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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/P46/006-007

Note

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

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Introduction

On 30 August 2016, the MAH submitted two completed paediatric studies for lurasidone hydrochloride, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

1. Scientific discussion

1.1. Information on the development program

The MAH states that Study D1050301, which is Study 2 of the agreed Pediatric Investigation Plan (PIP) (EMEA-001230-PIP01-11-M02) for for lurasidone hydrochloride in the treatment of children with schizophrenia aged 6 to 17 years, is a part of a clinical development program. Study D1050325 is noted in the US Food and Drug Administration (FDA) Written Request (WR) for lurasidone. Study D1050325 evaluated lurasidone in pediatric patients aged 6 to 17 years with irritability associated with autistic disorder.

1.2. Information on the pharmaceutical formulation used in the studies

The investigational product for study D1050301 was lurasidone 40 mg/day film-coated tablets with matching placebo. And for the study D1050325, the study drug was lurasidone 20 mg tablets with matching placebo and lurasidone 40 mg tablets with matching placebo.

1.3. Clinical aspects

1.3.1. Introduction

The MAH submitted two final reports for:

- **D1050301**, A randomized, double-blind, placebo-controlled, multicenter, 6-week, fixed-dose, clinical study to evaluate the efficacy and safety of lurasidone in adolescent subjects (13 to <18 years old) with schizophrenia.
- **D1050325,** A randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of two fixed doses of lurasidone (20 mg and 60 mg/day) for six weeks compared with placebo in pediatric and adolescent subjects with irritability associated with autistic disorder.

1.3.2. Clinical studies

D1050301, A randomized, double-blind, placebo-controlled, multicenter, 6-week, fixed-dose, clinical study to evaluate the efficacy and safety of lurasidone in adolescent subjects (13 to <18 years old) with schizophrenia

Description

The efficacy of lurasidone for the treatment of adolescent subjects (13-17 years) with schizophrenia was studied in a randomized, parallel, double-blind, placebo-controlled, fixed-dose, 6 week multi-centre study.

Methods

Objectives

Primary Objective

The primary objective of this study was to evaluate the efficacy of lurasidone (40 mg/day and 80 mg/day) compared with placebo in adolescent subjects with acute schizophrenia (diagnosed by Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision [DSM-IV-TR] criteria) as measured by the change from Baseline in the Positive and Negative Syndrome Scale (PANSS) total score at Week 6.

Key Secondary Objective

The key secondary objective of this study was to evaluate the efficacy of lurasidone (40 mg/day and 80 mg/day) compared with placebo as measured by the change from Baseline in the Clinical Global Impression – Severity (CGI-S) at Week 6.

Other Secondary Objectives

The secondary objectives of this study were:

• To evaluate the efficacy of lurasidone compared with placebo as measured by the change from Baseline in PANSS positive, negative, general psychopathology, and excitability subscale scores at Week 6;

• To evaluate the efficacy of lurasidone compared with placebo in changes in quality of life as measured by the change from Baseline in the Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q) at Week 6;

• To evaluate the efficacy of lurasidone compared with placebo in changes in global functioning as measured by the change from Baseline in the Clinician-rated Children's Global Assessment Scale (CGAS) at Week 6;

• To evaluate the safety and tolerability of lurasidone at 40 mg/day and 80 mg/day.

Study design

The study was a 6-week randomized, parallel, double-blind, placebo-controlled, fixed-dose, multicenter study in adolescent subjects with acute schizophrenia. The study included a screening period, a baseline assessment, a 6-week double-blind treatment period, and a follow-up visit. During the 21-day screening period, eligible subjects were tapered off all psychotropic medications.

Study population /Sample size

Subjects could be inpatient, outpatient, or partial hospitalized, and could attend therapeutic day programs, other supported rehabilitation programs, or school. If necessary, subjects could be 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 and was allowed up to the entire study period.

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

During the double-blind treatment phase, subjects were treated with lurasidone or placebo for six weeks, at doses shown in Table 1.

Table 1: Number of Randomized Subjects in Study D1050301

Study Number	Placebo	Lurasidone [a]			All Groups
		40 mg	80 mg	All	
D1050301	113	108	106	214	327

Approximately 2/3 of the study population were male (63.8%) and approximately 1/3 were female (36.2%). The mean age was 15.4 ± 1.35 years. Approximately 2/3 were White (67.5%) and 86.5% were non-Hispanic/Latino. Approximately 2/3 were from countries outside the United States (66.3%), with more than half (53.7%) from Europe. In total, 160 patients were 13-15 years old (n=55 placebo, n=50 40 mg, n=55 80 mg groups and 166 patients were 16-17 years old (n=57 placebo, n=60 40 mg, n=49 80 mg).

Patients were recruited in multiple study sites (n, %); Bulgaria 24 (7.3%), Romania 17 (5.2%), Russia 46 (14.1%), Ukraine 74 (22.6%), USA 110 (33.6%), Poland 8 (2.4), Spain 3 (0.9), France 2 (0.6), Hungary 2 (0.6), Korea 5 (1.5), Malaysia 4 (1.2), Philippines 6 (1.8), Columbia 16 (4.9), Mexico 10 (3.1) .

The overall mean Baseline BMI was 22.48 ± 3.448 kg/m2 and the Baseline mean BMI Z-score was 0.53 ± 1.021, with no imbalances across the treatment groups. At Baseline, 28.8% of the study population was overweight and 6.1% was obese, according to the WHO 2007 growth reference.

When comparing the baseline characteristics for US versus non-US subjects, there were some notable differences between the subject populations from these 2 regions. The non-US subjects were enrolled in sites in Europe (81.0%), South America (12.0%), and Asia (6.9%). Although the proportions of male and female subjects from US sites were 54.5% and 45.5%, respectively, for non-US subjects, 68.5% were male and 31.5% were female.

For subjects in the US, 2/3 of the subjects were in the 13 to 15 years age category (66.4%), with 1/3 in the 16 to 17 years age category (33.6%); for non-US subjects, a higher proportion were aged 16 to 17 years (59.7%) than those aged 13 to 15 years (40.3%). The mean age was 14.8 ± 1.42 years for US subjects and 15.6 ± 1.23 years for non-US subjects.

In the US, 54.5% of the study subjects were Black compared to no Black non-US subjects. The proportion of White subjects was nearly double in non-US subjects (81.0%) than in US subjects (40.9%). The proportions of overweight and obese subjects were greater among US (33.6% and 12.7%, respectively) than non-US subjects (26.4% and 2.8%, respectively).

When comparing the baseline characteristics for the 2 age groups (13 to 15 vs. 16 to 17), baseline mean PANSS and CGI-S scores were similar across the two age categories. Mean baseline body weight was higher in the 16 to 17 age group than in the 13 to 15 age group, but the baseline mean BMI was similar across the 2 age categories. The mean height at baseline was greater in the 16 to 17 age group than in the 13 to 15 age group.

Baseline demographic characteristics were the same for the ITT population and similar for the PP population.

The majority of the subjects (77.9%) in the ITT population had been previously diagnosed with paranoid type schizophrenia (DSM-IV 295.30) at Baseline, with 14.1% having the undifferentiated type

(DSM-IV 295.90) and 8.0% having the disorganized type (DSM-IV 295.10). Baseline psychiatric history was generally balanced across the treatment groups, except for the following characteristics: the proportion of subjects with a history of disorganized schizophrenia was higher in the lurasidone 40 mg/day treatment group (12.0%) than in the lurasidone 80 mg/day (5.7%) and placebo (6.3%) groups; the proportions of subjects with a history of undifferentiated schizophrenia was lower in the lurasidone 40 mg/day group (8.3%) than in the lurasidone 80 mg/day (16.0%) and placebo (17.9%) groups; and a greater proportion of subjects in the lurasidone 80 mg/day (14.2%) and 40 mg/day (12.0%) treatment groups than in the placebo group (8.0%) had other concurrent psychiatric disorders.

The mean age of onset of the initial behavioral disturbance was 12.30 ± 3.295 years with the duration from this onset to Screening being a mean of 3.57 ± 2.964 years. The mean age of onset of psychotic symptoms was 13.12 ± 2.763 years, and the mean age of onset of the current episode of schizophrenia was 15.75 ± 1.458 years.

Approximately 53% of subjects had been hospitalized for schizophrenia, with no imbalances across the treatment groups. A total of 25.5% of subjects had 1 prior hospitalization, 14.7% had 2 prior hospitalizations, 5.8% had 3 prior hospitalizations, and 7.1% of subjects had 4 or more prior hospitalizations. There were generally no imbalances across the treatment groups.

When comparing US versus non-US subjects, there was a notable difference between the 2 regions in the proportion of subjects with other concurrent psychiatric disorders, which affected 29.1% of US subjects and only 2.3% of non-US subjects. In addition, there were regional differences in the proportions of subjects with specific DSM-IV diagnoses of schizophrenia, with higher proportions of US subjects having disorganized (12.7% vs. 5.6%) or undifferentiated schizophrenia (25.5% vs. 8.3%) and a lower proportion of US subjects having a history of paranoid schizophrenia (61.8% vs. 86.1%) when compared to non-US subjects.

When examining baseline psychiatric history between the 2 age groups, the percentages of histories were generally similar except for the categorical number of prior hospitalizations due to schizophrenia, which were higher in the 16 to 17 years age category. The proportion of subjects with no prior hospitalizations for schizophrenia was 55.0% for the 13 to 15 age group compared with 39.2% for the 16 to 17 age group. The proportion of subjects with 1 or 2 prior hospitalizations for their disease was 22.5% and 12.5%, respectively, for the 13 to 15 age group compared with 28.3% and 16.9%, respectively, for the 16 to 17 age group. The proportion of subjects with 3 or 4 or more prior hospitalizations for schizophrenia was 4.4% and 5.6%, respectively, for the 13 to 15 age group compared with 7.2% and 8.4%, respectively, for the 16 to 17 age group.

The Baseline mean PANSS Total Score for all subjects was 93.8 ± 11.04, and mean CGI-S score was 4.8 ± 0.63, with no imbalances across the treatment groups.

Treatments

Subjects randomized to the 40 mg/day arm received lurasidone 40 mg/day from Day 1 to Week 6. Subjects randomized to the 80 mg/day arm received lurasidone 40 mg/day from Day 1 to Day 3 and 80 mg/day from Day 4 to Week 6. Subjects randomized to the placebo arm received placebo to match lurasidone from Day 1 to Week 6.

Outcomes/endpoints

Primary Endpoint

The primary efficacy endpoint was the change from Baseline in the Positive and Negative Syndrome Scale (PANSS) Total Score at Week 6.

Key Secondary Endpoint

The key secondary endpoint was the change from Baseline in Clinical Global Impression Severity (CGI-S) scale at Week 6.

Other Secondary Endpoints

• Change from Baseline in PANSS positive, negative, general psychopathology, and excitability subscale scores;

• Change from Baseline in Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q);

• Change from Baseline in Clinician-rated Children's Global Assessment Scale (CGAS);

• Proportion of responders, where response is based on ≥ 20% improvement from Baseline in PANSS total score at Week 6;

• Proportion of remitters, defined as subjects who have score not exceeding 3 (mild severity) for items P1, P2, P3, N1, N4, N6, G5, and G9 of the PANSS at Week 6.

Safety Endpoints

Safety measurements included AE reporting, laboratory tests, vital signs, physical examination, height (as measured by stadiometer), electrocardiogram (ECG), body weight, body mass index (BMI) and waist circumference. Other safety assessments include the Cogstate Computerized Cognitive Test Battery, Barnes Akathisia Rating Scale (BARS), the Abnormal Involuntary Movement Scale (AIMS), the Simpson-Angus Scale (SAS), the Columbia Suicide Severity Rating Scale (C-SSRS), Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU), Tanner staging, menstrual cyclicity (female subjects), and hormonal parameters.

Statistical Methods

The Intent-to-Treat (ITT) population was used in the analysis to assess efficacy. In Study D1050301, the ITT population was defined as all randomized subjects who received at least one dose of study medication and had at least one post-baseline assessment in any efficacy variable.

The Per Protocol (PP) population was used to conduct supportive analyses assessing the primary efficacy endpoint and selected secondary efficacy endpoints. The PP population included all ITT subjects who met the following criteria: received assigned study medication; had a Baseline measurement and at least one post-Baseline observation; had 14 days or more continuous exposure; had 75-125% compliance, inclusive; and had no other major protocol violations. The PP population was used to assess robustness of the primary efficacy analysis. The PP analysis population was determined through blinded data review and identified prior to the database lock.

All statistical inference analyses were performed with 2-sided tests at a significance level of 0.05, and 2-sided 95% confidence intervals (CI) were calculated whenever appropriate. Efficacy analyses from the short-term, placebo-controlled study are listed in Table 2.

Table 2: Efficacy Assessments in Study D1050301

Efficacy Endpoints	Type of Analysis Method, Study Population, and Handling of Missing Data
Primary Efficacy Endpoint	
PANSS total score change from Baseline to Week 6	MMRM, ITT, Observed ANCOVA, ITT, LOCF MMRM, PP, Observed PMM, ITT
Key Secondary Efficacy Endpoint	
CGI-S score change from Baseline to Week 6	MMRM, ITT, Observed ANCOVA, ITT, LOCF MMRM, PP, Observed PMM, ITT
Other Secondary Efficacy Endpoints	
PANSS subscale scores (positive, negative, general psychopathology, and excitability) change from Baseline to Week 6	MMRM, ITT, Observed ANCOVA, ITT, LOCF
PQ-LES-Q % maximum possible score change from Baseline to Week 6	ANCOVA, ITT, LOCF
CGAS score change from Baseline to Week 6	ANCOVA, ITT, LOCF
Proportion of responders (≥20% improvement in PANSS total score from Baseline to Week 6)	Logistic regression, ITT, LOCF
Proportion of remitters (score not exceeding 3 [mild severity] for items P1, P2, P3, N1, N4, N6, G5, and G9 of the PANSS at Week 6)	Logistic regression, ITT, LOCF

Abbreviations: ANCOVA=analysis of covariance, CGAS=Clinician-rated Children's Global Assessment Scale, CGI-S=Clinical Global Impression – Severity Scale, ITT=Intent-to-Treat, LOCF=last observation carried forward, MMRM=mixed model repeated measures, PANSS=Positive and Negative Syndrome Scale, PMM=pattern mixture model, PP=Per Protocol, PQ-LES-Q=Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire

Results

Recruitment / Number analysed

A total of 327 subjects were randomized and 326 were included in the ITT population used for efficacy evaluations. Of the subjects in the ITT population, 108 subjects were randomized to lurasidone 40 mg/day, 106 subjects were randomized to lurasidone 80 mg/day, and 112 subjects were randomized to placebo. Overall subject disposition in Study D1050301 is presented in Table 3. During the study, a higher percentage of subjects treated with lurasidone completed the study (89.7%) than placebo (82.3%). The most common reason for discontinuation from the study was due to adverse event (AE); the proportion of subjects who discontinued due to an AE was lower while on lurasidone (3.7% in the "all lurasidone" group versus 8.0% in the placebo group).

Across the two lurasidone treatment groups, a similar proportion of subjects completed the study, and no differences were seen in reasons for discontinuation.

Table 3: Subject Disposition: Study D1050301 (All Randomized Subjects)

Disposition	Placebo (N=113) n (%)	Lurasidone		
		40 mg/day (N=108) n (%)	80 mg/day (N=106) n (%)	All (N=214) n (%)
Number of Subjects Completed	93 (82.3)	96 (88.9)	96 (90.6)	192 (89.7)
Number of Subjects Discontinued	20 (17.7)	12 (11.1)	10 (9.4)	22 (10.3)
Lack of Efficacy	4 (3.5)	1 (0.9)	2 (1.9)	3 (1.4)
Adverse Event	9 (8.0)	5 (4.6)	3 (2.8)	8 (3.7)
Lost to Follow-Up	1 (0.9)	0	0	0
Protocol Violation	1 (0.9)	0	0	0
Withdrawal of Consent	4 (3.5)	5 (4.6)	5 (4.7)	10 (4.7)
Other	1 (0.9)	1 (0.9)	0	1 (0.5)

Baseline data

Eligible subjects met Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) axis I criteria for a primary diagnosis of schizophrenia and had an acute exacerbation of psychotic symptoms (no longer than two months in duration) and marked deterioration of function from baseline (by history), or had been hospitalized for the treatment of an acute psychotic exacerbation, for two consecutive weeks or less, immediately before screening. The diagnosis of schizophrenia was confirmed by an adequately trained clinician at the time of screening according to the Schedule for Affective Disorders and Schizophrenia for School-age Children, a semi-structured diagnostic interview that is designed to evaluate past and present episodes of psychopathology in children and adolescents. Eligible subjects also had a Positive and Negative Syndrome Scale (PANSS) total score $\geq$ 70 to <120 at Screening and Baseline, and a Clinical Global Impression-Severity Scale (CGI-S) score $\geq$ 4 at Screening and Baseline. The majority of the subjects (77.9%) in the ITT population had been previously diagnosed with paranoid type schizophrenia (DSM-IV 295.30) at Baseline, with 14.1% having the undifferentiated type (DSM-IV 295.90) and 8.0% having the disorganized type (DSM-IV 295.10). Baseline psychiatric history was generally balanced across the treatment groups, except for the following characteristics: the proportion of subjects with a history of disorganized schizophrenia was higher in the lurasidone 40 mg/day treatment group (12.0%) than in the lurasidone 80 mg/day (5.7%) and placebo (6.3%) groups; the proportions of subjects with a history of undifferentiated schizophrenia was lower in the lurasidone 40 mg/day group (8.3%) than in the lurasidone 80 mg/day (16.0%) and placebo (17.9%) groups; and a greater proportion of subjects in the lurasidone 80 mg/day (14.2%) and 40 mg/day (12.0%) treatment groups than in the placebo group (8.0%) had other concurrent psychiatric disorders.

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symptoms was 13.12 ± 2.763 years, and the mean age of onset of the current episode of schizophrenia was 15.75 ± 1.458 years.

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The Baseline mean PANSS Total Score for all subjects was 93.8 ± 11.04, and mean CGI-S score was 4.8 ± 0.63, with no imbalances across the treatment groups.

Efficacy results

Primary Efficacy Analyses

The primary efficacy parameter for Study D1050301, PANSS total score, was evaluated at each visit using MMRM and ANCOVA-LOCF models. These assessments provide information about the onset and persistence of efficacy for the 6-week study period.

In the placebo-controlled study, MMRM analysis showed that the change from Baseline in PANSS total score was statistically significant compared with placebo starting at Week 1 for the lurasidone 40 mg/day and 80 mg/day dose groups. Lurasidone was superior to placebo for all subsequent visits through Week 6 (Table 4; Figure 1).

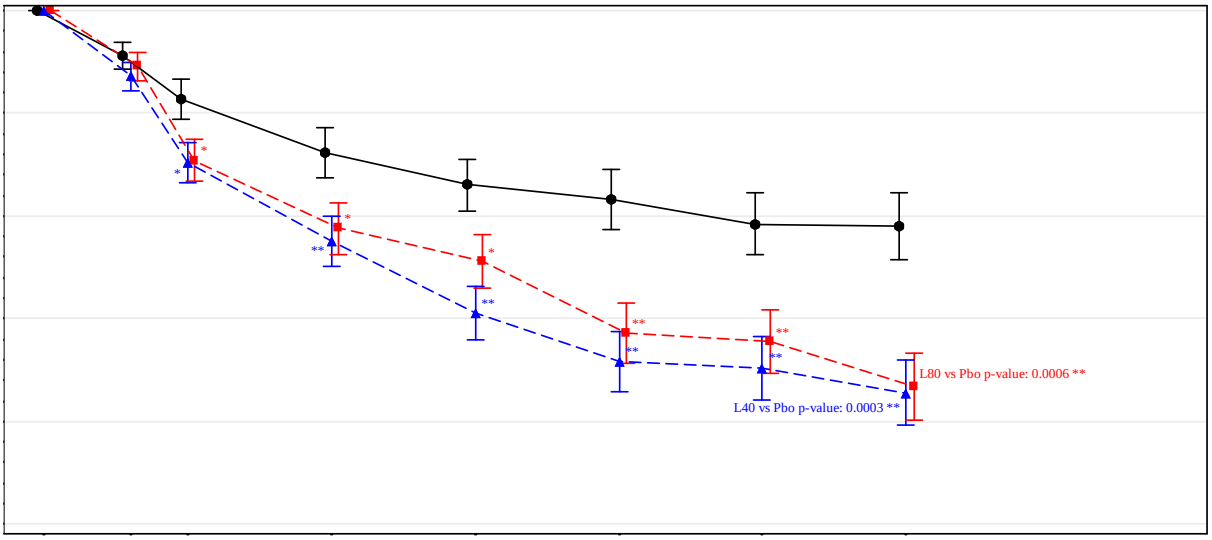
Table 4: Change from Baseline in PANSS Total Score at Week 6 – Mixed Model for Repeated Measures (ITT Population) in Study D1050301

PANSS Total Score [a] Week 6	Placebo (N=112)	Lurasidone	
		40 mg/day (N=108)	80 mg/day (N=106)
n	93	96	97
LS Mean (SE)	−10.5 (1.59)	−18.6 (1.59)	−18.3 (1.60)
Difference of LS Mean (SE) (vs. Placebo)		−8.0 (2.21)	−7.7 (2.2)
95% CI of Difference		−12.4, −3.7	−12.1, −3.4
p-value (vs. Placebo)		0.0003**	0.0006**

** $p \leq 0.01$ vs placebo.
[a] LS Mean, LS mean difference, and the associated 95% CI and p-value for change from Baseline are based on Mixed Model for Repeated Measures with fixed effects terms for treatment, visit (as a categorical variable), pooled country, age strata, PANSS total score at Baseline, and treatment-by-visit interaction.
Note: Higher values of PANSS total score represent greater severity of illness.

In the supportive analysis of the primary efficacy endpoint using the ANCOVA model at Week 6 with LOCF, there were significantly differences from placebo for both the lurasidone 80 mg/day (7.8, p = 0.0004) and 40 mg/day (8.2 , p = 0.0002) treatment groups.

Figure 1: LS Mean Treatment Difference (95% CI) for PANSS Total Score Change from Baseline to Week 6: MMRM Analysis, ITT Population



*p≤0.05; **p≤0.01 vs placebo.

Key Secondary Efficacy Analyses

The key secondary efficacy results for Study D1050301, which used the change in CGI-S score from Baseline to endpoint (Week 6) based on the MMRM model for the ITT population as the key secondary analysis, are shown in Table 5. The key secondary analysis used a similar MMRM model described for the primary variable.

Table 5: Change from Baseline in Clinical Global Impression – Severity (CGI-S) at Week 6 – Mixed Model for Repeated Measures (ITT Population) in Study D1050301

CGI-S Score [a] Week 6	**Placebo (N=112)**	**Lurasidone**	
		40 mg/day (N=108)	**80 mg/day (N=106)**
n	93	96	97
LS Mean (SE)	–0.50 (0.094)	–0.97 (0.093)	–0.92 (0.093)
Difference of LS Mean (SE) (vs. Placebo)		–0.47 (0.130)	–0.42 (0.130)
95% CI of Difference		–0.73, –0.22	–0.67, –0.16
p-value (vs. Placebo)		0.0003**	0.0015**

** p ≤ 0.01 vs placebo.
[a] LS Mean, LS mean difference, and the associated 95% CI and p-value for change from Baseline are based on Mixed Model for Repeated Measures with fixed effects terms for treatment, visit (as a categorical variable), pooled country, age strata, CGI-S scores at Baseline, and treatment-by-visit interaction.
Note: Higher values of CGI-S scores represent greater severity of illness.

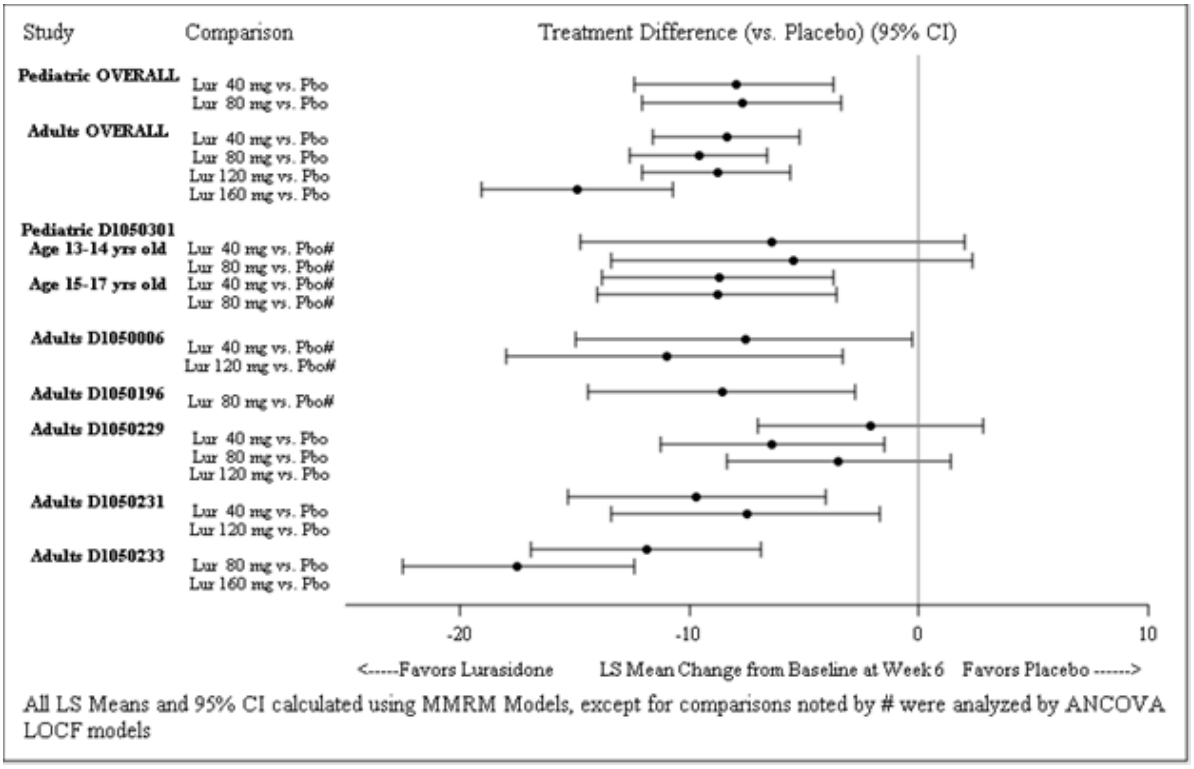
Comparison of Results in Subpopulations

Pre-specified efficacy analyses of subgroups, or subpopulations, were conducted in Study D1050301. The results of these analyses suggest that age group, gender, race, baseline BMI, ethnicity, and country (non-US vs US) did not influence the treatment effect of lurasidone.

Comparison of Results to Adult Studies

Study D1050301 demonstrated efficacy in adolescent subjects with schizophrenia that is similar to that observed in adults, within a dose range (40 to 80 mg/day) that is currently approved for adults (Figure 2).

Figure 2: Forest Plot Comparing Short-term Adult to Short-term Adolescent



Safety results

In Study D1050301, a total of 326 subjects received at least one dose of study medication; of these, 110 subjects received 40 mg lurasidone once daily, 104 subjects received 80 mg once daily, and 112 subjects received placebo once daily. Overall, the majority (80.1%) of subjects received treatment for at least 41 days. For the 214 lurasidone-treated subjects, 83.6% had at least six weeks (≥ 41 days) of

exposure; the mean number of days of exposure was 39.8 days. The number of days of exposure was generally similar across lurasidone dose groups.

There were no deaths during the study. The majority of TEAEs were mild-to-moderate in severity. Serious adverse events were more common among subjects receiving placebo (nine subjects, 8.0%) than among subjects receiving lurasidone (six subjects, 2.8%). Exacerbations of schizophrenia were reported in 7 (6.3%) subjects receiving placebo, along with psychotic disorder and suicidal ideation, each in 1 subject. Two subjects in each of the lurasidone treatment groups had serious exacerbations/worsening of schizophrenia, and 1 subject receiving lurasidone 40 mg/day was reported

to have homicidal ideation. In addition, 1 subject in the lurasidone 40 mg/day treatment group

developed diarrhea that was serious. Among subjects receiving lurasidone 40 mg/day, SAEs were more common among subjects 13 to 15 years of age (6.0%) than among subjects who were 16 to 17 years of age (1.7%). The incidence of SAEs in the placebo group was similar in both age groups, and all events were psychiatric disorders.

Safety discontinuations occurred most frequently among subjects receiving placebo (8.0%), followed by subjects receiving lurasidone 40 mg (5.5%), and least frequently among subjects receiving lurasidone 80 mg (1.9%). Five of the 6 subjects in the lurasidone 40 mg/day dose group discontinued due to psychiatric disorders (anxiety, homicidal ideation, and suicidal ideation, each in 1 subject, and schizophrenia in 2 subjects) and 1 discontinued due to irritability. Of the 2 subjects in the lurasidone 80 mg/day dose group who discontinued study treatment due to an AE, 1 did so for worsening of schizophrenia and the other due to hypersensitivity (allergic reaction). The majority of safety discontinuations in the placebo group were due to psychiatric disorders (ie, schizophrenia and psychotic disorder). There were no apparent trends with respect to age group in discontinuation of study treatment due to TEAEs.

The incidence of treatment-related TEAEs was higher and similar among subjects receiving lurasidone 80 mg/day (44.2%) or 40 mg/day (43.6%) than among subjects receiving placebo (29.5%) (Table 6).

Table 6: Summary of Treatment-Emergent Adverse Events (Safety Population)

Subjects with at least one TEAE of following types	Placebo (N=112) n (%)	Lurasidone		
		40 mg (N=110) n (%)	80 mg (N=104) n (%)	All (N=214) n (%)
Any Adverse Events	64 (57.1)	70 (63.6)	67 (64.4)	137 (64.0)
Adverse Events Leading to Discontinuation	9 (8.0)	6 (5.5)	2 (1.9)	8 (3.7)
Adverse Events Related to Study Drug [a]	33 (29.5)	48 (43.6)	46 (44.2)	94 (43.9)
Adverse Events Related to Study Drug [a] and Leading to Discontinuation	4 (3.6)	3 (2.7)	2 (1.9)	5 (2.3)
Serious Adverse Events	9 (8.0)	4 (3.6)	2 (1.9)	6 (2.8)
Serious Adverse Events Leading to Discontinuation	7 (6.3)	3 (2.7)	1 (1.0)	4 (1.9)
Serious Adverse Events Related to Study Drug [a]	4 (3.6)	1 (0.9)	1 (1.0)	2 (0.9)
Serious Adverse Events Related to Study Drug [a] and Leading to Discontinuation	2 (1.8)	1 (0.9)	1 (1.0)	2 (0.9)
Death	0	0	0	0
Total No. Subjects with EPS-Related TEAEs	3 (2.7)	15 (13.6)	11 (10.6)	26 (12.1)
Total No. Subjects with any Non-Akathisia TEAEs	2 (1.8)	7 (6.4)	4 (3.8)	11 (5.1)
Akathisia	2 (1.8)	10 (9.1)	9 (8.7)	19 (8.9)
Salivary Hypersecretion	0	2 (1.8)	2 (1.9)	4 (1.9)
Parkinsonism	1 (0.9)	3 (2.7)	0	3 (1.4)
Dyskinesia	1 (0.9)	1 (0.9)	1 (1.0)	2 (0.9)
Oculogyric Crisis	0	1 (0.9)	1 (1.0)	2 (0.9)
Extrapyramidal Disorder	0	1 (0.9)	0	1 (0.5)
Tardive Dyskinesia	0	1 (0.9)	0	1 (0.5)
Total No. Subjects with Metabolic TEAEs	3 (2.7)	1 (0.9)	4 (3.8)	5 (2.3)
Weight Increased	3 (2.7)	1 (0.9)	3 (2.9)	4 (1.9)
Hyperinsulinaemia	0	0	1 (1.0)	1 (0.5)

Subjects with at least one TEAE of following types	Placebo (N=112) n (%)	Lurasidone		
		40 mg (N=110) n (%)	80 mg (N=104) n (%)	All (N=214) n (%)
Total No. Subjects with Suicide Related TEAEs	2 (1.8)	1 (0.9)	0	1 (0.5)
Suicidal Ideation	1 (0.9)	1 (0.9)	0	1 (0.5)
Suicidal Ideation	1 (0.9)	1 (0.9)	0	1 (0.5)
Suicide Attempt	1 (0.9)	0	0	0
Intentional Self-Injury	1 (0.9)	0	0	0
Total No. Subjects with Hypersensitivity TEAEs	1 (0.9)	2 (1.8)	4 (3.8)	6 (2.8)
Dermatitis Contact	0	0	1 (1.0)	1 (0.5)
Hypersensitivity	0	0	1 (1.0)	1 (0.5)
Pruritus	0	0	1 (1.0)	1 (0.5)
Urticaria	0	0	1 (1.0)	1 (0.5)
Glossodynia	0	1 (0.9)	0	1 (0.5)
Lip Swelling	0	1 (0.9)	0	1 (0.5)
Rash	1 (0.9)	0	0	0

Abbreviations: EPS = extrapyramidal symptoms; TEAE = treatment-emergent adverse event
[a] Related to study drug includes relationship determined by investigators: definite, possibly, probably related.
Note: Percentage is calculated by using the number of subjects in each treatment group as denominator.
Note: Incidence is based on the number of subjects experiencing at least one TEAE, not the number of events.

The most common TEAEs for subjects receiving lurasidone were in the SOC categories of Nervous System Disorders (70 subjects, 32.7%), Gastrointestinal Disorders (57 subjects, 26.6%), and Psychiatric Disorders (48 subjects, 22.4%). For subjects receiving placebo, the most common TEAEs were in the SOC categories of Psychiatric Disorders (31 subjects, 27.7%) and Nervous System Disorders (25 subjects, 22.3%).

With respect to nervous system disorders, somnolence, akathisia, and dizziness were appreciably more common among subjects receiving lurasidone (10.3%, 8.9%, and 4.7%, respectively) than among subjects receiving placebo (5.4%, 1.8%, and 0.9%, respectively). Headache was reported in 18 (8.4%) subjects receiving lurasidone and 14 (12.5%) subjects receiving placebo. Parkinsonism was reported in 3 (1.4%) subjects receiving lurasidone, all in the 40 mg/day treatment group (2.7%), compared to 1 (0.9%) subject receiving placebo.

With regard to gastrointestinal disorders, nausea, vomiting, diarrhea, and dry mouth were more common among subjects receiving lurasidone (13.6%, 7.5%, 3.7%, and 2.3%, respectively) than among subjects receiving placebo (2.7%, 1.8%, 0.9%, and 0, respectively).

With regard to psychiatric disorders, insomnia, anxiety, and schizophrenia were more common among subjects receiving placebo (8.9%, 8.0%, and 8.0%, respectively) than among subjects receiving lurasidone (6.1%, 6.5%, and 2.3%, respectively), with the most pronounced difference being in the incidence of schizophrenia. Agitation was reported in 5.1% of subjects receiving lurasidone and 4.5% of subjects receiving placebo.

Tachycardia was reported in 3 (2.9%) subjects in the lurasidone 80 mg/day treatment group; all cases were mild in severity.

Treatment-emergent AEs related to EPS were more common in the lurasidone group (12.1%) than in the placebo group (2.7%). The most common event was akathisia, which was reported in 19 (8.9%) subjects receiving lurasidone compared to 2 (1.8%) subjects receiving placebo. Parkinsonism was reported in 4 (1.9%) subjects receiving lurasidone, with all cases in the 40 mg/day treatment group

(3.6%) compared to 1 (0.9%) subject receiving placebo. Dyskinesia was reported in 1 subject in each of the 3 treatment groups, and dystonia was reported in 1 subject in each of the lurasidone treatment groups. Tardive dyskinesia was reported in 1 subject in the lurasidone 40 mg/day group. Salivary hypersecretion was reported only in the lurasidone treatment groups, with 2 cases each in the 80 mg/day (1.9%) and 40 mg/day (1.8%) dose groups, respectively).

Metabolic-related TEAEs were reported with low and similar frequency in the combined lurasidone and placebo groups. Weight gain was reported with a higher incidence in the lurasidone 80 mg group (2.9%) than in the 40 mg group (0.9%), with the higher incidence being similar to that of the placebo group (2.7%).

Treatment-emergent AEs related to suicidality and self-injury were uncommon, with a similar incidence across the treatment groups.

Treatment-emergent AEs related to hypersensitivity reactions were uncommon, but reported with a higher incidence among subjects receiving lurasidone (2.8%) than among subjects who receiving placebo (0.9%) and with a higher incidence in the lurasidone 80 mg group (3.8%) than in the 40 mg group (1.8%).

Serum prolactin levels increased from Baseline to Endpoint in the lurasidone treatment groups and decreased in the placebo group, with the mean change in the lurasidone 80 mg being statistically significant compared to placebo. In female subjects, the mean increase of 7.94 ± 14.351 ng/mL for the lurasidone 80 mg group was statistically significant compared to the mean decrease of 2.27 ± 22.769 ng/mL for the placebo group ($p = 0.0318$).

For laboratory parameters, there were no notable or clinically meaningful differences between the lurasidone treatment groups and the placebo group in the mean change from Baseline for any hematology or urinalysis parameter or in fasting or overall glucose, insulin, HOMA-IR, HDL, LDL, or triglycerides. For the change from Baseline to Endpoint in fasting total cholesterol, the mean increase in the lurasidone 80 mg group was statistically significant compared to the mean decrease in the placebo group.

With respect to hormone parameters, in female subjects, both lurasidone treatment groups had mean decreases from Baseline to Endpoint in FSH, whereas the placebo group had a mean increase in FSH. Larger mean decreases in estradiol were observed for the lurasidone 80 mg group than the lurasidone 40 mg or placebo groups, with the lowest decrease observed for the placebo group.

Treatment with lurasidone had no notable effect on vital signs parameters.

A greater number of subjects in the lurasidone groups had upward shifts in BMI category from Baseline to Endpoint than subjects in the placebo group; thus, there was a modest weight gain associated with lurasidone treatment. Overall, after 6 weeks of treatment, there was a minimal increase in body weight in subjects treated with lurasidone, as demonstrated by the small mean changes from Baseline in body weight and BMI Z-score of 0.49 ± 0.225 kg and 0.011 ± 0.2055, respectively, for the 80 mg/day group, and 0.17 ± 0.223 kg and -0.011 ± 0.2534, respectively, for the 40 mg/day group. The corresponding mean changes from Baseline for the placebo group were 0.05 ± 0.225 kg and -0.018 ± 0.2562, respectively.

With respect to ECG measurements, no subject experienced an ECG-related SAE or discontinued double-blind treatment due to an ECG-related TEAE. Although larger mean increases in uncorrected QT interval were observed in the lurasidone treatment groups compared to the placebo group, using the QTcB correction formula, a small increase was observed in the lurasidone 80 mg group, with small

decreases observed in both the lurasidone 40 mg and placebo groups. The QTcF correction formula showed small mean increases for both lurasidone groups compared to a very small mean decrease for the placebo group. The results for QTcF, which are considered more sensitive in the pediatric and adolescent populations, showed that no subject in any treatment group had a QTcF > 460 msec or a ≥ 60 msec increase from Baseline at Week 6, Endpoint, or any other post-Baseline visit during double-blind treatment.

The changes from Baseline to Endpoint in the BARS Total Score, BARS global clinical assessment of akathisia, and SAS showed small mean increases for all three treatment groups, with no statistically significant differences between lurasidone and placebo for any of these measures. For the AIMS, the mean increases from Baseline for the lurasidone groups were not statistically significant compared to the small mean decrease for the placebo group. Also, there were no shifts from normal at Baseline to abnormal at Endpoint in any treatment group; however, in the lurasidone group, there were two subjects in each dose group who worsened from Baseline to Endpoint.

For the Cogstate Computerized Cognitive Test Battery, there was a statistically significant difference between the lurasidone 80 mg group and placebo for the Working Memory–One Back Task–Speed task, with the lurasidone group showing an improvement over placebo ($p = 0.0238$).

There were no statistically significant differences between either of the lurasidone groups and placebo in suicidality, as measured by the C-SSRS.

The UKU side effect rating scale showed that sleepiness/sedation increased in frequency in the lurasidone 80 mg and 40 mg groups from Baseline (15.7% and 13.9%, respectively) to post-Baseline (21.6% and 22.6%, respectively). Akathisia increased in frequency in the lurasidone 80 mg and 40 mg groups from Baseline (2.0% and 5.6%, respectively) to post-Baseline (9.8% and 13.2%, respectively), with all cases of akathisia in the lurasidone groups worsening during double-blind treatment. Nausea/vomiting increased in frequency in all 3 treatment groups, with the most pronounced increase from Baseline in the lurasidone treatment groups, and most cases worsened during double-blind treatment. Weight gain increased in incidence from Baseline to post-Baseline and worsened in all 3 treatment groups.

There were no marked changes in Tanner staging from Baseline to Endpoint for male or female subjects.

D1050325, A randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of two fixed doses of lurasidone (20 mg and 60 mg/day) for six weeks compared with placebo in pediatric and adolescent subjects with irritability associated with autistic disorder.

Description

Study D1050325 was a randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of two fixed doses of lurasidone (20 mg and 60 mg/day) for six weeks compared with placebo in pediatric and adolescent subjects with irritability associated with autistic disorder aged 6-17 years.

Methods

Objective(s)

Primary Objective

The primary objective was to evaluate the efficacy of lurasidone in the treatment of pediatric and adolescent subjects with irritability associated with autistic disorder. The primary outcome measure was the least squares (LS) mean change from Baseline the Aberrant Behavior Checklist irritability subscale score at Week 6.

Key Secondary Objective

The secondary objectives included efficacy evaluations of lurasidone as measured by change from Baseline to Week 6 in the CGI-S, Clinical Global Impression – Improvement, other Aberrant Behavior Checklist subscale (hyperactivity, stereotypy, inappropriate speech, and lethargy/social withdrawal) scores, Children's Yale-Brown Obsessive Compulsive Scales modified for pervasive developmental disorders, and Caregiver Strain Questionnaire, as well as safety and tolerability.

Study design

Subjects randomized to the 20 mg/day arm were to receive 20 mg/day from Day 1 to Week 6 Visit. Subjects randomized to the 60 mg/day arm were to receive lurasidone 20 mg/day from Days 1-3, 40 mg/day from Days 4-6 and 60 mg/day from Day 7 to Week 6 Visit. Subjects randomized to the placebo arm were to receive placebo to match lurasidone from Day 1 to Week 6 Visit. If, in the opinion of the investigator, the subject was not tolerating the assigned dose of study medication, a one-time dose reduction could have occurred in Weeks 2, 3 or 4 (ie, between Day 8 to Day 29, inclusive). It was planned that subjects would maintain the stepped down dose for the remainder of the study. Subjects assigned to 60 mg/day lurasidone could have been stepped down to receive 40 mg/day; subjects assigned to 20 mg/day lurasidone and placebo continued to receive their assigned dose. If, in the judgment of the investigator (with input from the subject and caregiver), the subject did not tolerate the stepped-down dose, the subject was discontinued from the study.

Study population /Sample size

Subjects were evaluated for eligibility during a screening period of up to 21 days, during which they were tapered off all psychotropic medications in a manner that was consistent with labeling recommendations and conventional medical practice. Following the screening period, subjects who continued to meet entry criteria were randomly assigned to one of three double-blind treatment arms: lurasidone 20 mg/day, lurasidone 60 mg/day, or placebo (1:1:1 ratio) (Table 7).

Table 7: Number of Randomized Subjects in Study D1050325

Study Number	Placebo	Lurasidone [a]			All Groups
		20 mg	60 mg	All	
D1050325	50	50	50	100	150

[a] Dose given once daily.

Treatments

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

Outcomes/endpoints

Primary Endpoint

The primary endpoint was the change from Baseline to Week 6 in the ABC irritability

subscale. Secondary Endpoints

- Change from Baseline in Clinical Global Impression severity (CGI-S) scale as compared to placebo;
- Clinical Global Impression Improvement (CGI-I) scale;
- Change from Baseline in other Aberrant Behavior Checklist (ABC) subscale scores (hyperactivity, stereotypy, inappropriate speech, and lethargy/social withdrawal);
- Change from Baseline in Children's Yale-Brown Obsessive Compulsive Scales (CY-BOCS) modified for pervasive developmental disorders (PDDs);
- Change from Baseline in the Caregiver Strain Questionnaire (CGSQ);
- Proportion of subjects who have CGI-I score of 1 (very much improved) or 2 (much improved) at Week 6;
- Proportion of subjects who have at least 25% reduction from Baseline to Week 6 in the ABC irritability subscale score.

Safety Endpoints

Safety measurements included adverse event (AE) reporting, laboratory tests, vital signs, body weight, body mass index (BMI), waist circumference, physical examination, height (as measured by stadiometer), electrocardiogram (ECG). Other safety assessments include the Barnes Akathisia Rating Scale (BARS), the Abnormal Involuntary Movement Scale (AIMS), the Simpson-Angus Scale (SAS), Tanner staging, and menstrual cyclicity (female subjects).

Statistical Methods

Unless otherwise specified, 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 mg/day versus placebo and lurasidone 60 mg/day versus placebo was strongly controlled at the 5% level across the primary endpoint.

The primary and the key secondary endpoints were assessed using an MMRM model and supportive analyses were conducted using an ANCOVA model with the LOCF approach.

The primary analysis population for the efficacy analysis was the Intent-to-Treat (ITT) population. The ITT population included all randomized subjects who received at least one dose of study medication and had at least one post-baseline assessment in any efficacy variable.

The Per Protocol (PP) population included all ITT subjects who had no major protocol deviations that may have impacted the efficacy analysis. Subjects in the PP population were summarized with the treatment group to which they were randomized.

The safety analysis population consisted of all randomized subjects who received at least one dose of study medication. The safety population was used for all safety data analyses.

Results

Recruitment/ Number analysed

A total of 150 subjects were randomized and 148 were included in the Intent-to-Treat (ITT) population used for efficacy evaluations (randomization ratio was 1:1:1). Of the subjects in the ITT population, 48 subjects received lurasidone 20 mg, 51 subjects received lurasidone 60 mg, and 49 subjects received placebo. Overall subject disposition in Study D1050325 is presented in Table 8.

During the study, a higher percentage of subjects treated with lurasidone completed the study ("all lurasidone", 90.0%) than placebo (76.0%). The most common reason for discontinuation from the study was due to adverse event (AE) and withdrawal of consent, though the proportion of subjects who discontinued for these reasons was higher in the placebo group (8.0% and 12%, respectively) than in the "all lurasidone" group (4.0% and 1.0%, respectively).

Across the two lurasidone treatment groups, no significant differences were seen in the number of subjects who completed the study or in reasons for discontinuation from the study.

Table 8: Subject Disposition: Study D1050325 (All Randomized Subjects)

		Lurasidone		
Disposition	**Placebo (N=50) n (%)**	**20 mg/day (N=49) n (%)**	**60 mg/day (N=51) n (%)**	**All (N=100) n (%)**
Number of Subjects Completed	38 (76.0)	43 (87.8)	47 (92.2)	90 (90.0)
Number of Subjects Discontinued	12 (24.0)	6 (12.2)	4 (7.8)	10 (10.0)
Lack of Efficacy	1 (2.0)	1 (2.0)	1 (2.0)	2 (2.0)
Adverse Event	4 (8.0)	2 (4.1)	2 (3.9)	4 (4.0)
Lost to Follow-Up	1 (2.0)	2 (4.1)	0	2 (2.0)
Withdrawal of Consent	6 (12.0)	1 (2.0)	0	1 (1.0)
Other	0	0	1 (2.0)	1 (1.0)

Baseline data

Per inclusion criterion, all subjects had a diagnosis of autistic disorders. The average (mean ± SD) age at initial onset of autistic disorders was 4.78 ± 3.513 years for the combined lurasidone group and 5.05 ± 3.765 years for the placebo group. The average duration of autistic disorders from onset to Screening was 6.27 ± 3.954 years for the combined lurasidone group and 6.50 ± 3.942 years for the

placebo group. The proportion of subjects with other psychiatric disorders present was 60.0% for the combined lurasidone group and 55.1% for the placebo group.

Selected Efficacy Parameters at Baseline

A summary of the Baseline scores of selected efficacy parameters is provided in Table 9.

Table 9: Selected Efficacy Parameter Baseline Scores (ITT Population)

Characteristic	Placebo (N=49)	Lurasidone			Total (N=148)
		20 mg (N=48)	60 mg (N=51)	All (N=99)	
Baseline ABC Irritability Subscale Score					
n	49	48	51	99	148
Mean (SD)	29.1 (6.87)	28.3 (5.88)	27.1 (5.70)	27.7 (5.79)	28.1 (6.18)
Median	27.0	28.0	26.0	28.0	27.0
Min, Max	18, 43	19, 41	18, 39	18, 41	18, 43
Baseline CGI-Severity of Illness					
n	49	48	51	99	148
Mean (SD)	5.0 (0.79)	4.9 (0.83)	4.7 (0.82)	4.8 (0.83)	4.9 (0.82)
Median	5.0	5.0	5.0	5.0	5.0
Min, Max	4, 6	4, 7	4, 7	4, 7	4, 7

Abbreviations: ABC = Aberrant Behavior Checklist; CGI = Clinical Global Impression; Max = maximum; Min = minimum; SD = standard deviation.
Notes: Higher observed ABC Irritability subscale score and CGI-S score indicate greater severity of illness.

Efficacy results

Primary Efficacy Analyses

The efficacy of lurasidone for the treatment of children and adolescent patients with irritability associated with autistic disorder was not demonstrated in a randomized, parallel, double-blind, placebo-controlled, multicenter study (Study D1050325).

The LS mean change (± SE) from Baseline to Week 6 in the Aberrant Behavior Checklist irritability subscale score based on a MMRM model was -9.4 ± 1.43 for the lurasidone 60 mg/day group, -8.8 ± 1.50 for the lurasidone 20 mg/day group, and -7.5 ± 1.52 for the placebo group. Although the decreases in the Aberrant Behavior Checklist irritability subscale scores were larger in the lurasidone groups, these treatment differences were not significant from placebo: -1.9 (p = 0.36) for the lurasidone 60 mg/day group and -1.3 (p = 0.55) for the lurasidone 20 mg/day group (10 and Figure 3).

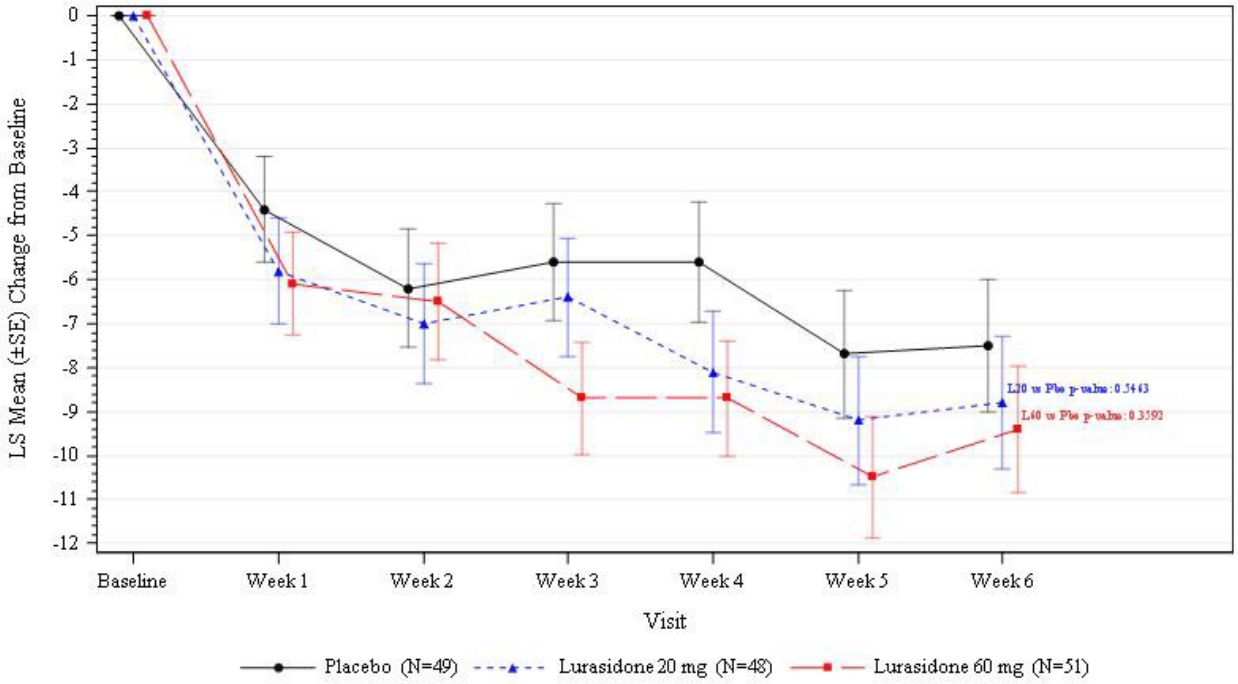
Table 10: Change from Baseline in Aberrant Behavior Checklist (ABC) Irritability Subscale Score – Repeated Measures (ITT Population) in Study D1050325

ABC Irritability Subscale Score	Placebo (N=49)	Lurasidone 20 mg (N=48)	Lurasidone 60 mg (N=51)
Change from Baseline			
Week 6			

ABC Irritability Subscale Score	Placebo (N=49)	Lurasidone 20 mg (N=48)	Lurasidone 60 mg (N=51)
n	38	43	47
LS Mean (SE)	-7.5 (1.52)	-8.8 (1.50)	-9.4 (1.43)
Difference of LS Mean (SE) (vs. Placebo)		-1.3 (2.15)	-1.9 (2.09)
95% CI of Difference		(-5.6, 3.0)	(-6.1, 2.2)
p-value (vs. Placebo)		0.5463	0.3592

Abbreviations: CI = confidence intervals; MMRM = mixed model for repeated measures; SE = standard errors.
Notes: LS Mean, LS mean difference, and the associated 95% CI and p-value for change from baseline are based on Mixed Model for Repeated Measures with fixed effects terms for treatment, visit (as a categorical variable), pooled center, ABC irritability score at baseline, and treatment-by-visit interaction. Note: Higher values of ABC subscale scores represent greater severity of illness.

Figure 3: Change from Baseline (LS Mean ± SE) in the Aberrant Behavior Checklist (ABC) Irritability Subscale Score - Mixed Model for Repeated Measures (ITT Population) in Study D1050325



Secondary Efficacy Analyses

The average (mean ± SD) Baseline CGI-S score was 4.7 ± 0.82 for the lurasidone 60 mg/day group, 4.9 ± 0.83 for the lurasidone 20 mg/day group, and 5.0 ± 0.79 for the placebo group.

Based on the MMRM model, the decrease (LS mean ± SE) in the CGI-S score from Baseline to Week 6 was -1.0 ± 0.16 for the lurasidone 60 mg/day group, -1.1 ± 0.17 for the lurasidone 20 mg/day group, and -0.7 ± 0.17 for the placebo group, indicating an improvement in symptoms. Although the decreases in CGI-S score from Baseline to Week 6 were greater in the lurasidone groups, these treatment differences were not significant from placebo (Table 11).

Table 11: Change from Baseline in Clinical Global Impression – Severity Scale Score – Repeated Measures (ITT Population) in Study D1050325

CGI-Severity of Illness	Placebo (N=49)	Lurasidone 20 mg (N=48)	Lurasidone 60 mg (N=51)
Change from Baseline			
Week 6			

CGI-Severity of Illness	Placebo (N=49)	Lurasidone 20 mg (N=48)	Lurasidone 60 mg (N=51)
n	38	43	47
LS Mean (SE)	-0.7 (0.17)	-1.1 (0.17)	-1.0 (0.16)
Difference of LS Mean (SE) (vs. Placebo)		-0.3 (0.25)	-0.3 (0.24)
95% CI of Difference		(-0.8, 0.2)	(-0.8, 0.2)
p-value (vs. Placebo)		0.1755	0.2402

Abbreviations: CGI-S = Clinical Global Impression – Severity; CI = confidence intervals; LS = least squares; MMRM = mixed model for repeated measures; SE = standard errors.

Notes: LS Mean, LS mean difference, and the associated 95% CI and p-value for change from baseline are based on Mixed Model for Repeated Measures with fixed effects terms for treatment, visit (as a categorical variable), pooled center, CGI-S scores at baseline, and treatment-by-visit interaction.

Note: Higher values of CGI-S scores represent greater severity of illness.

Safety results

A total of 149 subjects received at least one dose of study medication in Study D1050325. Of the 149 subjects, 100 subjects received lurasidone (daily doses of 20 and 60 mg) and 49 subjects received placebo once daily. Per protocol, the double-blind treatment period was to last six weeks.

Overall, the highest mean exposure was in the lurasidone 60 mg/day group (39.9 ± 7.98) and the lowest was in the placebo group (36.7 ± 11.91). For the "all lurasidone" group, 83.0% had at least 6 weeks (≥ 41 days) of exposure. For the 100 lurasidone-treated subjects in the "all lurasidone" group, the number of days of exposure (mean ± SD) was 39.2 ± 9.31 days. The number of days of exposure was generally similar across lurasidone dose groups. The overall exposure to lurasidone was 10.7 subject-years.

Severe TEAEs occurred in seven (7.0%) lurasidone treated subjects and five (10.2%) placebo treated subjects; the only severe TEAEs reported by >1 lurasidone-treated subject was gastritis. The discontinuation rate due to AEs was 4.0% (four subjects) in the combined lurasidone group and 8.2% (4 subjects) in the placebo group. A total of five SAEs were reported by 5 subjects (5.0%) in the combined lurasidone groups and no subject (0%) in the placebo group. None of these SAEs were study medication related, and the only serious event experienced by more than one lurasidone treated subject was torus fracture.

Although the majority of the subjects were in 6-12 year old group (107 subjects, 71.8%) compared to the 13-17 year old group (42 subjects, 28.2%), all TEAE leading to subject discontinuation occurred in the 6-12 year old group. While the addition of lurasidone treatment did not adversely impact of TEAE leading to subject discontinuation (11.4% placebo vs 5.6% lurasidone), there are no factors which would explain this age disparity observation.

There were no deaths reported during the study.

An overall summary of TEAEs is presented in Table 12.

Table 12: Summary of Treatment-Emergent Adverse Events (Safety Population)

Subjects with at least one TEAE of following types	Placebo (N=49) n (%)	Lurasidone		
		20 mg (N=49) n (%)	60 mg (N=51) n (%)	All (N=100) n (%)
Any TEAE	28 (57.1)	35 (71.4)	38 (74.5)	73 (73.0)
Drug-related[a] TEAEs	16 (32.7)	21 (42.9)	26 (51.0)	47 (47.0)
EPS-related TEAEs	4 (8.2)	7 (14.3)	5 (9.8)	12 (12.0)

Hypersensitivity-related TEAEs	0	2 (4.1)	5 (9.8)	7 (7.0)
Metabolic-related TEAEs	1 (2.0)	1 (2.0)	5 (9.8)	6 (6.0)
Suicidality/self-injury-related TEAEs	2 (4.1)	0	1 (2.0)	1 (1.0)
Serious TEAEs	0	3 (6.1)	2 (3.9)	5 (5.0)
Serious Drug-related[a] TEAEs	0	0	0	0
TEAE Leading to Discontinuation	4 (8.2)	2 (4.1)	2 (3.9)	4 (4.0)
Drug-related[a] TEAE Leading to Discontinuation	3 (6.1)	1 (2.0)	1 (2.0)	2 (2.0)
Death	0	0	0	0

Abbreviations: EPS = extrapyramidal symptoms; TEAE = treatment-emergent adverse event.
a Related to study drug includes relationship determined by investigators: definite, possibly, probably related.
Note: Percentage is calculated by using the number of subjects in each treatment group as denominator.

A summary of study medication-related TEAEs occurring in ⩾ 5% of subjects in any group are presented in Table 13.

Table 13: Number and Percentage of Subjects with Treatment-Emergent Adverse Events Related to Study Medication Occurring in ⩾ 5% of Subjects within Any Treatment Group (Safety Population)

System Organ Class (SOC)/ Preferred Term	Placebo (N=49) n (%)	Lurasidone		
		20 mg (N=49) n (%)	60 mg (N=51) n (%)	All (N=100) n (%)
Total Number of Subjects with Related TEAEs	**16 (32.7)**	**21 (42.9)**	**26 (51.0)**	**47 (47.0)**
Gastrointestinal Disorders	**2 (4.1)**	**3 (6.1)**	**10 (19.6)**	**13 (13.0)**
Nausea	0	2 (4.1)	3 (5.9)	5 (5.0)
Vomiting	1 (2.0)	2 (4.1)	7 (13.7)	9 (9.0)
General Disorders And Administration Site Conditions	**4 (8.2)**	**1 (2.0)**	**3 (5.9)**	**4 (4.0)**
Fatigue	1 (2.0)	1 (2.0)	3 (5.9)	4 (4.0)
Investigations	**1 (2.0)**	**4 (8.2)**	**5 (9.8)**	**9 (9.0)**
Weight Increased	1 (2.0)	1 (2.0)	4 (7.8)	5 (5.0)
Metabolism And Nutrition Disorders	**4 (8.2)**	**2 (4.1)**	**3 (5.9)**	**5 (5.0)**
Increased Appetite	3 (6.1)	0	1 (2.0)	1 (1.0)
Nervous System Disorders	**6 (12.2)**	**12 (24.5)**	**12 (23.5)**	**24 (24.0)**
Akathisia	0	3 (6.1)	3 (5.9)	6 (6.0)
Sedation	1 (2.0)	3 (6.1)	1 (2.0)	4 (4.0)
Somnolence	2 (4.1)	3 (6.1)	8 (15.7)	11 (11.0)

Abbreviations: SOC = System Organ Class; TEAE = Treatment-Emergent Adverse Event.
Note: Percentage is calculated by using the number of subjects in each treatment group as denominator.
Note: Incidence is based on the number of subjects experiencing at least one TEAE, not the number of events.

The most commonly (⩾ 5%) reported TEAEs by the combined lurasidone treated subjects, at the preferred term level were: vomiting (18.0%); somnolence (16.0%, including the preferred terms of hypersomnia, sedation, somnolence, and hypersomnolence); nasopharyngitis (8.0%); akathisia (6.0%); fatigue, weight increased, diarrhoea, cough, headache, and nausea (5.0% each).

TEAEs reported by >2 subjects in at least one lurasidone group that were more common in the 60 mg/day group than the 20 mg/day group were: vomiting (27.5% vs 8.2% in the lurasidone 60 mg and lurasidone 20 mg groups, respectively); somnolence as a combined term (19.6% vs 12.2%); fatigue, weight increased and diarrhoea, (7.8% vs 2.0%); cough, headache, and nausea (5.9% vs 4.1%); and constipation (5.9% vs 0%).

TEAEs related to EPS were reported by 12 subjects (12.0%) in the combined lurasidone group and 4 subjects (8.2%) in the placebo group.

Metabolic-related TEAEs were reported by six subjects (6.0%) in the combined lurasidone group and one subject (2.0%) in the placebo group.

TEAEs related to suicidality or self-injury were reported by one subject (1.0%) in the combined lurasidone group and two subjects (4.1%) in the placebo group.

Minimal changes were observed in movement disorder signs or symptoms, as measured by change in BARS, AIMS, and SAS scores.

There were few stage changes in males or females by Tanner staging.

There were no observed clinically relevant effects in subjects who received lurasidone versus placebo on the following parameters: clinical chemistry, hematology, hormone, and urinalysis.

There were no observed clinically relevant ECG abnormalities (based on incidences of marked abnormalities) in the lurasidone versus placebo treatment groups.

There were no observed clinically relevant effects in subjects who received lurasidone versus placebo on the following parameters: pulse rate, blood pressure (systolic or diastolic), respiratory rate, or body temperature.

Change (LS mean ± SE) from Baseline to Week 6 in body weight was 1.2 ± 0.23 kg, 0.5 ± 0.24 kg and 0.4 ± 0.24 kg for the lurasidone 60 mg, lurasidone 20 mg, and placebo groups, respectively. Similar results were observed for BMI, with a change (LS mean ± SE) from Baseline to Week 6 of 0.4 ± 0.10 kg/m2, -0.0 ± 0.11 kg/m2 and -0.0 ± 0.11 kg/m2 for the lurasidone 60 mg, lurasidone 20 mg, and placebo groups, respectively.

1.3.3. Discussion on clinical aspects

In study D1050301, 6-weeks treatment with lurasidone (40 mg and 80mg) led to decrease in the positive and negative symptoms of schizophrenia as well as general psychopathology for both dose groups and a modest improvement in the cognition for the higher dose. This short-term efficacy data can be considered clinically meaningful for the treatment of acute schizophrenia in children aged 13-17 years, however should be evaluated more extensively as a part of an eventual submission package including long-term data for efficacy and safety.

The safety profile based on the provided data did not differ significantly from what is so far known for the adults. The most common TEAEs included akathisia, somnolence, nausea, vomiting, insomnia, anxiety and schizophrenia. The SAEs and treatment discontinuations were mainly in the category of

psychiatric disorders. When compared to the frequencies in the placebo controlled short-term studies in adults the frequency of nausea and somnolence were slightly more common among children compared to adults. As expected due to the short study duration, EPS, with the most frequent akathisia, was reported. Although the study duration was short, increase in prolactin levels and decreases in FSH and estradiol levels were reported. Changes in the metabolic parameters were modest and no clinically relevant effects on vital signs or ECG assessments were reported.

In study D1050325, the efficacy of 6-weeks lurasidone treatment with doses of 20 mg or 60 mg per day in child and adolescents (aged 6 to 17 years) with irritability associated with autistic disorder did not differ from placebo based on the primary (the ABC irritability subscale score) or secondary endpoint assessments.

Administration of lurasidone (20 mg and 60 mg/day) for six weeks in children aged 6 to 17 years with irritability associated with autistic disorder did not lead to improvement in the ABC irritability subscale score. This study is noted in the US Food and Drug Administration (FDA) Written Request (WR) for lurasidone and is not included in the European PIP. Therefore, the safety information from this study is considered valuable.

Severe TEAEs were uncommon and none was medication related. Vomiting (18 %), somnolence (18 %), nasopharyngitis (8%), akathisia (6%), fatigue (5%), weight increased (5%), diarrhoea (5%), cough (5%), headache (5%), and nausea (5%) were most commonly reported TEAEs in the lurasidone groups. Increases in body weight, BMI, overall cholesterol and prolactin levels were reported especially in the 60 mg group. No clinically meaningful changes in EKG, pulse rate, blood pressure (systolic or diastolic), respiratory rate, or body temperature were reported.

Overall, long-term efficacy and safety data is required in order to evaluate the potential impact of lurasidone on cognitive development, school performance, endocrinological and metabolic parameters and growth of pediatric and adolescent subjects. Data from the study 3 (D1050302) in the PIP titled “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” should be taken into account within any risk benefit discussion. As there are substantial developmental differences in terms of cognition, hormonal changes and growth within the age span of 6-18 years, any potential difference for safety between age groups of both study populations should be taken into account in the evaluation of risk benefit.

Concerning the hormonal parameters, presentation of the safety data according to age as well as gender, and menarche status would benefit the assessment of the magnitude of hormonal changes related to the study drug. Moreover, for the assessment of the overall safety profile of lurasidone, a summary and discussion of the differences between the age groups and comparison to the adults would be beneficial to include in the eventual submission package for extent of indication.

The MAH has not submitted any plasma concentration data of lurasidone from the studies within the current Article 46 procedure. However there seems to be data on the exposure to lurasidone in one of the studies. Any plasma lurasidone concentration data in paediatric population is of value for

establishment of pharmacokinetic-pharmacodynamic relation of lurasidone and should be summarised and provided within the eventual submission package for the extension of indication.

2. Rapporteur's overall conclusion and recommendation

Overall conclusion

The conclusion of the Applicant concerning that there is no need to update the SmPC is endorsed. The efficacy and safety of lurasidone in the treatment of schizophrenia in patients aged 13-17 years needs to be established with the totality of evidence including data for the maintenance of effect and long-term safety The results of the on-going long-term safety-efficacy study (D1050302) included in PIP should be awaited in order to conclude on the risk benefit of lurasidone in patients with schizophrenia aged 13-17 years. Update of the product information could be discussed when the Applicant submits and application with the totality of the paediatric data from all studies agreed in PIP.

Recommendation

☒ **Fulfilled:**

No regulatory action required.

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

The studies should be listed by chronological date of completion:

Clinical studies

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

Study title [a]	Study number	Completed	Final study report submitted
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		
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		

[a]: Studies are listed by chronological date of completion.
[b]:Part of the agreed Pediatric Investigation Plan