bdm\SDD\project/sm13496/pediatric/d1050326\stat\pgm\tlf\t-cdrsrtot-chg-ancova-strata-ittfl.sas
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CHMP comment

It was noted that the number of patients were similar in the two treatment groups, both for 10-14 years strata and for 15-17 years strata.

Forest Plot for Change from Baseline to Week 6 in CDRS-R Total Score (ITT, LOCF)





Abbreviations: ADHD = Attention Deficit/Hyperactivity Disorder; BMI = body mass index; CDRS-R = Children's Depression Rating Scale, Revised; CI = confidence interval; ITT = Intent-to-Treat; IXRS = Interactive Voice/Web Response System; L20-80 mg = lurasidone 20 to 80 mg/day; LOCF = last observation carried forward; LS = least squares; PBO = placebo; US = United States.
Note: Age stratum (a) = age at screening per IXRS; age group (b) = age at screening per Rave.
Source: Figure 14.2.3.1.

Sensitivity Analyses

Two sensitivity analyses were conducted to verify the robustness of the primary efficacy results and the missing-at-random assumption underlying the primary efficacy MMRM analyses. The first sensitivity analysis used a PMM with placebo-based multiple imputation, which assumed that the efficacy profiles of dropouts after discontinuation were similar to those of placebo subjects. This was

considered to be a very conservative assumption, as it tends to minimize the difference between the lurasidone and placebo groups. The results of this sensitivity analysis were similar to the results of the primary efficacy analysis conducted with the MMRM (see table below).

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

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

Abbreviations: CDRS-R = Children's Depression Rating Scale, Revised; CI = confidence interval; ITT = Intent-to-Treat; LS = least squares; MMRM = mixed model for repeated measures; PMM = pattern mixture model; SE = standard error.
Note: PMM used1000 placebo-based multiple imputations using a monotone regression imputation method.
Note: MMRM was based on the fixed effects for treatment, pooled country, age stratum, visit as a categorical variable, Baseline score, and treatment by visit interaction, assuming an unstructured covariance matrix. Refer to the statistical analysis plan for details.
Note: * $p \leq 0.05$; ** $p \leq 0.01$.
Source: Table 14.2.1.1.4.

As a second sensitivity analysis, a random effects PMM with 2 patterns (completers and dropouts) was used to assess the impact of dropout pattern on the primary efficacy variable. The table below presents the results of the random effects model (REM), which ignores dropout pattern, and the PMM, which is a weighted average of the parameter estimates for completers and dropouts. The numerical estimates were similar for the REM and the PMM, indicating that the dropout status did not alter the overall results with respect to the treatment comparisons.

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

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

Abbreviations: CDRS-R = Children's Depression Rating Scale, Revised; CI = confidence interval; ITT = Intent-to-Treat; LS = least squares; PMM = pattern mixture model; REM = random effects model.
Note: REM = REM without dropout pattern; PMM Overall = overall random effects PMM using a weighted average of the parameter estimates for each dropout pattern (completers and dropouts); PMM Completers = random effects PMM for completers only; PMM Dropouts = random effects PMM for dropouts only.
Note: Time = sqrt (visit week).
Note: * $p \leq 0.05$; ** $p \leq 0.01$.
Source: Table 14.2.1.1.5.

Key Secondary Endpoint

Clinical Global Impression-Bipolar Version, Severity of Illness (CGI-BP-S) 11.1.2.1.1. CGI-BP-S Depression Score

The mean (± SD) CGI-BP-S depression score at Baseline was 4.6 ± 0.65 for the lurasidone group and 4.5 ± 0.57 for the placebo group.

The LS mean change (± SE) from Baseline to Week 6 for the CGI-BP-S depression score based on an MMRM was -1.49 ± 0.085 for the lurasidone group and -1.05 ± 0.087 for the placebo group. The placebo-adjusted LS mean change from Baseline to Week 6 in CGI-BP-S depression score for the lurasidone group (-0.44 ± 0.112) was significantly different from placebo (95% CI: -0.66, -0.22; p<0.0001; adjusted p < 0.0001) (Table 28 of the CSR).

The LS mean decrease in the CGI-BP-S depression score in the lurasidone group was significantly greater than placebo beginning at Week 2 and continuing through Week 6 (see table and graphical presentation below).

CGI-BP-S Depression Score	Placebo (N = 170)	Lurasidone 20 to 80 mg (N = 173)
Week 1		
n	170	173
LS Mean (SE)	-0.33 (0.059)	-0.37 (0.058)
Difference of LS Mean (SE) (vs. Placebo)	-	-0.04 (0.068)
95% CI of Difference[a]	-	(-0.18, 0.09)
Effect Size (vs. Placebo)[b]	-	0.07
p-value (vs. Placebo)[a]	-	0.5115
Week 2		
n	169	171
LS Mean (SE)	-0.48 (0.070)	-0.72 (0.069)
Difference of LS Mean (SE) (vs. Placebo)	-	-0.24 (0.086)
95% CI of Difference[a]	-	(-0.41, -0.07)
Effect Size (vs. Placebo)[b]	-	0.30
p-value (vs. Placebo)[a]	-	0.0058
Week 3		
n	167	167
LS Mean (SE)	-0.67 (0.078)	-1.03 (0.077)
Difference of LS Mean (SE) (vs. Placebo)	-	-0.36 (0.098)
95% CI of Difference[a]	-	(-0.55, -0.16)
Effect Size (vs. Placebo)[b]	-	0.40
p-value (vs. Placebo)[a]	-	0.0003
Week 4		
n	165	163
LS Mean (SE)	-0.81 (0.081)	-1.20 (0.079)
Difference of LS Mean (SE) (vs. Placebo)	-	-0.38 (0.103)
95% CI of Difference[a]	-	(-0.59, -0.18)
Effect Size (vs. Placebo)[b]	-	0.41
p-value (vs. Placebo)[a]	-	0.0002

CGI-BP-S Depression Score	Placebo (N = 170)	Lurasidone 20 to 80 mg (N = 173)
Week 5		
n	160	163
LS Mean (SE)	-0.91 (0.086)	-1.38 (0.085)
Difference of LS Mean (SE) (vs. Placebo)	-	-0.46 (0.111)
95% CI of Difference[a]	-	(-0.68, -0.24)
Effect Size (vs. Placebo)[b]	-	0.46
p-value (vs. Placebo)[a]	-	< 0.0001
Week 6		
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[a]	-	(-0.66, -0.22)
Effect Size (vs. Placebo)[b]	-	0.44
p-value (vs. Placebo)[a]	-	< 0.0001
Adjusted p-value (vs. Placebo)[c]	-	< 0.0001

Abbreviations: CGI-BP-S = Clinical Global Impression-Bipolar Version, Severity of Illness; CI = confidence interval; ITT = Intent-to-Treat; LS = least-squares; MMRM = mixed model for repeated measures; SD = standard deviation; SE = standard error.

[a] Least squares mean, LS mean difference, and the associated 95% CI and p-value for change from Baseline were based on a MMRM with fixed effects terms for treatment, visit (as a categorical variable), pooled country, age stratum, CGI-BP-S Depression score at Baseline, and treatment-by-visit interaction.

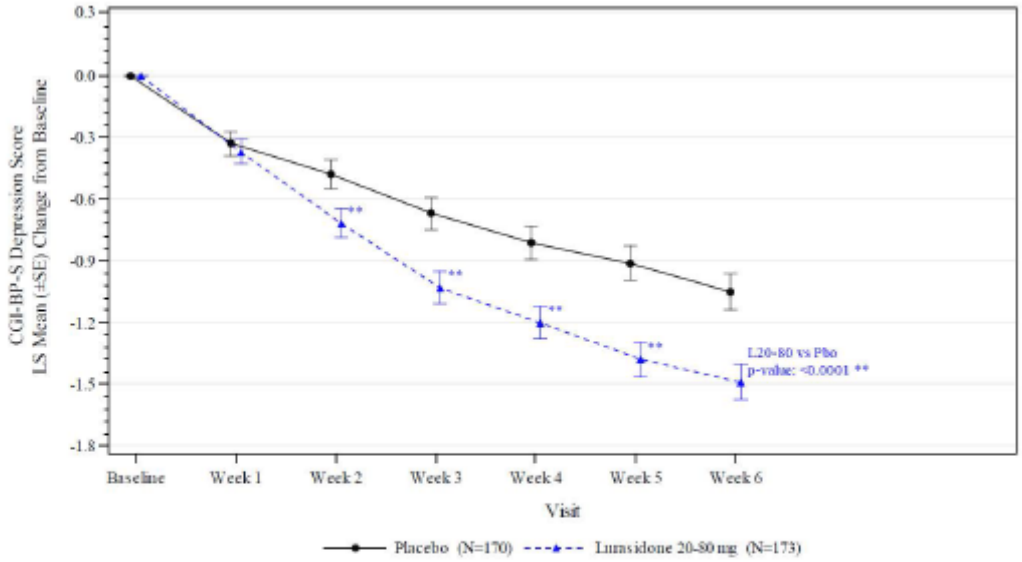
[b] Between-group effect size was calculated as the absolute value of LS mean difference divided by the model estimate of the pooled SD, obtained from the square root of the diagonal element, associated with that week, from the covariance matrix.

[c] The adjusted p-value for the key secondary endpoint was calculated as the maximum of the raw p-value or the adjusted p-value from the previous level.

Note: Higher values of CGI-BP-S depression score represent greater severity of illness.

Source: Table 14.2.1.0.0 and Table 14.2.2.1.1.

CGI-BP-S Depression Score: LS Mean (± SE) Change from Baseline over Time – Mixed Model for Repeated Measures (ITT Population)



Abbreviations: CGI-BP-S = Clinical Global Impression-Bipolar Version, Severity of Illness; ITT = Intent-to-Treat; L20-80 = lurasidone 20 to 80 mg/day; LS = least squares; Pbo = placebo; SE = standard error.
Note: * $p \leq 0.05$; ** $p \leq 0.01$.
Source: Figure 14.3.2.1.1.

The result of the MMRM analysis in the PP Population was similar to that observed in the ITT Population. The placebo-adjusted LS mean change from Baseline to Week 6 in CGI-BP-S depression score for the lurasidone group (-0.46 ± 0.118) was significantly different from placebo (95% CI: -0.70, -0.23; p = 0.0001). As was observed in the ITT Population, the change from Baseline in CGI-BP-S depression score over time in the PP Population was significantly greater than placebo beginning at Week 2 and continuing through Week 6 (Table 14.2.2.1.3 and Figure 14.3.2.2).

Results of the supportive analysis using ANCOVA in the ITT Population were similar to that of the MMRM analysis, with the lurasidone group showing a statistically significant improvement in CGI-BP-S depression score compared with placebo at Week 6 (Table 14.2.2.1.2 and Figure 14.3.2.3.1).

There were no significant treatment-by-pooled-country, treatment-by-age-group, or treatment-by-ADHD-stimulant-usage interactions on the change from Baseline in CGI-BP-S depression score using an MMRM in the ITT Population (Table 14.2.2.1.6).

Sensitivity Analyses

Sensitivity analysis using a PMM with placebo-based multiple imputation yielded results that were similar to those observed with the MMRM analysis. The lurasidone group demonstrated a statistically significant improvement over placebo in the change from Baseline in CGI-BP-S at Week 6 (Table 14.2.2.1.4). Sensitivity analysis using a random effects PMM showed that dropout status did not alter the overall results with respect to the treatment comparisons. The numerical estimates were similar for the REM and the PPM (Table 14.2.2.1.5).

Subgroup Analyses

There were no treatment-by-subgroup interactions for the change from Baseline to Week 6 in the CGI-BP-S depression score with respect to age stratum (Table 14.2.2.3.1), gender (Table 14.2.2.3.2), race group (Table 14.2.2.3.3), ethnicity (Table 14.2.2.3.4), BMI (Table 14.2.2.3.5), ADHD stimulant usage

(Table 14.2.2.3.6), country (Table 14.2.2.3.7), rapid cycling versus non-rapid cycling (Table 14.2.2.3.8), or age group (Table 14.2.2.3.9).

Other secondary endpoints

- CDRS-R response rate (ie, subjects with a ≥ 50% reduction from Baseline in the adjusted CDRS-R total score) at Week 6 LOCF was significantly higher in the lurasidone group compared with the placebo group (59.5% vs. 36.5%, respectively). The odds ratio comparing the CDRS-R response rate of the lurasidone group with the placebo group was 2.617, which was statistically significant ($p < 0.0001$).
- The change from Baseline to Week 6 in the CDRS-R total score was further examined to explore the consistency of the treatment effect across various predefined subgroups. Differences were observed in the age stratum subgroup, with a change in the CDRS-R total score of -1.8 (-5.6, 2.0) for subjects in the 10- to 14-year-old age stratum and -8.6 (-12.4, -4.8) for subjects in the 15- to 17-year-old age stratum. No differences were observed in CDRS-R total score between subjects with a history of rapid cycling versus subjects with a non-rapid cycling history.
- Change (LS mean ± SE) from Baseline to Week 6 in CGI-BP-S overall bipolar illness score (using MMRM) was significantly greater in the lurasidone group (-1.40 ± 0.085) compared with the placebo group (-0.98 ± 0.087; $p = 0.0002$).
- Change (LS mean ± SE) from Baseline to Week 6 in CGI-BP-S mania score (using MMRM) was significantly greater in the lurasidone group (-0.16 ± 0.042) compared with the placebo group (-0.05 ± 0.044; $p = 0.0467$).
- A significantly greater improvement (LS mean ± SE) from Baseline to Week 6 in PARS total score (using MMRM) was observed in the lurasidone group (-3.4 ± 0.44) compared with the placebo group (-2.3 ± 0.45; $p = 0.0385$).
- Change (LS mean ± SE) from Baseline to Week 6 in PQ-LES-Q percentage of maximum possible score (using MMRM) was significantly greater in the lurasidone group (11.8 ± 1.10%) compared with the placebo group (7.9 ± 1.13%; $p = 0.0044$).
- Change (LS mean ± SE) from Baseline to Week 6 in CGAS score (using MMRM) was significantly greater in the lurasidone group (14.0 ± 0.96%) compared with the placebo group (9.3 ± 0.99%; $p < 0.0001$).
- Remitter rate (ie, subjects with CDRS-R total score ≤ 28, YMRS total score ≤ 8, and CGI-BP-S depression score ≤ 3) at Week 6 LOCF was not significantly higher in the lurasidone group compared with the placebo group (26.0% vs. 18.8%, respectively), with an odds ratio of 1.608, $p=0.0825$. For completers at Week 6, the odds ratio (1.820) was statistically significant ($p=0.0357$).

Efficacy Conclusions

Primary Efficacy Endpoint:

There was a significant treatment difference in the change from Baseline to Endpoint in CDRS-R total score that favored the lurasidone group (-5.7 ± 1.39; adjusted $p < 0.0001$). The LS mean change (± SE) from Baseline to Week 6 for the CDRS-R total score based on MMRM analysis was -21.0 ± 1.06 for the lurasidone group compared with -15.3 ± 1.08 for the placebo group. The robustness of the primary efficacy analysis in the ITT Population was supported by ANCOVA analysis in the ITT Population, MMRM analysis in the PP Population, and sensitivity analyses using PMM and REM in the ITT Population. In this

6-week, placebo-controlled study, lurasidone 20 to 80 mg/day (flexibly dosed) significantly improved symptoms of depression in children and adolescents with bipolar depression, as measured by the CDRS-R total score.

Key Secondary Efficacy Endpoint:

There was a significant treatment difference in the change from Baseline to Endpoint in CGI-BP-S depression score that favored the lurasidone group (-0.44 ± 0.112; adjusted p < 0.0001). The LS mean change (± SE) from Baseline to Week 6 for the CGI-BP-S depression score based on MMRM analysis was -1.49 ± 0.085 for the lurasidone group compared with -1.05 ± 0.087 for the placebo group. The robustness of the key secondary efficacy analysis in the ITT Population was supported by ANCOVA analysis in the ITT Population, MMRM analysis in the PP Population, and sensitivity analyses using PMM and REM in the ITT Population. In this 6-week, placebo-controlled study, lurasidone 20 to 80 mg/day (flexibly dosed) significantly improved the overall severity of depressive symptoms in children and adolescents with bipolar depression, as measured by the CGI-BP-S depression score.

CHMP comment

This short-term double-blind, placebo-controlled study evaluated the efficacy of flexibly dosed lurasidone (20 to 80 mg/day) for 6 weeks compared with placebo in 347 children and adolescent subjects with major depressive episode associated with bipolar I disorder (bipolar depression). The study showed statistically significant but modest improvements compared with placebo across primary (CDRS-R), key secondary (CGI-BP-S), and other secondary efficacy endpoints. There were approximately equal numbers of subjects in the 10- to 14-year-old age stratum and the 15- to 17-year-old age stratum (50.7% and 49.3%, respectively). The placebo-adjusted LS mean change from Baseline to Week 6 LOCF in CDRS-R total score was statistically significant (p=0.0134) for the lurasidone group -8.6 (-12.4, -4.8) for subjects in the 15- to 17-year-old age stratum but not for the subjects in the 10- to 14-year-old age stratum, -1.8 (-5.6, 2.0). The results for other secondary endpoints were in line with results for primary and key secondary endpoints, ie data was supportive.

Safety results

Overall Adverse Events

Adverse events were coded by SOC and preferred term using the MedDRA (Version 16.0). The overall incidence of TEAEs was higher in the lurasidone group (64.0%) compared with the placebo group (51.7%). The incidence of treatment-related TEAEs was higher in the lurasidone group (45.1%) compared with the placebo group (25.6%).

Serious TEAEs and discontinuations due to TEAEs were uncommon and occurred at a similarly low rate in both treatment groups. There were no deaths during the study.

The incidence of EPS-related TEAEs and hypersensitivity-related TEAEs was similarly low in both the lurasidone and placebo groups (4.6% vs. 4.1% and 2.9% vs. 2.3%, respectively). The most common EPS-related TEAE was akathisia, which occurred in 2.9% of subjects in the lurasidone group and 3.5% of subjects in the placebo group. No other EPS-related or hypersensitivity-related TEAE was reported by more than 1 (0.6%) subject in either treatment group .

The incidence of metabolic-related TEAEs was higher in the lurasidone group (9.1%) compared with the placebo group (2.9%). This difference was primarily due to a higher number of subjects reporting

TEAEs of weight increased in the lurasidone group (12 [6.9%] subjects) compared with the placebo group (3 [1.7%] subjects]) .

There were no suicide-related TEAEs reported in the lurasidone group and 1 suicide-related TEAE (suicidal ideation) reported in in the placebo group .

The overall incidence of TEAEs was similar in both the 10- to 12-years-old and 13- to 17-years-old age groups (Table 14.3.1.1.2).

Common TEAEs

The SOCs with the highest incidence of TEAEs in both the lurasidone and placebo groups were Nervous System Disorders (29.1% and 25.6%, respectively), Gastrointestinal Disorders (29.1% and 13.4%, respectively), Psychiatric Disorders (16.0% and 12.2%, respectively), and Infections and Infestations (14.9% and 12.8%, respectively) (Table 14.3.1.2.1).

At the preferred term level, the TEAE with the highest incidence in the lurasidone group was nausea (16.0%), which was notably higher than the incidence in the placebo group (5.8%). The only other TEAEs that were reported at a frequency ≥ 5% higher in the lurasidone group than in the placebo group were somnolence and weight increased. Somnolence (which includes the preferred terms of hypersomnia, sedation, somnolence, and hypersomnolence) was reported byv11.4% of subjects in the lurasidone group compared with 5.8% of subjects in the placebo group. Weight increased was reported by 6.9% of subjects in the lurasidone group compared withv1.7% of subjects in the placebo group (Table 14.3.1.3.3).

Treatment-emergent AEs with an incidence ≥ 2% by preferred term in either treatment group are presented in the table below.

Treatment-emergent Adverse Events (Combined Terms) with an Incidence ≥2 % in Either Treatment Group by Preferred Term (Safety Population)

System Organ Class (SOC)/ Preferred Term	Placebo (N = 172) n (%)	Lurasidone 20 to 80 mg (N = 175) n (%)
Total No. Subjects with TEAEs	**89 (51.7)**	**112 (64.0)**
Gastrointestinal Disorders	**23 (13.4)**	**51 (29.1)**
Abdominal Pain	2 (1.2)	5 (2.9)
Abdominal Pain Upper	4 (2.3)	6 (3.4)
Diarrhoea	3 (1.7)	5 (2.9)
Nausea	10 (5.8)	28 (16.0)
Vomiting	6 (3.5)	11 (6.3)
General Disorders And Administration Site Conditions	**12 (7.0)**	**15 (8.6)**
Fatigue	4 (2.3)	6 (3.4)
Infections And Infestations	**22 (12.8)**	**26 (14.9)**
Influenza	1 (0.6)	4 (2.3)
Nasopharyngitis	10 (5.8)	7 (4.0)
Investigations	**10 (5.8)**	**21 (12.0)**
Weight Increased	3 (1.7)	12 (6.9)
Metabolism And Nutrition Disorders	**7 (4.1)**	**11 (6.3)**
Decreased Appetite	4 (2.3)	7 (4.0)
Nervous System Disorders	**44 (25.6)**	**51 (29.1)**
Akathisia	6 (3.5)	5 (2.9)
Dizziness	8 (4.7)	10 (5.7)
Headache	26 (15.1)	25 (14.3)
Somnolence[a]	10 (5.8)	20 (11.4)
Psychiatric Disorders	**21 (12.2)**	**28 (16.0)**
Abnormal Dreams	3 (1.7)	4 (2.3)
Anxiety	6 (3.5)	5 (2.9)
Insomnia	4 (2.3)	9 (5.1)
Respiratory, Thoracic And Mediastinal Disorders	**8 (4.7)**	**9 (5.1)**
Oropharyngeal Pain	3 (1.7)	4 (2.3)

Abbreviations: SOC = System Organ Class; TEAE = treatment-emergent adverse event.
[a] Somnolence includes the preferred terms of hypersomnia, sedation, somnolence, and hypersomnolence.
Note: Percentages are relative to the number of subjects per treatment group.
Note: Incidence is a count of subjects and not a count of TEAEs.
Source: Table 14.3.1.2.2.

When analyzed by age group, the incidences of nausea and vomiting were higher in the 10- to 12-years-old age group (lurasidone: 18.4% and 13.2%, respectively; placebo: 8.1% and 8.1%, respectively) compared with the 13- to 17-years-old age group (lurasidone: 15.3% and 4.4%, respectively; placebo: 5.2% and 2.2%, respectively). The incidence of somnolence was greater in the 13- to 17-years-old age group (lurasidone: 13.1%; placebo: 5.9%) compared with 10- to 12- years-

old age group (lurasidone: 5.3%; placebo: 5.4%). The incidence of weight increased was greater in the 10- to 12-years-old age group (lurasidone: 7.9%; placebo: 0%) compared with 13- to 17-years-old age group (lurasidone: 6.6%; placebo: 2.2%) (Table 14.3.1.3.3.1). The majority of TEAEs in both treatment groups were mild-to-moderate in severity.

Two subjects in the lurasidone group experienced 3 severe TEAEs (nausea, tendon injury, and restless legs syndrome), and 6 subjects in the placebo group experienced 6 severe TEAEs (asthenia, blood potassium increased, somnolence, bipolar I disorder, mania, and psychotic disorder). No severe TEAEs were reported by more than 1 subject (Table 14.3.1.5.2).

Of the 2 subjects with severe TEAEs in the lurasidone group, 1 subject experienced 2 TEAEs (nausea and restless legs syndrome) that were considered to be at least possibly related to study drug by the Investigator (Table 14.3.1.6.3). The non-serious TEAE of nausea started on Day 1 and was reported as recovered/resolved on Day 4 with no change in the dose of study drug. The non-serious TEAE of restless legs syndrome was reported on Day 4 (severe), Day 5 (moderate), and Day 6 (mild), each with a duration of 1 day; there were no changes in the dose of study drug as a result of these events. Restless legs syndrome was reported again on Day 7 (severe) with a duration of 3 days. The TEAE of restless legs syndrome on Day 7 led to permanent withdrawal of study drug on Day 14.

The subject was receiving lurasidone 20 mg/day at the time of these TEAEs.

A summary of treatment-related TEAEs reported in $\geq$ 2% of subjects in either treatment group is presented in the table below.

Treatment-emergent Adverse Events Related to Study Drug and Occurring in ≥ 2% of Subjects in Either Treatment Group (Safety Population)

System Organ Class (SOC)/ Preferred Term	Placebo (N = 172) n (%)	Lurasidone 20 to 80 mg (N = 175) n (%)
Total No. Subjects with TEAEs	**89 (51.7)**	**112 (64.0)**
Total No. Subjects with Related TEAEs	**44 (25.6)**	**79 (45.1)**
Gastrointestinal Disorders	**16 (9.3)**	**40 (22.9)**
Abdominal pain	1 (0.6)	4 (2.3)
Abdominal pain upper	2 (1.2)	5 (2.9)
Nausea	7 (4.1)	24 (13.7)
Vomiting	2 (1.2)	8 (4.6)
General Disorders and Administration Site Conditions	**3 (1.7)**	**10 (5.7)**
Fatigue	1 (0.6)	6 (3.4)
Investigations	**3 (1.7)**	**15 (8.6)**
Weight increased	2 (1.2)	10 (5.7)
Metabolism and Nutrition Disorders	**3 (1.7)**	**8 (4.6)**
Decreased appetite	1 (0.6)	5 (2.9)
Nervous System Disorders	**26 (15.1)**	**45 (25.7)**
Akathisia	5 (2.9)	5 (2.9)
Dizziness	4 (2.3)	7 (4.0)
Headache	11 (6.4)	18 (10.3)
Somnolence	8 (4.7)	15 (8.6)
Psychiatric Disorders	**13 (7.6)**	**16 (9.1)**
Abnormal dreams	3 (1.7)	4 (2.3)
Anxiety	4 (2.3)	2 (1.1)
Insomnia	3 (1.7)	5 (2.9)

Abbreviations: SOC = System Organ Class; TEAE = treatment-emergent adverse event.
Note: Percentages are relative to the number of subjects per treatment group.
Note: Incidence is a count of subjects and not a count of TEAEs.
Note: Related includes TEAEs classified by the Investigator as possibly, probably, or definitely related.
Source: Table 14.3.1.6.1 and Table 14.3.1.6.2.

Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

There were no deaths reported during this study.

Non-fatal Serious Adverse Events

Two (1.1%) subjects in the lurasidone group and 4 (2.3%) subjects in the placebo group reported serious TEAEs. The only serious TEAE reported by more than 1 subject was bipolar I disorder, which was reported by 1 subject in each treatment group .

Of the 2 serious TEAEs reported in the lurasidone group:

- One event of humerus fracture (mild severity) occurred on Day 26 and was reported as not recovered/not resolved. The dose of study drug was not changed as a result of this event, and the event was considered not related to study drug by the Investigator (Listing 16.2.12.3).

• One event of bipolar I disorder (moderate severity) occurred on Day 9 and was reported as recovered/resolved. The subject had discontinued study drug prior to this event due to lack of efficacy, and the event was considered unlikely to be related to study drug by the Investigator (Listing 16.2.12.3).

A serious TEAE of abortion spontaneous was reported in 1 subject receiving placebo.

Adverse Events Related to Extrapyramidal Symptoms

The incidence of EPS-related TEAEs was similar in the lurasidone and placebo treatment groups (4.6% and 4.1%, respectively), with no notable difference between treatment groups in the incidence of individual TEAE preferred terms. The most common EPS-related TEAE was akathisia, which was reported by 2.9% of subjects in the lurasidone group and 3.5% of subjects in the placebo group.

Metabolic-related Adverse Events

The incidence of treatment-emergent metabolic AEs was higher in the lurasidone group (9.1%) compared with the placebo group (2.9%). The most common treatment-emergent metabolic AE was weight increased, with a higher incidence reported in the lurasidone group (6.9%) than in the placebo group (1.7%). The only other treatment-emergent metabolic AE reported by more than 1 subject was weight decreased, which was reported by 2 subjects in the lurasidone group (see table below).

For subjects with TEAEs of weight increased, the mean maximal weight increase from Baseline during the double-blind period was 2.83 kg (range: 1.1 to 5.4 kg) in the lurasidone group (n = 12 subjects) and 4.50 kg (range: 1.8 to 7.4 kg) in the placebo group (n = 3 subjects) (Post-hoc Table 14.3.6.3.3). For the overall Safety Population, the LS mean (± SD) age-and-gender adjusted expected weight increase from Baseline to Endpoint (based on CDC growth charts) was 0.39 ± 0.209 kg in the lurasidone group and 0.39 ± 0.194 in the placebo group (Table 14.3.6.1.5), and the placebo-adjusted LS mean (± SE) change in body weight from Baseline to Endpoint in the lurasidone group (based on MMRM analysis) was 0.30 ± 0.187 (Table 14.3.6.1.1).

Treatment-emergent Metabolic Adverse Events by Preferred Term (Safety Population)

Preferred Term	Placebo (N = 172) n (%)	Lurasidone 20 to 80 mg (N = 175) n (%)
Total No. Subjects with Metabolic TEAEs	**5 (2.9)**	**16 (9.1)**
Weight increased	3 (1.7)	12 (6.9)
Weight decreased	0	2 (1.1)
Dyslipidaemia	0	1 (0.6)
Hyperglycaemia	0	1 (0.6)
Hyperinsulinaemia	0	1 (0.6)
Hypertriglyceridaemia	0	1 (0.6)
Blood insulin increased	1 (0.6)	0
Blood triglycerides increased	1 (0.6)	0

Abbreviations: TEAE = treatment-emergent adverse event.
Note: Percentages are relative to the number of subjects per treatment group.
Note: Incidence is a count of subjects and not a count of TEAEs.
Source: Table 14.3.2.4.3.

Clinical Chemistry

Changes from Baseline to Endpoint for the metabolic parameters of particular clinical interest (included triglycerides, cholesterol, HDL, LDL, glucose, HbA1c, insulin, and HOMA-IR) are presented in Table 48.

Blood samples were to be collected under fasting conditions for assessment of glucose, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, insulin, and HOMA-IR.

Descriptive statistics are presented for these parameters by Fasting and Overall (which includes fasting, non-fasting, and unknown)

There were no statistically significant or clinically meaningful differences between treatment groups in the median change from Baseline to Endpoint in overall HDL or HbA1c, or in fasting or overall triglycerides, cholesterol, glucose, insulin, or HOMA-IR.

For fasting HDL, the difference in the median change from Baseline to Endpoint between the lurasidone group (-1.0) and the placebo group (-2.0) was marginally statistically significant (p = 0.0473). For fasting LDL, the difference in the median change from Baseline to Endpoint between the lurasidone group (-5.0) and the placebo group (-1.0) was statistically significant (p = 0.0389). For overall LDL, the difference in the median change from Baseline to Endpoint between the lurasidone group (-5.0) and the placebo group (-2.0) was statistically significant (p = 0.0297).

Vital Signs, Physical Findings, and Other Observations Related to Safety

The change from Baseline in body weight over time using an MMRM is summarized in Table 52 and presented graphically in Figure 6 of the CSR.

The average (mean ± SD) Baseline body weight was 56.5 ± 13.03 kg in the lurasidone group and 57.0±13.51 kg in the placebo group.

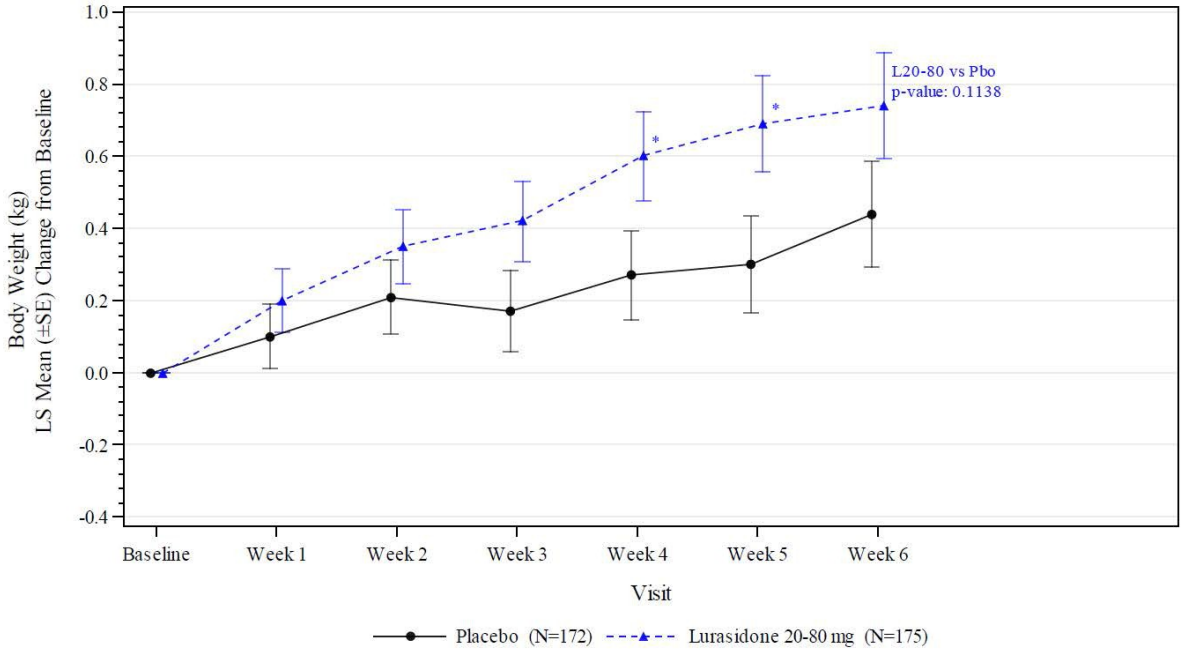
The LS mean change (± SE) from Baseline to Week 6 for body weight based on MMRM was 0.74 ± 0.145 kg in the lurasidone group and 0.44 ± 0.147 kg in the placebo group. The placebo-adjusted LS mean change from Baseline to Week 6 in body weight for the lurasidone group (0.30 ± 0.187 kg) was not significantly different from placebo (95% CI: -0.07, 0.66; p = 0.1138).

The LS mean change in the body weight from Baseline was positive at all time points for both treatment groups, with a greater increase in the lurasidone group than in the placebo group. The difference in LS mean change from Baseline between the lurasidone group and placebo group tended to increase over time, from a minimum of 0.10 ± 0.090 kg at Week 1 to a maximum of 0.40 ± 0.169 kg at Week 5.

Analysis of change from Baseline in body weight over time using ANCOVA yielded similar results to the MMRM analysis (Table 14.3.6.1.5).

As weight-for-age reference data are not available beyond the age of 10 years in the WHO 2007 growth reference for 5 to 19 years old, no age-and-sex specific Z-score of weight was derived in this study.

Body Weight (kg): LS Mean (± SE) Change from Baseline over Time - Mixed Model for Repeated Measures (Safety Population)



Safety Conclusions

Treatment with lurasidone 20 to 80 mg/day (flexibly dosed) in children and adolescent subjects with bipolar I depression was generally safe and well tolerated. The safety profile was consistent with the findings from previous studies of lurasidone in adult subjects with bipolar depression.

Of the 347 subjects who were randomized and received at least 1 dose of study drug, a total of 318 (91.6%) subjects completed the study (92.6% of lurasidone-treated subjects and 90.7% of subjects receiving placebo).

The mean daily lurasidone dose (± SD) was 32.5 ± 12.71 mg and 33.1 ± 12.76 mg overall and for completers, respectively. The most frequent modal daily dose was 20 mg/day (52.3%), followed by 40 mg (26.2%), 60 mg (12.8%), and 80 mg (8.7%).

- The most commonly (≥ 5%) reported TEAEs in the lurasidone group, at the preferred term level, were nausea (16.0%), headache (14.3%), somnolence (11.4%; including the preferred terms of hypersomnia, sedation, somnolence, and hypersomnolence), weight increased (6.9%), vomiting (6.3%), dizziness (5.7%), and insomnia (5.1%).
- Treatment-emergent AEs reported at a frequency ≥ 5% higher in the lurasidone group than in the placebo group, at the preferred term level, were nausea (16.0% vs. 5.8%), somnolence (11.4% vs. 5.8%), and weight increased (6.9% vs. 1.7%).
- Severe TEAEs occurred in 2 subjects in the lurasidone group and 6 subjects in the placebo group. No subject reported more than 1 severe TEAE.
- The most common (≥ 5%) treatment-related TEAEs in the lurasidone group were nausea (13.7%), headache (10.3%), somnolence (8.6%), and weight increased (5.7%).
- There were no deaths during the study.

- Serious TEAEs were reported by 2 (1.1%) subjects in the lurasidone group and 4 (2.3%) subjects in the placebo group. The only serious TEAE to be reported by more than 1 subject was bipolar I disorder, which was reported by 1 subject in each treatment group. One subject in the placebo group experienced a serious TEAE of spontaneous abortion that was considered not related to study drug by the Investigator.
- Treatment-emergent AEs leading to permanent discontinuation of study drug occurred in 3 (1.7%) subjects in each treatment group. No TEAE leading to permanent discontinuation of study drug occurred in more than 1 subject.
- There were 9 subjects in the lurasidone group and 2 subjects in the placebo group who experienced 1 or more TEAEs leading to a dose reduction of study drug. The only preferred term that occurred in more than 1 subject was nausea, which was reported by 3 subjects in the lurasidone group.
- The incidence of EPS-related TEAEs was similar in the lurasidone and placebo treatment groups (4.6% vs. 4.1%, respectively). The most common EPS-related TEAE was akathisia, which was reported by 2.9% of subjects in the lurasidone group and 3.5% of subjects in the placebo group.
- The incidence of metabolic-related TEAEs was higher in the lurasidone group compared with the placebo group (9.1% vs. 2.9%, respectively). The most common metabolic-related TEAE was weight increased, which was reported for 12 (6.9%) subjects in the lurasidone group and 3 (1.7%) subjects in the placebo group. The only other metabolic-related TEAE that occurred in more than 1 subject was weight decreased, which was reported for 2 subjects in the lurasidone group.
- There were no reports of TEAEs related to suicidality and self-injury for any subject in the lurasidone group, and 1 TEAE related to suicidality and self-injury was reported in the placebo group.
- The incidence of TEAEs related to hypersensitivity was similar in the lurasidone and placebo groups (2.9% vs. 2.3%, respectively). No hypersensitivity-related TEAE was reported by more than 1 subject.
- Overall increase from Baseline to Endpoint in median serum prolactin levels was greater in the lurasidone group compared with the placebo group (1.10 vs. 0.50 ng/mL, respectively).
- For metabolic parameters, there were no clinically meaningful differences between treatment groups in the change from Baseline to Endpoint in cholesterol, LDL and HDL cholesterol, triglycerides, glucose, HbA1c, insulin, and HOMA IR.
- Change (LS mean ± SE) from Baseline to Week 6 for body weight using MMRM analysis was 0.74 ± 0.145 kg in the lurasidone group and 0.44 ± 0.147 kg in the placebo group. The change (LS mean ± SE) from Baseline to Endpoint in BMI Z-score was 0.055 ± 0.0217 in the lurasidone group and 0.016 ± 0.0224 in the placebo group.
- There were no clinically meaningful differences between treatment groups in any vital sign parameters.
- No subject in either treatment group had QTcF > 460 msec or a ≥ 60 msec increase in QTcF from Baseline. There were 2 subjects in each treatment group with a ≥ 30 msec increase in QTcF from Baseline at Week 6 and at Endpoint.
- Changes in movement disorder signs or symptoms, as measured by the change in BARS, SAS, and AIMS scores, were generally absent to mild in subjects treated with lurasidone. Relatively small

changes from Baseline were observed in the BARS total score, SAS mean score, and AIMS total score over the course of the study, which were not considered statistically significant or clinically relevant.

- Change in the Cogstate Computerized Cognitive Battery standardized composite score was similar for lurasidone and placebo treated subjects.
- Changes from Baseline to Endpoint for the 4 UKU category scores (psychic, neurological, autonomic, and other) and the UKU total score were generally similar between the lurasidone and placebo groups.
- Rates of suicidal ideation or behavior, as measured by the C-SSRS, were comparable for the lurasidone and placebo groups.
- Changes in Tanner staging from Baseline to Endpoint for male and female subjects were comparable for the lurasidone and placebo groups.
- Reduction from Baseline to Endpoint in YMRS total score indicating a decreased severity of mania was significantly greater in the lurasidone group (LS mean ± SE using MMRM)compared with the placebo group (-1.95 ± 0.305 vs. -1.09 ± 0.311, respectively; p = 0.0245).

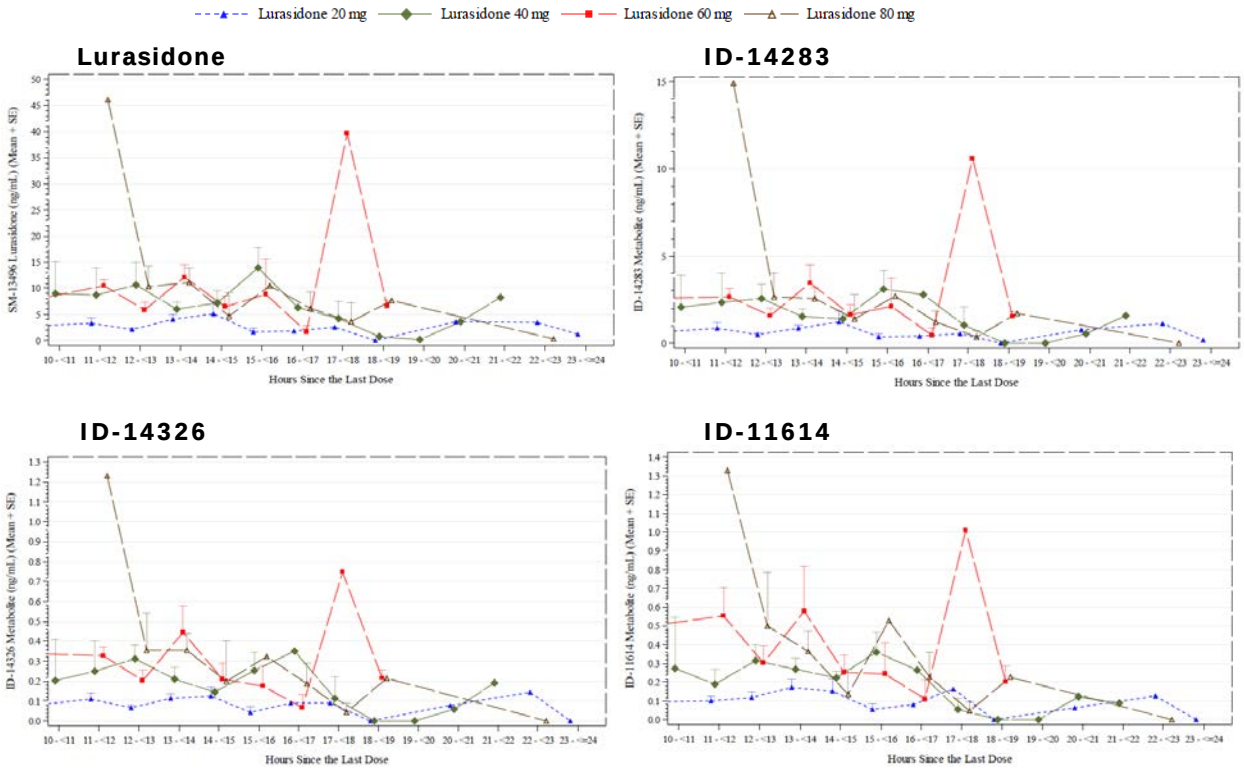
CHMP comment:

It was noted that treatment with lurasidone was generally safe and well tolerated in the dose range studied (20-80 mg/day) according to the CSR of Study D1050326. However, the frequency for weight increased (TEAEs and MMRM analysis) was higher in the lurasidone group than in the placebo group and there was an increase in BMI in the lurasidone group compared to the placebo group. These findings are not surprising but of special importance in children and adolescents. No clinically meaningful differences for other metabolic parameters were found.

Pharmacokinetics

Trough serum concentration of lurasidon and the metabolites ID-14283, ID-14326 and ID-11614, are shown in Figure 7 following flexibly dosed lurasidone (20 to 80 mg/day) once daily for 6 weeks.

Figure 7: Trough serum concentration of lurasidon and the metabolites ID-14283, ID-14326 and ID-11614, following flexibly dosed lurasidone (20 to 80 mg/day) for 6 weeks. *NB!* Different y-axes



CHMP comment:

Trough serum concentration of lurasidone and three metabolites have been determined following flexibly dosed lurasidone (20 to 80 mg/day) once daily for 6 weeks.

Based on the reported lists/figures, it is unclear whether the values are mean or individual values. Neither are any data presented on systemic exposure depending on age.

2.3.3. Discussion on clinical aspects

This was a randomized, parallel, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of flexibly dosed lurasidone (20 to 80 mg/day) for 6 weeks compared with placebo in children and adolescent subjects with major depressive episode associated with bipolar I disorder (bipolar depression).

For the primary efficacy analysis parameter, change in the CDRS-R total score from Baseline to Week 6, there was a significant treatment difference favoring lurasidone over placebo in improving depressive symptoms. Significant treatment differences from placebo were observed in the lurasidone group beginning at Week 2 and maintained at each study visit through to the end of the study.

For the key secondary efficacy analysis parameter, change in the CGI-BP-S depression score from Baseline to Week 6, there was a significant treatment difference favoring lurasidone over placebo in improving the severity of depressive symptoms. Significant treatment differences from placebo were

observed in the lurasidone group beginning at Week 2 and maintained at each study visit through to the end of the study.

The responder rate, defined as subjects with a ≥ 50% reduction in CDRS-R total score at study endpoint, was significantly greater in the lurasidone group than in the placebo group.

A significant treatment difference favored lurasidone over placebo in improving the severity of anxiety symptoms, as measured by the PARS; quality of life, as assessed by the PQ-LES-Q; and global assessment of functioning, as assessed by the CGAS.

The overall rate of discontinuation was 9%, with fewer subjects discontinuing in the lurasidone group (8%) compared with placebo group (10%). The rate of discontinuation of study drug due to TEAEs was similarly low (1.7%) in both treatment groups.

Minimal increases in body weight and BMI were observed in lurasidone-treated subjects. There were minimal increases in serum prolactin levels associated with lurasidone, and there were no clinically meaningful differences between lurasidone- and placebo-treated subjects in metabolic parameters including cholesterol, LDL and HDL cholesterol, and glucose. No subjects had QTcF >460 msec or a ≥ 60msec increase in QTcF from Baseline during double-blind treatment, and very few subjects in either treatment group had a ≥ 30 msec increase in QTcF from Baseline.

Change in cognitive function, as measured by the Cogstate Computerized Cognitive Test Battery, was similar between the treatment groups. The emergence of suicidal ideation or behaviors, as measured by the C-SSRS, was comparable in lurasidone- and placebo-treated subjects, and there were no marked differences in changes of Tanner staging from Baseline to Endpoint between lurasidone- and placebo-treated subjects.

According to the MAH, lurasidone (20 to 80 mg/day, flexibly-dosed) demonstrated statistically significant improvements compared with placebo across primary (CDRS-R), key secondary (CGI-BP-S), and other secondary efficacy endpoints (PARS, PQ-LES-Q, and CGAS) in children and adolescent subjects with major depressive episode associated with bipolar I disorder (bipolar depression). Lurasidone treatment was generally safe and well-tolerated no adverse effects on weight, cardiometabolic parameters, and cognition, and was consistent with the well-known and established safety profile of lurasidone in adult subjects with bipolar depression.

3. CHMP overall conclusion and recommendation

The clinical study was well designed, well conducted and results were provided which was adequate and possible to assess. The efficacy of lurasidone in children and adolescents was demonstrated, although the effect was moderate and non-significant in the 10-14 years strata. The safety was in line with the safety profile of earlier experience and studies in adults.

☐ **Fulfilled:**

No regulatory action required.

4. Additional clarification requested

Question 1

Based on the data submitted, the MAH should address the following questions as part of this procedure:

- Trough serum concentration of lurasidone and three metabolites have been determined following flexibly dosed lurasidone (20 to 80 mg/day) once daily for 6 weeks.
  Based on the reported lists/figures, it is unclear whether the values are mean or individual values. Neither are any data presented on systemic exposure depending on age

MAH response

The values noted on the reported figures for the Trough serum concentration of lurasidone and the three metabolites are mixed with either mean or individual values as shown in Table 14.3.16.1 of the Clinical Study Report (CSR) for D1050326.

Only one serum concentration sample was collected per study subject, thus no systemic exposure could be obtained within the study.

CHMP assessment MAH response

The MAH has provided the requested clarification. Pharmacokinetic data from the study are primarily descriptive and are currently not used for label claims.

Issue resolved

Co rapporteur comments

The Co rapporteur has reviewed the Rapporteur's assessment report who concludes the following: '*The clinical study was well designed, well conducted and results were provided which was adequate and possible to assess. The efficacy of lurasidone in children and adolescents was demonstrated, although the effect was moderate, and the safety was in line with the safety profile of earlier experience and studies in adults. No regulatory action required.'*

Treatment of bipolar depression remains a major unmet medical need in children and adolescents. No drugs are licensed and only very few randomised, double-blind, placebo-controlled studies have been conducted for this indication. Results of relevant trials are not reflected in SmPCs, e.g. there is no relevant information in the quetiapine SmPC (negative results).

The data provide clear evidence of efficacy of lurasidone *over a 6-week treatment duration*, at least in the older age stratum (15 to 18 years).

As a single pivotal study, this study may well be inadequate for granting an indication (see POINTS TO CONSIDER ON APPLICATION WITH 1. META-ANALYSES; 2. ONE PIVOTAL STUDY, CPMP/EWP/2330/99).

There are, however, data available from adult trials in this indication which could be used as supportive data (the drug is licensed for bipolar depression in the US. It is unclear why no relevant indication has been sought/granted in the EU) . In addition, supportive efficacy endpoints and additional safety data will be available on completion of the 104-Week, Flexible-Dose, Open-Label, Multicenter, Extension Study to Evaluate the Long-Term Safety and Effectiveness of Lurasidone in Pediatric Subjects.

In conclusion, we consider that the data obtained in this study constitute important information and consideration should be given to:

1. Including them in the SmPC in section 5.1 and 4.8.
2. Requesting that the company submit a variation application to extend the indication to 'short term treatment of bipolar depression in adolescents aged 15 years and above' once the study report of the extension study has become available. This variation application should include supportive efficacy data from adults and supportive safety data from other paediatric indications.

Rapporteur´s comment

According to the Co Rapporteur, data provide clear evidence of efficacy of lurasidone in patients with bipolar depression, at least in the older age stratum (15 to 18 years), and constitute important information to include in the SmPC. A variation application to extend the indication was requested.

The Rapporteur reconsidered the possibilities for regulatory actions within and outside the procedure. Although the results of Study D1050326 support an effect of lurasidone in the older age stratum, this was not the case for the younger age stratum and, the data thus far are limited to short-term treatment only. It should also be considered that the indication is different from any authorised indication in the EU.

*However, paediatric data is accumulating since Studies D1050300, D1050301 and D1050325 are already available and data on long-term safety and effectiveness as well as on maintenance of the efficacy will be available soon according to the PIP. Furthermore, according to paediatric guidelines it is possible to present paediatric clinical efficacy data in Section 5.1 from non-authorised indications (see "Frequently asked questions on SmPC paediatric information"(*http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/01/WC500137092.pdf *"Results of all pharmacodynamic (clinically relevant) or efficacy studies conducted in children should be presented in section 5.1, even if there is no authorised indication in any subset of the population (adult and paediatric populations) and no paediatric investigation plan for the condition covering this non-authorised indication if the information is considered relevant to prescribers.")*

Taken together, new paediatric data is available and the suggestion to include relevant information in Section 5.1 of the SmPC, in a separate procedure, would be in line with paediatric legislation and guidelines.

The Rapporteur does not recommend changes in Section 4.8 of the SmPC before further data are available based on a more extensive exposure in number of patients and duration.

Finally, considering the unmet medical need in the paediatric population with bipolar depression, it would be valuable to have more data on efficacy and safety, including data on long term efficacy and safety and maintenance of effect, in the future in order to assess a possible paediatric indication for bipolar depression.

Member state comments

MS1 overall agrees with the Rapporteur´s conclusion but have one additional point for clarification.

The effect size estimates in study D1050326 are based on an analysis using a Mixed Model for Repeated Measures (MMRM). No details on handling of missing data are provided, but it can be assumed that the MMRM analysis estimates a treatment effect as if patients who discontinue treatment and withdraw from the study adhered to treatment until the study end. With approximately 10% of withdrawals, the treatment effect estimate based on an MMRM analysis could be too optimistic. An appropriate sensitivity analysis is not apparent from the assessment report. A supportive analysis based on an ANCOVA with LOCF cannot be regarded as appropriate sensitivity analysis as it is based on single imputations, typically reducing the variability in effect estimates and making potentially improper assumptions on the time course of the effect.

The Applicant should be asked for an appropriate sensitivity analysis for the primary analysis that would have to be applied also to the responder analysis. An analysis using a multiple imputation technique using appropriately justified imputations should be part of this exercise. Although it might not be assumed that conclusions on statistical significance of the primary results will change, effect size estimates and results of the responder analysis including NNT estimates may be different.

Rapporteur´s comment

Handling of missing data and sensitivity analyses using multiple imputation technique was provided by the MAH in the CSR. Several relevant paragraphs on these matters have now been copied from the CSR into the Final Assessment Report by the Rapporteur. However, these analyses will not be fully assessed within this procedure. Overall, the paediatric data obtained in this study are considered to constitute important information and consideration should be given to including them in the SmPC in section 5.1. For this purpose, a separate variation application together with all sensitivity analyses would be required.

5. CHMP updated overall conclusion and recommendation

The MAH has provided acceptable responses to Question 1.

The clinical study was well designed and well conducted. The short-term efficacy of lurasidone in the treatment of bipolar depression in children and adolescents was demonstrated in a single clinical study, although the effect was moderate in this paediatric population. Efficacy was mainly demonstrated in the 15 to 17 years old age stratum and not in younger patients. Placebo-adjusted LS mean change from Baseline to Week 6 LOCF in CDRS-R total score for the lurasidone group was -1.8 (-5.6, 2.0) for subjects in the 10- to 14-year-old age stratum. No long-term data on effectiveness will be generated by this study. The safety was in line with the safety profile of earlier experience and studies in adults.

In the EU, Latuda is only authorised for the treatment of schizophrenia in adults, i.e. not in paediatric patients with schizophrenia, nor for treatment of bipolar depression in adults. Considering the unmet medical need, safety risks with other treatments and potentially lower metabolic safety risks with lurasidone compared to other atypical antidepressants, it should be valuable to receive more data on efficacy and safety, including data on long term efficacy and safety and maintenance of effect, in order to assess approval of authorisation of a paediatric indication for bipolar depression. Nevertheless, the data obtained in this study constitute important information and consideration should be given to including them in the SmPC in section 5.1, which is in line with paediatric legislation and guidelines.

Regarding the indication for treatment of schizophrenia, the results of the on-going long-term safety-efficacy study (D1050302) and the maintenance of effect study (5474) included in the PIP for

schizophrenia should be awaited in order to conclude on the risk benefit of lurasidone in adolescent patients with schizophrenia.

According to the CSR provided by the MAH, subjects in Study D1050326, i.e. on bipolar depression, who completed the study were eligible to participate in the separate 104-week open-label extension Study D1050302 in adolescent patients with schizophrenia. However, in the Clinical overview provided by the MAH, the title of Study Long-term D1050302 is as follows: “A 2-year, open-label extension to D1050301, multicenter, flexible-dose clinical study to evaluate the long-term safety and efficacy of lurasidone in children and adolescent subjects (6 to <18 years old).” Thus, it is not fully clear from the current submission whether long-term safety and effectiveness data in the bipolar paediatric population are forthcoming. This should be clarified in the to be submitted variation.

The MAH agrees to submit a variation application for SmPC Section 5.1, after completion of this procedure. This Article 46 paediatric study is considered fulfilled.

☒ **Fulfilled:**

No further action required, however further data are expected in the context of a variation application prior any conclusion on product information amendments is made. The MAH should submit the appropriate variation within 6 months from the adoption of this Opinion (i.e. 22 August 2018).

Annex 1 Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion according to PIP P/0214/2016.

Clinical studies

Product Name: Latuda **Active substance: lurasidone**

Study title[a]	Study number	Completed	Final study report submitt
Open-label, multicenter, single and multiple fixed ascending dose study to evaluate pharmacokinetics, safety, and tolerability of lurasidone in the pediatric population[b]	D1050300	Last visit: 06 May 2013 CSR: 23 October 2013	Article 46: May 2014
Randomized, parallel, double-blind, placebo-controlled, fixed-dose regimen, multicenter, study to evaluate the efficacy and safety of lurasidone in adolescent patients with schizophrenia[b]	D1050301	Last visit: 29 Dec 2015 CSR: 06 Jun 2016	Article 46: August 2016
A 104-week, flexible-dose, open-label multicenter extension study to evaluate the long-term safety and effectiveness of lurasidone in adolescent patients with schizophrenia[b]	D1050302	Date of completion (last patient, last visit): By April 2018	
Randomized, double-blind, active-controlled, non-inferiority, flexible dose study to evaluate the maintenance of the efficacy of lurasidone compared to aripiprazole in the treatment of adolescent patients with schizophrenia	5474	Date of completion (last patient, last visit): By April 2018	