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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/P46/009

Note

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

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Need for plenary discussion	No

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1. Introduction

On 24th of May, the MAH submitted a completed paediatric study for lurasidone hydrochloride, 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 paediatric study D1050302, A 104-week, Flexible-dose, Open-label, Multicentre, Extension Study to Evaluate the Long-term Safety and Effectiveness of Lurasidone in Paediatric Subjects, which is study 3 of the agreed paediatric investigation plan (PIP) (EMEA-001230-PIP01-11-MO4) is part of a clinical development program. The variation to register a new indication - schizophrenia in adolescents-consisting of the full relevant data package (i.e containing several studies) is expected to be submitted by 11/19. A line listing of all the concerned studies is annexed.

2.2. Information on the pharmaceutical formulation used in the study

The primary objective of this study was to evaluate the long-term safety, tolerability, and effectiveness of lurasidone (20, 40, 60, or 80 mg/day, flexibly dosed) in paediatric subjects who had completed a prior lurasidone study.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

1050302, A 104-week, Flexible-dose, Open-label, Multicentre, Extension Study to Evaluate the Long-term Safety and Effectiveness of Lurasidone in Paediatric Subjects.

2.3.2. Clinical study

1050302, A 104-week, Flexible-dose, Open-label, Multicentre, Extension Study to Evaluate the Long-term Safety and Effectiveness of Lurasidone in Paediatric Subjects.

Description

The study was an open-label (OL), 104-week, multicentre, extension study designed to evaluate the long-term safety, tolerability, and effectiveness of flexibly dosed lurasidone (20, 40, 60, or 80 mg/day) in paediatric subjects who completed a 6-week treatment period in one of three preceding studies of various indications: Study D1050301 (schizophrenia), Study D1050325 (irritability associated with autistic disorder), or Study D1050326 (bipolar depression). Subjects who met entry criteria were transitioned to this extension study directly after their last assessment in the preceding study. The study included an OL baseline assessment (for which some evaluations were based on data from the

last visit in the preceding study), a 104-week treatment period, and a follow-up visit (that occurred one week after the last dose of lurasidone). Safety and effectiveness assessments were conducted at scheduled visits during the study

As this application is being submitted to support an indication for adolescent subjects with schizophrenia, only results for subjects with schizophrenia who enrolled from Study D1050301 are discussed.

CHMP comment: The MAH has only provided discussion and analysis on results from subjects with schizophrenia who enrolled from Study D1050301 in the Clinical overview of this procedure as this application is being submitted to support an indication for adolescent subjects with schizophrenia.

Methods

Objectives

Primary: The primary objective of this study was to evaluate the long-term safety, tolerability, and effectiveness of lurasidone (20, 40, 60, or 80 mg/day, flexibly dosed) in paediatric subjects who had completed a prior lurasidone study.

Secondary:

For all subjects:

• Proportions of subjects with adverse events (AEs), discontinuations due to AEs, and serious adverse events (SAEs)

For subjects continued from Study D1050301 (schizophrenia):

• Change in Positive and Negative Syndrome Scale (PANSS) total, positive, negative, general psychopathology, and excitability subscale scores

• Change in the Clinical Global Impression-Severity (CGI-S)

• Change in the Clinician-rated Children's Global Assessment Scale (CGAS)

• Change in the Paediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)

For subjects continued from Study D1050325 (autistic disorder):

• Change in Aberrant Behaviour Checklist (ABC) irritability subscale, and the following subscale scores (hyperactivity, stereotypy, inappropriate speech, and lethargy/social withdrawal)

• Change in the CGI-S

Change in Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) modified for pervasive developmental disorders (PDDs)

• Change in the Caregiver Strain Questionnaire (CGSQ)

For subjects continued from Study D1050326 (bipolar depression):

• Change in the Children's Depression Rating Scale, Revised (CDRS-R)

• Change in the Clinical Global Impression-Bipolar Version, Severity of Illness (CGI-BP-S)

• Change in the CGAS

• Change in the PQ-LES-Q

• Change in anxiety symptoms as measured by the Paediatric Anxiety Rating Scale (PARS)

• Change in attention-deficit/hyperactivity symptoms as measured by the Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS) total score

Study design

This was an open-label, 104-week, multicentre, extension study designed to evaluate the long-term safety, tolerability, and effectiveness of flexibly-dosed lurasidone (20, 40, 60, or 80 mg/day) in paediatric subjects who completed a 6-week treatment period in 1 of 3 preceding studies of various indications: D1050301 (schizophrenia), D1050325 (irritability associated with autistic disorder), or D1050326 (bipolar depression).

Subjects meeting Study D1050302 entry criteria were transitioned directly from the short-term study (D1050301, D1050325, or D1050326) to the long-term extension study (D1050302). Study D1050302 included an open-label Baseline assessment (for which some evaluations were based in part on data from the final visit of the preceding study), a 104-week treatment period, and a follow-up visit (1 week after the last dose of lurasidone). Safety and effectiveness assessments were conducted at scheduled visits during the study.

Study population /Sample size

Subjects who completed the respective double-blind studies (D1050301, D1050325, or D1050326), signed the consent form, and met all entry criteria were included in this study. A total of 271 subjects from Study D1050301, 125 subjects from Study D1050325, and 306 subjects from Study D1050326 were enrolled in Study D1050302.

For this open-label extension study (D1050302), the Safety Population was utilized for all analyses and consisted of all subjects who received at least 1 dose of study drug.

For subjects with schizophrenia discussed in this report, the study enrolled a total of 271 subjects who completed the 6-week treatment period in Study D1050301 and, as judged by the investigator, for whom an outpatient setting was appropriate. Of these, 186 subjects (68.6%) completed through 52 weeks and 156 (57.6%) subjects completed 104 weeks of flexible dosing with lurasidone 20 to 80 mg/day.

<u>Exclusion Criteria</u>

1. Subject was considered by the Investigator to be at imminent risk of suicide.

2. Exhibited evidence of moderate or severe extrapyramidal symptoms (EPS), dystonia, tardive dyskinesia, or any other moderate or severe movement disorder. Severity was determined by the Investigator.

Treatments

The study drug was open-label lurasidone 20 mg tablets and lurasidone 40 mg tablets, administered once daily at a dose of 20, 40, 60, or 80 mg. Lurasidone was to be taken once daily in the evening with food (at least 350 calories) or within 30 minutes after eating. Eligible subjects were treated with lurasidone 40 mg/day for Days 1 to 7. Beginning with Day 8, dose adjustments to 20, 40, 60, or 80 mg/day were permitted, based on Investigator judgment, to optimize tolerability and effectiveness.

Duration of treatment were 104 weeks.

Outcomes/endpoints

Safety endpoints

All Subjects:

• Treatment-emergent adverse events (TEAEs), TEAEs leading to discontinuation, and SAEs

• Laboratory tests, vital signs, body weight and body mass index (BMI), waist circumference, physical examination, height, electrocardiogram (ECG), and hormonal parameters

• Movement disorders as assessed by Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and the Simpson-Angus Scale (SAS)

• Tanner staging (all subjects) and menstrual cyclicity (female subjects)

For subjects continued from Study D1050301 and D1050326:

• Columbia Suicide Severity Rating Scale (C-SSRS) (Study D1050301) or C-SSRS Children's Version (Study D1050326)

• Cogstate Computerized Cognitive Test Battery

• Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU)

For subjects continued from Study D1050326:

• Young Mania Rating Scale (YMRS) score

Effectiveness Endpoints

For subjects continued from Study D1050301:

• Change in PANSS total, positive, negative, general psychopathology, and excitability subscale scores

• Change in the CGI-S

• Change in the PQ-LES-Q percentage maximum possible score

• Change in the CGAS total score

For subjects continued from Study D1050325:

• Change in the ABC irritability subscale score and the other subscale scores (hyperactivity, stereotypy, inappropriate speech, and lethargy/social withdrawal)

• Change in the CGI-S

• Change in the CY-BOCS modified for PDDs

• Change in the CGSQ

For subjects continued from Study D1050326:

• Change in the CDRS-R total score

• Change in CGI-BP-S score (depression, mania, overall bipolar illness)

• Proportion of subjects who met symptom remission, defined as CDRS-R Total Score ≤ 28 and YMRS total score ≤ 8 and CGI-BP-S depression score ≤ 3 at a given study visit

• Change in the PARS total score

• Change in the PQ-LES-Q score

• Change in the CGAS score

• Change in the ADHD-RS total score

Statistical Methods

All safety and effectiveness analyses for this extension study were based on the Safety Population, which consisted of all subjects who received at least 1 dose of study drug in this study. Subgroup analyses per age group and geographic region (United States [US] vs non-US) were conducted as appropriate. A total of 3 analysis groups (ie, 301-LUR, 325-LUR, and 326-LUR) were formed based on a subject's previous participation status in the double-blind core studies. In addition, a group combining the 3 analysis groups (ie, 301/325/326-LUR) was also presented. Subjects continued from each core study (Study D1050301, D1050325, and D1050326) were further grouped into analysis subgroups based on prior randomized treatment in the respective core study.

Safety and effectiveness analyses were presented by analysis group and by analysis subgroup, as needed.

In the analyses, the pre-treatment Baseline from the double-blind studies (D1050301, D1050325, or D1050326) was referred to as the double-blind study Baseline or "DB Baseline," and the last assessment prior to the first dose in the open-label Study D1050302 was referred to as the open-label study Baseline or "OL Baseline." No statistical comparisons were conducted for treatment groups.

Safety Analyses:

TEAEs, serious TEAEs, and discontinuations due to TEAEs were summarized by presenting the overall incidence (ie, number and percentage of subjects having each individual TEAE [or serious TEAE]) by analysis group and by analysis subgroup.

Descriptive statistics were provided for the following safety variables and the corresponding changes from Baseline: laboratory tests (covering hematology, chemistry, hormonal parameters, and urinalysis), body weight, height, BMI, gender-and-age specific Z-scores of weight, height, and BMI per World Health Organization (WHO) or US Centres for Disease Control and Prevention (CDC) growth charts, waist circumference, vital signs, electrocardiogram (ECG) parameters, movement disorders (as assessed by AIMS, BARS, and the SAS), Tanner staging, menstrual cyclicity (female subjects), and YMRS (for subjects continued from Study D1050326). The number and percentage of subjects with treatment-emergent occurrences of Potentially Markedly Abnormal Laboratory Values (PMALV), Potentially Markedly Abnormal Vital Signs (PMAVS), and abnormal ECG values were also summarized by analysis group and by analysis subgroup.

Descriptive statistics were also provided for the Cogstate standardized composite score and 4 standardized domain scores, and UKU total and subscale scores by visit for each analysis group. For C-

SSRS data, number and percentage of subjects with suicidal ideations and behaviours were summarized.

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

Effectiveness Analyses:

Descriptive statistics of observed values and change from DB Baseline and OL Baseline were provided by visit and by analysis group for the following: PANSS total score and subscale scores, CGI-S, CGAS, and PQ-LES-Q scores in subjects continued from Study D1050301; ABC irritability subscale score and other ABC subscale scores, CGI-S, CY-BOCS, and CGSQ in subjects continued from Study D1050325; and CDRS-R total score, CGI-BP-S, PARS, PQ-LES-Q, CGAS, and ADHD-RS total score in subjects continued from Study D1050326.

In addition, frequencies and percentages over time were reported by analysis group for the following: PANSS responders relative to DB Baseline and OL Baseline in subjects continued from Study D1050301; ABC responders relative to DB and OL Baseline for subjects continued from Study D1050325; and CDRS-R responders and CDRS-R remitters relative to DB and OL Baseline for subjects continued from Study D1050326. PANSS responders were defined as those who showed a 20% or more reduction (ie, improvement) from Baseline. ABC responders were defined as those who showed a 25% or more reduction (ie, improvement) from Baseline in the ABC irritability subscale score. CDRS-R responders were defined as those who showed a 50% or more reduction (ie, improvement) from Baseline in CDRS-R total score, and CDRS-R remitters were defined as those who had a CDRS-R total score ≤ 28, YMRS total score ≤ 8, and CGI-BP-S depression score ≤ 3 at a given study visit.

No inferential statistics on effectiveness data were presented. For all the effectiveness assessments, descriptive summary statistics (number of observations [N], mean, standard deviation [SD], median, range, and a 95% confidence interval [CI]) were presented by analysis group at DB Baseline, OL Baseline, each post-OL visit, Week 52 Last Observation Carried Forward (LOCF), and at Endpoint (the last post-OL Baseline assessment during the open-label treatment period). All analyses for the scheduled assessments were based on observed cases.

Results

Recruitment/ Number analysed

Subjects with Schizophrenia Continued from Study D1050301

Of the 271 subjects who entered Study D1050302 from Study D1050301, 186 (68.6%) subjects completed 12 months of treatment, and 156 (57.6%) subjects completed the full 104 weeks of treatment.

The mean (± SD) duration of exposure to study drug in the Safety Population was 526.8 ± 271.09 days. Overall, 81.2% of subjects in the 301-LUR group received study drug treatment for at least 24 weeks (≥ 168 days exposure), 70.1% of subjects received study drug for at least 12 months (≥ 364 days exposure), and 45.8% of subjects received study drug for at least 24 months (≥ 728 days exposure). Overall cumulative exposure to lurasidone for subjects continued from Study D1050301 was 390.9 subject-years. The mean (± SD) total daily dose of lurasidone in the 301-LUR group during the overall OL period was 57.01 ± 15.825 mg/day. The most common modal daily dose of lurasidone during the overall OL treatment period was 80 mg/day (36.9% of subjects), followed by 40 mg/day (35.4%), 60 mg/day (24.4%), and 20 mg/day (3.3% of subjects).

Subjects with Autistic Disorder Continued from Study D1050325

Of the 125 subjects who entered Study D1050302 from Study D1050325, 64 (51.2%) subjects completed 12 months of treatment, and 54 (43.2%) subjects completed the full 104 weeks of treatment.

The mean (± SD) duration of exposure to study drug in the Safety Population was 433.8 ± 291.19 days. Overall, 76.8% of subjects in the 325-LUR group received study drug treatment for at least 24 weeks (≥ 168 days exposure), 52.8% of subjects received study drug for at least 12 months (≥ 364 days exposure), and 29.6% of subjects received study drug for at least 24 months (≥ 728 days exposure). Overall cumulative exposure to lurasidone was 148.5 subject-years for subjects continued from Study D1050325. The mean (± SD) total daily dose of lurasidone in the 325-LUR group during the overall OL period was 52.80 ± 15.791 mg/day. The most common modal daily dose of lurasidone during the overall OL treatment period was 40 mg/day (42.4% of subjects), followed by 80 mg/day (29.6% of subjects), 60 mg/day (23.2% of subjects), and 20 mg/day (4.8% of subjects).

Subjects with Bipolar Depression Continued from Study D1050326

Of the 306 subjects who entered Study D1050302 from Study D1050326, 195 (63.7%) subjects completed 12 months of treatment, and 168 (54.9%) subjects completed the full 104 weeks of treatment.

The mean (± SD) duration of exposure to study drug in the Safety Population was 501.9 ± 276.75 days. Overall, 79.0% of subjects in the 326-LUR group received study drug treatment for at least 24 weeks (≥ 168 days exposure), 64.9% of subjects received study drug for at least 12 months (≥ 364 days exposure), and 44.3% of subjects received study drug for at least 24 months (≥ 728 days exposure). Overall cumulative exposure to lurasidone was 419.1 subject-years for subjects continued from Study D1050326. The mean (± SD) total daily dose of lurasidone in the 326-LUR group during the overall OL period was 52.12 ± 15.702 mg/day. The most common modal daily dose of lurasidone during the overall OL treatment period was 40 mg/day (41.6% of subjects), followed by 80 mg/day and 60 mg/day (each with 25.9% of subjects), and 20 mg/day (6.6% of subjects).

Baseline data

Subjects with Schizophrenia Continued from Study D1050301

Of the 271 subjects who entered Study D1050302 from Study D1050301, the majority of subjects were male (62.7%), and the mean (± SD) age was 15.5 ± 1.44 years (range 13 to 18 years) at OL Baseline. Most subjects (94.8%) were aged 13 to 17 years, and there were similar numbers of subjects aged 13 to 15 years and 16 to 17 years (44.6% and 50.2%, respectively). Most of the subjects were from countries in Europe (57.9%), followed by the US (30.3%). White (72.7%) and Black or African American (14.0%) were the most common racial categories and most subjects (86.7%) were not Hispanic or Latino. The overall mean (± SD) Baseline BMI was 22.77 ± 3.669 kg/m2 and mean Baseline BMI Z-score was 0.58 ± 1.038. At Baseline, 26.2% of the study population was overweight and 8.9% was obese, according to the WHO 2007 growth reference (Table 17). Overall, demographic characteristics were well balanced across analysis groups at OL Baseline based on prior randomized treatment in Study D1050301.

At Screening of core Study D1050301, most subjects (76.8%) in the Safety Population had been previously diagnosed with paranoid type schizophrenia (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition [DSM-IV] 295.30) at DB Baseline, with 15.5% having the undifferentiated type (DSM-IV 295.90) and 7.7% having the disorganized type (DSM-IV 295.10). The mean (± SD) age of onset of the initial behavioural disturbance was 12.29 ± 3.287 years with mean duration from this

onset to Screening of the DB core study being 3.60 ± 2.940 years. The mean age of onset of psychotic symptoms was 13.09 ± 2.796 years, and the mean age of onset of the current episode of schizophrenia was 15.77 ± 1.476 years. Approximately 52% of subjects had a history of hospitalization for schizophrenia. Overall, 26.9% of subjects had 1 prior hospitalization, 12.9% had 2 prior hospitalizations, 5.9% had 3 prior hospitalizations, and 6.6% of subjects had 4 or more prior hospitalizations. The DB Baseline mean (± SD) PANSS total score for all subjects was 93.5 ± 11.01, and mean CGI-S score was 4.82 ± 0.629. Open-label Baseline scores were lower; mean PANSS total score was 76.0 ± 17.72 and mean CGI-S score was 3.99 ± 0.966.

For adolescent subjects with schizophrenia who entered the open-label extension study, there were no clinically meaningful differences in baseline clinical characteristics or psychiatric histories across analysis groups based on prior randomized treatment in Study D1050301.

Subjects with Bipolar Depression Continued from Study D1050326

Of the 305 subjects who entered Study D1050302 from Study D1050326, there was a similar distribution of males (50.2%) and females (49.8%). The mean (± SD) age was 14.4 ± 2.18 years (range 10 to 18 years) at OL Baseline. Most subjects (76.1%) were in the 13 to 17 years age group, and 20.3% of subjects were 12 years old or younger. Overall, 77.0% of subjects were White and 82.3% of subjects were not Hispanic or Latino. The majority of subjects (59%) were enrolled from non-US countries. The overall mean (± SD) Baseline BMI was 21.74 ± 3.453 kg/m2 and mean Baseline BMI Z-score was 0.52 ± 1.035. At Baseline, 28.6% of the study population was overweight and 8.2% was obese, according to the WHO 2007 growth reference. Overall, demographic characteristics were well balanced across analysis groups at OL Baseline based on prior randomized treatment in Study D1050326.

For subjects with bipolar depression continued from Study D1050326, the mean (± SD) age at onset of the initial behavioural disturbance was 10.60 ± 3.485 years and the mean duration from onset to informed consent was 4.18 ± 3.007 years. The mean age at onset of bipolar I disorder was 12.35 ± 2.765 years, the mean age at onset of the last manic episode of bipolar I disorder was 13.58 ± 2.340 years, and the mean age of onset of the current depression episode of bipolar I disorder was 14.55 ± 2.171 years. The mean duration from onset of the current depression episode of bipolar I disorder to informed consent was 0.23 ± 0.175 years. The majority (85.6%) of subjects had a history of bipolar I disorder without rapid cycling (0 to 3 cycles within the past 12 months), and 72.1% of subjects had no prior hospitalizations for bipolar I depression. The proportion of subjects with other psychiatric disorders present was 31.8% for the overall population. The DB Baseline mean (± SD) CDRS-R total score for all subjects was 59.0 ± 8.16, and mean CGI-BP-S depression score was 4.51 ± 0.591. Open-label Baseline scores were lower; mean Clinical Study Report: D1050302 Lurasidone Confidential and Proprietary 102 16 Apr 2019 CDRS-R total score was 39.2 ± 13.38 and mean CGI-BP-S depression score was 3.22 ± 1.089 (Table 22).

For children and adolescent subjects with bipolar depression who entered the open-label extension study, there were no clinically meaningful differences in baseline clinical characteristics or psychiatric histories across analysis groups based on prior randomised treatment in study D105326.

Subjects with Autistic Disorder Continued from Study D1050325

Of the 125 subjects who entered Study D1050302 from Study D1050325, the majority were male (81.6%), with a mean (± SD) age of 11.1 ± 3.12 years (range 6 to 17 years) at OL Baseline. Most subjects (65.6%) were ≤ 12 years old with 34.4% of subjects being ≤ 9 years old. The majority of subjects were White (76.8%) or Black/African American (16.8%). All subjects were from the US. The overall mean (± SD) Baseline BMI was 19.34 ± 3.425 kg/m2 and mean Baseline BMI Z-score was 0.40 ± 0.893. At Baseline, 18.4% of the study population was overweight and 4.8% was obese, according

to the CDC 2000 growth chart (Table 18). Overall, demographic characteristics were well balanced across analysis groups at OL Baseline based on prior randomized treatment in Study D1050325.

At Screening of core Study D1050325, all subjects had a diagnosis of autistic disorder. Overall, the average (mean ± SD) age at initial onset of autistic disorders was 4.99 ± 3.667 years, and the average duration of autistic disorders from onset to Screening was 6.44 ± 4.116 years. The proportion of subjects with other psychiatric disorders present was 58.4% for the overall population. The DB Baseline mean ABC irritability total score for all subjects was 28.0 ± 6.20, and mean CGI-S score was 4.86 ± 0.807. Open-label Baseline scores were lower; mean ABC irritability total score was 19.0 ± 10.63 and mean CGI-S score was 3.90 ± 1.250.

For children and adolescent subjects with autism who entered the open-label extension study, there were no clinically meaningful differences in baseline clinical characteristics or psychiatric histories across analysis groups based on prior randomized treatment in Study D1050325.

CHMP comment: The MAH has only provided discussion and analysis on results from subjects with schizophrenia who enrolled from Study D1050301 in the Clinical overview of this procedure as this application is being submitted to support an indication for adolescent subjects with schizophrenia.

Efficacy results

Subjects with Schizophrenia Continued from Study D1050301

• The mean (± SD) change in PANSS total score from DB Baseline in the overall 301-LUR group was -29.2 ± 14.73 at Week 28, and decreased to -32.4 ± 14.61 at Week 52 and -34.3 ± 16.32 at Week 104. Mean change from DB Baseline to Endpoint was -29.5 ± 18.48. Mean change relative to OL Baseline in the overall 301-LUR group was -11.9 ± 13.74 at Week 28, -15.6 ± 14.97 at Week 52, -18.4 ± 16.73 at Week 104, and -12.2 ± 19.54 at Endpoint. Long-term treatment with lurasidone showed a trend toward improvement in mean PANSS total score in the overall subject population and each analysis group prior to Week 12, then consistent minor decreases after Week 12 and through Week 64. Thereafter, maintenance of mean PANSS total scores was observed through Week 104.

• At OL Baseline, the proportion of PANSS responders (ie, ≥ 20% reduction in PANSS total score) relative to DB Baseline was 63.1% overall, with a continued increase in the proportion of responders over long-term treatment. At Week 104, 91.0% of subjects were considered responders relative to DB Baseline and 76.9% relative to OL Baseline. At Endpoint, the proportions of responders were 82.8% relative to DB Baseline and 58.1% relative to OL Baseline.

• Consistent with the PANSS total score, improvements in PANSS subscale scores (ie, positive, negative, general psychopathology, and excitability) as compared with DB and OL Baseline were reported at each timepoint in this study. For each subscale, the patterns of reduction in values over time were similar to that observed for the PANSS total score, and the reductions from DB Baseline were sustained through Week 104. An expected greater mean change from OL Baseline was observed for all subscale scores in subjects previously treated with placebo.

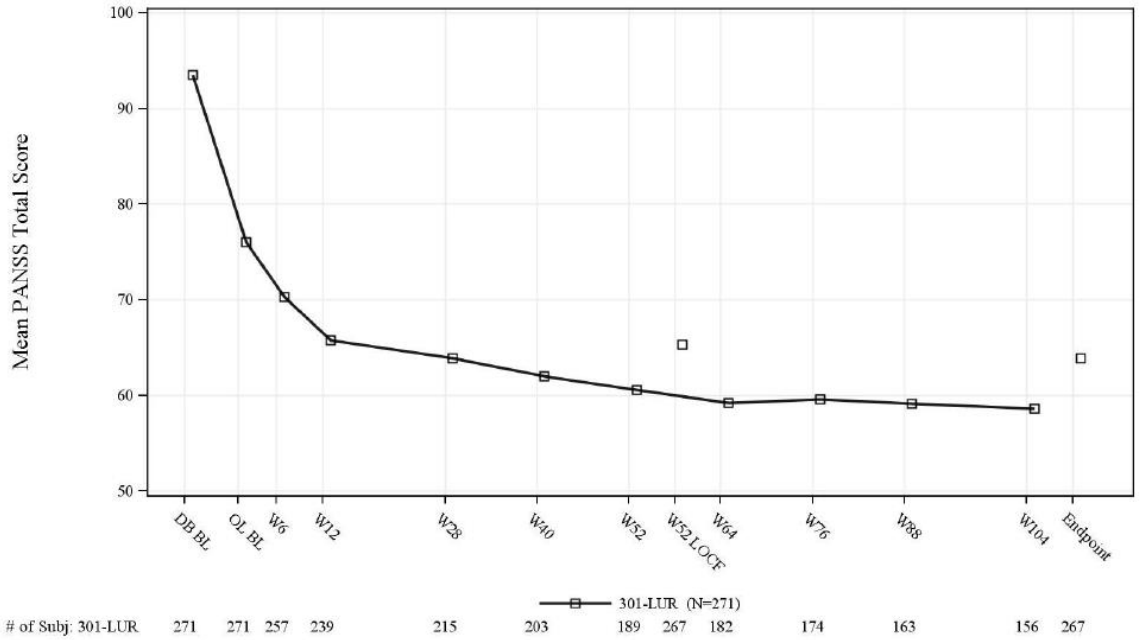
• A trend toward improvement in mean (± SD) CGI-S score from DB Baseline was observed over time. The overall 301-LUR group demonstrated a reduction of -1.87 ± 1.084 at Week 52 and -2.04 ± 1.121 at Week 104. Mean change from DB Baseline to Endpoint was -1.67 ± 1.194.

• Additional analyses of PANSS and CGI-S according to subgroups provided no evidence to suggest that age or geographic region (US vs non-US) influenced the long-term treatment effect of lurasidone.

• A trend toward improvement in mean PQ-LES-Q score from DB Baseline was observed over time, as demonstrated by a mean (± SD) increase of 15.67 ± 17.419 at Week 52 and 17.09 ± 19.950 at Week 104. Mean change from DB Baseline to Endpoint was 12.47 ± 20.596.

• Similarly, a trend toward improvement in mean (± SD) CGAS score from DB Baseline was observed over time. The overall 301-LUR group demonstrated an increase of 24.37 ± 12.600 at Week 52 and 27.62 ± 14.168 at Week 104. Mean change from DB Baseline to Endpoint was 22.15 ± 15.783.

Mean Observed Values over Time in PANSS Total Score for Subjects Continued from Study D1050301 – Overall 301-LUR Group (Safety Population)



Subjects with Autistic Disorder Continued from Study D1050325

• The mean (± SD) change in ABC irritability subscale score from DB Baseline in the overall 325-LUR group was -11.9 ± 10.55 at Week 28, and decreased to -13.2 ± 10.18 at Week 52 and -15.4 ± 10.34 at Week 104. Mean change from DB Baseline to Endpoint was -10.4 ± 11.43. Mean change relative to OL Baseline in the overall 325-LUR group was -2.1 ± 9.16 at Week 28, -2.9 ± 9.85 at Week 52, -4.2 ± 11.62 at Week 104, and -1.5 ± 10.15 at Endpoint. Long-term treatment with lurasidone showed numerical decreases in mean ABC irritability subscale score in the overall subject population and each analysis group prior to Week 12, then consistent further improvement after Week 12 and through Week 104.

• At OL Baseline, the proportion of ABC responders (ie, ≥ 25% reduction in ABC irritability subscale score) relative to DB Baseline was 58.4% overall, with a continued increase in the proportion of responders over long-term treatment. At Week 104, 81.5% of subjects were considered responders relative to DB Baseline and 50.0% relative to OL Baseline. At Endpoint, the proportions of responders were 59.0% relative to DB Baseline and 34.4% relative to OL Baseline.

• Consistent with the ABC irritability subscale score, decreases in the other ABC subscale scores (ie, hyperactivity, stereotypy, inappropriate speech, and lethargy/social withdrawal) as compared with DB

and OL Baseline were reported at each timepoint in this study. For each of the remaining subscales, the patterns of reduction in values over time were similar to those observed for the ABC irritability subscale score, and the reductions from DB Baseline were sustained through Week 104. A greater mean change from OL Baseline was observed for all subscale scores in subjects previously treated with placebo.

• A trend toward improvement in mean (± SD) CGI-S score from DB Baseline was observed over time. The overall 325-LUR group demonstrated a reduction of -1.74 ± 1.244 at Week 52 and -1.91 ± 1.186 at Week 104. Mean change from DB Baseline to Endpoint was -1.31 ± 1.322.

• A trend toward improvement in mean (± SD) CY-BOCS compulsion total score from DB Baseline was observed over time, as demonstrated by a mean decrease of -3.9 ± 4.33 at Week 52 and -4.6 ± 5.34 at Week 104. Mean change from DB Baseline to Endpoint was -2.9 ± 4.69.

• Decreases in mean CGSQ global strain score and subscale scores as compared with DB Baseline and OL Baseline were demonstrated through Week 52, with the reductions from DB Baseline sustained through Week 104. For all CGSQ subscale scores, a greater mean change from OL Baseline was observed in subjects previously treated with placebo.

Subjects with Bipolar Depression Continued from Study D1050326

• The mean (± SD) change in CDRS-R total score from DB Baseline in the overall 326-LUR group was -29.0 ± 12.13 at Week 28, and decreased to -32.2 ± 11.08 at Week 52 and -34.8 ± 11.29 at Week 104. Mean change from DB Baseline to Endpoint was -31.1 ± 13.20. Mean change relative to OL Baseline in the overall 326-LUR group was -9.9 ± 13.48 at Week 28, -13.4 ± 13.01 at Week 52, -16.4 ± 13.24 at Week 104, and -11.3 ± 15.02 at Endpoint. Long-term treatment with lurasidone showed reduction in mean CDRS-R total scores in the overall subject population and each analysis group prior to Week 12, then consistent further minor decreases after Week 12 and through Week 104.

• At OL Baseline, the proportion of CDRS-R responders (ie, ≥ 50% reduction in adjusted CDRS-R total score) relative to DB Baseline was 51.0% overall, with a continued increase in the proportion of responders over long-term treatment. At Week 104, 91.1% of subjects were considered responders relative to DB Baseline and 73.2% relative to OL Baseline. At Endpoint, the proportions of responders were 81.7% relative to DB Baseline and 59.9% relative to OL Baseline.

• At OL Baseline, the proportion of CDRS-R remitters (ie, defined as subjects who had CDRS-R total score ≤ 28, YMRS total score ≤ 8, and CGI-BP-S depression score ≤ 3 at a given study visit) was 24.3% overall, with a continued increase in the proportion of remitters over long-term treatment. At Week 104, 75.6% of subjects were considered remitters. At Endpoint, the proportion of remitters was 61.7%.

• A trend toward improvement in mean (± SD) CGI-BP-S depression score from DB Baseline was observed over time. The overall 326-LUR group demonstrated a reduction of -2.53 ± 1.043 at Week 52 and -2.78 ± 1.011 at Week 104. Mean change from DB Baseline to Endpoint was -2.39 ± 1.283.

• A trend toward improvement in mean (± SD) PQ-LES-Q score from DB Baseline was observed over time. The overall 326-LUR group demonstrated an increase of 23.07 ± 17.283 at Week 52 and 27.35 ± 16.800 at Week 104. Mean change from DB Baseline to Endpoint was 20.24 ± 19.241.

• A trend toward improvement in mean (± SD) CGAS score from DB Baseline was observed over time. The overall 326-LUR group demonstrated an increase of 25.88 ± 13.295 at Week 52 and 30.34 ± 13.982 at Week 104. Mean change from DB Baseline to Endpoint was 24.05 ± 16.649.

• A trend toward improvement in mean (± SD) PARS total score from DB Baseline was observed over time. The overall 326-LUR group demonstrated a reduction of -6.7 ± 6.87 at Week 52 and -8.4 ± 7.38 at Week 104. Mean change from DB Baseline to Endpoint was -6.4 ± 7.97.

• For ADHD-RS total score as summarized by prior attention deficit/hyperactivity disorder (ADHD) diagnosis status, the overall 326-LUR group demonstrated a mean (± SD) reduction from DB Baseline of -11.3 ± 9.42 at Week 52, -11.4 ± 11.56 at Week 104, and -8.4 ± 11.99 at Endpoint for subjects with an ADHD diagnosis compared with mean reductions of -3.9 ± 6.77, -4.9 ± 5.89, and -3.4 ± 7.63, respectively, for subjects without an ADHD diagnosis at DB Baseline.

• Additional analyses of CDRS-R total score, CDRS-R responders, CDRS-R remitters, and CGI-BP-S scores according to subgroups provided no evidence to suggest that age or geographic region (US vs non-US) influenced the long-term treatment effect of lurasidone. Subgroup analysis of ADHD-RS total score indicated that subjects with an ADHD diagnosis prior to the study showed greater improvement in ADHD-RS total score as compared with those subjects without a prior ADHD diagnosis.

Safety results

Subjects with Schizophrenia Continued from Study D1050301

Of the 271 subjects who entered Study D1050302 from Study D1050301, 186 (68.6%) subjects completed 12 months of treatment, and 156 (57.6%) subjects completed the full 104 weeks of treatment.

The mean (± SD) duration of exposure to study drug in the Safety Population was 526.8 ± 271.09 days. Overall, 81.2% of subjects in the 301-LUR group received study drug treatment for at least 24 weeks (≥ 168 days exposure), 70.1% of subjects received study drug for at least 12 months (≥ 364 days exposure), and 45.8% of subjects received study drug for at least 24 months (≥ 728 days exposure). Overall cumulative exposure to lurasidone for subjects continued from Study D1050301 was 390.9 subject-years. The mean (± SD) total daily dose of lurasidone in the 301-LUR group during the overall OL period was 57.01 ± 15.825 mg/day. The most common modal daily dose of lurasidone during the overall OL treatment period was 80 mg/day (36.9% of subjects), followed by 40 mg/day (35.4%), 60 mg/day (24.4%), and 20 mg/day (3.3% of subjects).

• There were no deaths reported during this extension study.

• Serious TEAEs were reported by 28 (10.3%) subjects who continued from Study D1050301. Serious TEAEs reported by more than 1 subject included schizophrenia (11 subjects, 4.1%), suicidal ideation (8 subjects, 3.0%), psychotic disorder (5 subjects, 1.8%), and intentional overdose (2 subjects, 0.7%).

• There were also 28 (10.3%) subjects who discontinued study drug due to a TEAE. The most common TEAEs resulting in study drug discontinuation were schizophrenia (9 subjects, 3.3%), suicidal ideation (5 subjects, 1.8%), and psychotic disorder (3 subjects, 1.1%).

• The most commonly reported TEAE (preferred term level) was headache (24.0%). The only other TEAEs that were reported at a frequency ≥ 10% in the overall 301-LUR group were anxiety (12.9%), schizophrenia (12.5%), nausea (12.5%), and somnolence (12.2%). Note: Somnolence includes the combined preferred terms of hypersomnia, sedation, somnolence, and hypersomnolence.

• The most common treatment-related TEAEs were headache (13.7%) and nausea (11.4%). The only other related TEAEs that were reported at a frequency ≥ 5% in the 301-LUR group were somnolence (8.1%), akathisia (7.7%), and weight increased (6.3%).

• Severe TEAEs occurred in 20 (7.4%) subjects who continued from Study D1050301. Severe TEAEs experienced by more than 1 subject included schizophrenia in 6 (2.2%) subjects, suicidal ideation in 4 (1.5%) subjects, insomnia and psychotic disorder in 3 (1.1%) subjects each, and depression in 2 (0.7%) subjects. The majority of TEAEs across analysis groups were mild to moderate in severity. Severe TEAEs that were considered by the Investigator to be related to study drug were reported for 6 (2.2%) subjects.

• A total of 23 subjects experienced 1 or more TEAEs leading to a dose reduction of study drug, most commonly nausea (5 subjects), akathisia (4 subjects), and somnolence (3 subjects). All other TEAEs leading to dose reduction were reported in only 1 or 2 subjects each.

• A total of 44 (16.2%) subjects who continued from Study D1050301 experienced EPS-related TEAEs. The most common EPS-related TEAEs (combined terms) were akathisia (22 subjects, 8.1%) and Parkinsonism (15 subjects, 5.5%).

• Suicidal ideation was reported as an adverse event by 10 (3.7%) subjects and intentional overdose by 2 (0.7%) subjects. Episodes of suicidal behaviour, suicide attempt, and self-injurious behaviour were reported by 1 subject each.

• The incidence of TEAEs related to hypersensitivity was 4.4%. TEAE preferred terms related to hypersensitivity that were reported by more than 1 subject included urticaria (3 subjects), and pruritus, rash, and conjunctivitis (2 subjects each).

• The incidence of metabolic-related TEAEs was 14.0%. The most common metabolic-related TEAEs were weight increased (21 subjects, 7.7%) and weight decreased (13 subjects, 4.8%). All other metabolic-related TEAEs were reported by < 1% of subjects. Although mean and median changes from DB Baseline to Endpoint were minimal for most metabolic-related clinical chemistry parameters, small and clinically insignificant increases in triglycerides and decreases in high-density lipoprotein (HDL) cholesterol were observed.

• The mean (± SD) change in body weight from DB Baseline was 3.27 ± 6.324 kg at Week 52 and 4.90 ± 7.745 kg at Week 104, compared with an expected weight gain of 3.41 ± 1.837 kg and 5.74 ± 3.173 kg, respectively, based on the age-and-gender specific US CDC growth chart. Overall, any changes noted from DB Baseline in height, weight, or BMI were consistent with expected gains based on age-and-gender specific growth charts (CDC and WHO).

Median serum prolactin levels increased from DB Baseline to Endpoint by 1.00 ng/mL for females and by 0.30 ng/mL for males in the overall 301-LUR group. For other hormone parameters, there were no clinically meaningful changes in median values from DB Baseline for follicle stimulating hormone (FSH), luteinizing hormone (LH), or estradiol. Where small increases were observed, these would be consistent with puberty/sexual maturation in an adolescent population.

• Treatment with lurasidone had no notable effect on vital signs, including heart rate, systolic blood pressure, diastolic blood pressure, body temperature, and respiratory rate.

• No subjects who continued from Study D1050301 had a QT interval corrected for heart rate – Fridericia's formula (QTcF) > 460 msec at any time during the extension study. An increase in QTcF ≥ 60 msec was observed for 1 (0.4%) subject relative to DB Baseline and no subjects relative to OL Baseline. Increases in QTcF ≥ 30 msec were reported for 27 (10.0%) subjects relative to DB Baseline and 14 (5.2%) subjects relative to OL Baseline.

• 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 DB or/or OL Baseline were observed in the BARS total score, SAS mean score, and AIMS total score over the course of the study, which were considered not clinically relevant.

• Measurements of cognitive performance, as assessed by the Cogstate Computerized Cognitive Test Battery, showed no worsening over the course of the 104-week study.

• Mean decreases from Baseline to Endpoint were observed for the 4 UKU category scores (psychic, neurological, autonomic, and other) and the UKU total score.

• As measured by the C-SSRS, the majority (94.1%) of subjects who continued from Study D1050301 had no suicidal ideation at any extension visit.

• While a majority of subjects (male or female) had no change in Tanner stage from DB Baseline to Endpoint, approximately 35% of both male and female subjects increased in Tanner stage by 1 category at Endpoint. Few subjects had an increase in Tanner stage of more than 1 category.

• Reported frequency of menstrual cycles did not show any relevant change in lurasidone-treated females between DB Baseline and Endpoint.

Subjects with Autistic Disorder Continued from Study D1050325

Of the 125 subjects who entered Study D1050302 from Study D1050325, 64 (51.2%) subjects completed 12 months of treatment, and 54 (43.2%) subjects completed the full 104 weeks of treatment.

The mean (± SD) duration of exposure to study drug in the Safety Population was 433.8 ± 291.19 days. Overall, 76.8% of subjects in the 325-LUR group received study drug treatment for at least 24 weeks (≥ 168 days exposure), 52.8% of subjects received study drug for at least 12 months (≥ 364 days exposure), and 29.6% of subjects received study drug for at least 24 months (≥ 728 days exposure). Overall cumulative exposure to lurasidone was 148.5 subject-years for subjects continued from Study D1050325. The mean (± SD) total daily dose of lurasidone in the 325-LUR group during the overall OL period was 52.80 ± 15.791 mg/day. The most common modal daily dose of lurasidone during the overall OL treatment period was 40 mg/day (42.4% of subjects), followed by 80 mg/day (29.6% of subjects), 60 mg/day (23.2% of subjects), and 20 mg/day (4.8% of subjects).

• There were no deaths reported during this extension study.

• Serious TEAEs were reported by 13 (10.4%) subjects who continued from Study D1050325. The only serious TEAE reported by more than 1 subject was aggression (3 subjects, 2.4%).

• There were 18 (14.4%) subjects who discontinued study drug due to a TEAE. The most common TEAEs resulting in study drug discontinuation were aggression (4 subjects, 3.2%) and fatigue and akathisia (each with 2 subjects, 1.6%).

• The most commonly reported TEAE (preferred term level) was nasopharyngitis (22.4%). Other TEAEs that were reported at a frequency ≥ 10% overall were vomiting (21.6%), weight increased (16.0%), somnolence (14.4%), headache (14.4%), upper respiratory tract infection (11.2%), anxiety (11.2%), agitation (11.2%), cough (11.2%), and insomnia (10.4%).

• The most common treatment-related TEAEs were weight increased (15.2%) and somnolence (8.0%). Other related TEAEs that were reported at a frequency ≥ 5% in the 325-LUR group were fatigue (7.2%), irritability and akathisia (6.4% each), and headache (5.6%).

• Severe TEAEs occurred in 27 (21.6%) subjects who continued from Study D1050325. Severe TEAEs experienced by more than 1 subject included aggression in 6 (4.8%) subjects; agitation in 4 (3.2%) subjects; akathisia and anxiety in 3 (2.4%) subjects each; and irritability in 2 (1.6%) subjects. The majority of TEAEs across analysis groups were mild to moderate in severity. Severe TEAEs that were considered by the Investigator to be related to study drug were reported for 12 (9.6%) subjects.

• A total of 13 subjects experienced 1 or more TEAEs leading to a dose reduction of study drug, and each TEAE leading to dose reduction was reported in only 1 or 2 subjects, with the exception of somnolence which was reported in 3 subjects.

• A total of 19 (15.2%) subjects who continued from Study D1050325 experienced EPS-related TEAEs. The most common EPS-related TEAEs (combined terms) were akathisia (6.4%) and psychomotor hyperactivity (4.0%).

• Suicidal ideation was reported by 3 (2.4%) subjects. Other suicidality/self-injury TEAEs included self-injurious behaviour (4 subjects, 3.2%) and suicide attempt (1 subject, 0.8%).

• The incidence of TEAEs related to hypersensitivity was 6.4%. TEAE preferred terms related to hypersensitivity that were reported by more than 1 subject overall included rash (5 subjects) and urticaria (2 subjects).

• The incidence of metabolic-related TEAEs was 17.6%, consisting of weight increased (20 subjects, 16.0%) and hypertriglyceridemia (3 subjects, 2.4%). No other metabolic TEAEs were reported. Although mean and median changes from DB Baseline to Endpoint were minimal for most metabolic-related clinical chemistry parameters, small and clinically insignificant decreases in HDL cholesterol were observed.

• The mean (± SD) change from DB Baseline in weight was 5.61 ± 5.035 kg at Week 52 and 9.31 ± 6.704 kg at Week 104, compared with an expected weight gain of 4.58 ± 1.689 kg and 8.29 ± 3.220 kg, respectively, based on the age-and-gender specific US CDC growth chart. Overall, any changes noted from DB Baseline in height, weight, or BMI were consistent with expected gains based on age-and-gender specific CDC growth charts.

• Median serum prolactin levels increased from DB Baseline to Endpoint by 1.40 ng/mL for females and by 0.50 ng/mL for males in the overall 325-LUR group. For other hormone parameters, there were no clinically meaningful changes in median values from DB Baseline for FSH, LH, or estradiol. Where small increases were observed, these would be consistent with puberty/sexual maturation in an adolescent population.

• Treatment with lurasidone had no notable effect on vital signs, including heart rate, systolic blood pressure, diastolic blood pressure, body temperature, and respiratory rate.

• No subjects who continued from Study D1050325 had a QTcF > 460 msec at any time during the extension study. An increase in QTcF ≥ 60 msec was observed for 1 (0.8%) subject relative to DB Baseline and no subjects relative to OL Baseline. Increases in QTcF ≥ 30 msec were reported for 12 (9.8%) subjects relative to DB Baseline and 5 (4.1%) subjects relative to OL Baseline.

• 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 DB or/or OL Baseline were observed in the BARS total score, SAS mean score, and AIMS total score over the course of the study, which were considered not clinically relevant.

• While a majority of subjects (male or female) had no change in Tanner stage from DB Baseline to Endpoint, approximately 30% of male subjects and 23% of female subjects increased in Tanner stage

by 1 category at Endpoint. Few subjects overall had an increase in Tanner stage of more than 1 category.

• Reported frequency of menstrual cycles did not show any relevant change in lurasidone-treated females between DB Baseline and Endpoint.

Subjects with Bipolar Depression Continued from Study D1050326

Of the 306 subjects who entered Study D1050302 from Study D1050326, 195 (63.7%) subjects completed 12 months of treatment, and 168 (54.9%) subjects completed the full 104 weeks of treatment.

The mean (± SD) duration of exposure to study drug in the Safety Population was 501.9 ± 276.75 days. Overall, 79.0% of subjects in the 326-LUR group received study drug treatment for at least 24 weeks (≥ 168 days exposure), 64.9% of subjects received study drug for at least 12 months (≥ 364 days exposure), and 44.3% of subjects received study drug for at least 24 months (≥ 728 days exposure). Overall cumulative exposure to lurasidone was 419.1 subject-years for subjects continued from Study D1050326. The mean (± SD) total daily dose of lurasidone in the 326-LUR group during the overall OL period was 52.12 ± 15.702 mg/day. The most common modal daily dose of lurasidone during the overall OL treatment period was 40 mg/day (41.6% of subjects), followed by 80 mg/day and 60 mg/day (each with 25.9% of subjects), and 20 mg/day (6.6% of subjects).

• There were no deaths reported during this extension study.

• Serious TEAEs were reported by 37 (12.1%) subjects who continued from Study D1050326. Serious TEAEs reported by more than 1 subject included suicide attempt and bipolar I disorder (each with 6 subjects, 2.0%); suicidal ideation (5 subjects, 1.6%); bipolar disorder (4 subjects, 1.3%); depression (3 subjects, 1.0%); and appendicitis and hand fracture (each with 2 subjects, 0.7%).

• There were 31 (10.2%) subjects who discontinued study drug due to a TEAE. The most common TEAEs resulting in study drug discontinuation were suicide attempt (6 subjects, 2.0%); suicidal ideation (5 subjects, 1.6%); depression (4 subjects, 1.3%); and akathisia, mania, and bipolar I disorder (each with 3 subjects, 1.0%).

• The most commonly reported TEAE (preferred term level) was headache (23.9%). The only other TEAEs that were reported at a frequency ≥ 10% overall were nausea (16.4%), and somnolence (12.1%).

• The most common treatment-related TEAEs were nausea (13.1%), headache (9.8%), and somnolence (8.5%). Other related TEAEs reported at a frequency ≥ 5% in the 326-LUR group were weight increased (8.2%) and akathisia (6.2%).

• Severe TEAEs occurred in 41 (13.4%) subjects who continued from Study D1050326. Severe TEAEs experienced by more than 1 subject included depression in 6 (2.0%) subjects; bipolar I disorder and suicide attempt in 5 (1.6%) subjects each; anxiety and suicidal ideation in 3 (1.0%) subjects each; and bipolar disorder, mania, headache, and ligament sprain in 2 (0.7%) subjects each. The majority of TEAEs across analysis groups were mild to moderate in severity. Severe TEAEs that were considered by the Investigator to be related to study drug were reported for 10 (3.3%) subjects.

• A total of 46 subjects experienced 1 or more TEAEs leading to a dose reduction of study drug, most commonly nausea (11 subjects), followed by somnolence and fatigue (6 subjects each). All other TEAEs leading to dose reduction were reported in ≤ 5 subjects each.

• A total of 36 (11.8%) subjects who continued from Study D1050326 experienced EPS-related TEAEs. The most common EPS-related TEAEs (combined terms) were akathisia (6.2%) and dystonia (3.0%).

• Suicidal ideation was reported by 10 (3.3%) subjects and intentional overdose by 1 (0.3%) subject. Other suicidality/self-injury TEAEs included suicide attempt (6 subjects, 2.0%), self-injurious behaviour (2 subjects, 0.7%), and suicidal behaviour, intentional drug misuse, and intentional self-injury (1 subject, 0.3% each).

• The incidence of TEAEs related to hypersensitivity was 6.6%. TEAE preferred terms related to hypersensitivity that were reported by more than 1 subject included rash (9 subjects), pruritus and urticaria (each with 3 subjects), and conjunctivitis (2 subjects).

• The incidence of metabolic-related TEAEs was 13.1%. The most common metabolic-related TEAEs was weight increased (29 subjects, 9.5%). All other metabolic TEAEs were reported by ≤ 4 subjects each. Although mean and median changes from DB Baseline to Endpoint were minimal for most metabolic-related clinical chemistry parameters, small and clinically insignificant increases in triglycerides and decreases in low-density lipoprotein (LDL) and HDL cholesterol were observed.

• The mean (± SD) change in body weight from DB Baseline was 4.25 ± 5.604 kg at Week 52 and 6.75 ± 8.077 kg at Week 104, compared with an expected weight gain of 3.76 ± 1.953 kg and 6.67 ± 3.611 kg, respectively, based on the age-and-gender specific CDC growth chart. Overall, any changes noted from DB Baseline in height, weight, or BMI were consistent with expected gains based on age-and-gender specific growth charts (CDC and WHO).

• Median serum prolactin levels increased from DB Baseline to Endpoint by 1.10 ng/mL for females and by 0.70 ng/mL for males in the overall LUR-326 group. For other hormone parameters, there were no clinically meaningful changes in median values from DB Baseline for FSH, LH, or estradiol. Where small increases were observed, these would be consistent with puberty/sexual maturation in an adolescent population.

• Treatment with lurasidone had no notable effect on vital signs, including heart rate, systolic blood pressure, diastolic blood pressure, body temperature, and respiratory rate.

• No subjects who continued from Study D1050326 had a QTcF > 460 msec at any time during the extension study. An increase in QTcF from DB or OL Baseline ≥ 60 msec was observed for 1 (0.1%) subject. Increases in QTcF ≥ 30 msec were reported for 27 (9.2%) subjects relative to DB Baseline and for 12 (4.1%) subjects relative to OL Baseline.

• 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 DB or/or OL Baseline were observed in the BARS total score, SAS mean score, and AIMS total score over the course of the study, which were considered not clinically relevant.

• Measurements of cognitive performance, as assessed by the Cogstate Computerized Cognitive Test Battery, showed no worsening over the course of the 104-week study.

• Mean decreases from Baseline to Endpoint were observed for the 4 UKU category scores (psychic, neurological, autonomic, and other) and the UKU total score.

• As measured by the C-SSRS, the majority (85.5%) of subjects who continued from Study D1050326 had no suicidal ideation at any extension visit.

• For Tanner stage, approximately 45% of male subjects and 40% of female subjects reported a shift in Tanner stage by 1 category from DB Baseline at Endpoint. Few subjects overall had an increase in Tanner stage of more than 1 category.

• Reported frequency of menstrual cycles did not show any relevant change in lurasidone-treated females between DB Baseline and Endpoint.

2.3.3. **Discussion on clinical aspects**

The MAH has provided data on the open-label (OL), 104-week, multicentre, extension study designed to evaluate the long-term safety, tolerability, and effectiveness of flexibly dosed lurasidone (20, 40, 60, or 80 mg/day) in paediatric subjects who completed a 6-week treatment period in one of three preceding studies of various indications: Study D1050301 (schizophrenia), Study D1050325 (irritability associated with autistic disorder), or Study D1050326 (bipolar depression).

The MAH has only provided discussion and analysis on results from subjects with schizophrenia who enrolled from Study D1050301 in the Clinical overview of this procedure as this application is being submitted to support an indication for adolescent subjects with schizophrenia. However, it would have been desirable to include also a discussion of the overall population of the study in the clinical overview, especially for the safety population.

The safety profile based on provided data did not differ significantly from what is known for adults. The most commonly reported TEAEs of special interest overall for the entire population in the study was metabolic TEAEs (14.3%) primarily related to weight increases/decreases and EPS-related TEAEs (14.15), Hypersensitivity-related TEAEs (5.7 %) and suicidality/self-injury-related TEAEs (5.3%). No deaths occurred in the study.

10.3, 14.4 and 10.2 in study subjects continued from study D1050301, D1050325 and D1050326 discontinued due TEAEs in the study. The most common TEAE in the schizophrenia population continued form study D1050301 were schizophrenia (9 subjects, 3.3%) suicidal ideation (5 subjects, 1.8% and psychotic disorder (3 subjects, 1.1%).

Treatment with lurasidone had no significant effect on vital signs, including heart rate, systolic and diastolic blood pressure, body temperature and respiratory rate.

Changes in height weight and BMI were largely consistent expected gains based on the age and gender specific growth charts (CDC and WHO) in the overall population of the study. In the schizophrenia population reported in the clinical overview, the MAH states that increases were observed relative to expected weights predicted on the CDC growth charts, however this is not consistent with Figure 7 in the report.

Frequency of menstrual cycles did not show any relevant changes. The MAH har also reported sexual maturation assessed by analysis of the frequency distribution of Tanners stage over time. However, no analysis in relation to the overall general population is provided which makes interpretation of data difficult.

There was an increase in prolactin levels from DB baseline to the OL baseline that then stabilised to generate a small decrease form OL baseline to endpoint.

<u>Efficacy</u>

No inferential statistics on effectiveness were conducted.

A flexible dose of (20, 40, 60, 80 mg/day) lurasidone maintained a clinical improvement of symptoms of schizophrenia in adolescent subjects as measured in total PANSS score in subjects with schizophrenia continued from study D1050301. Also, other disease outcomes of symptoms of schizophrenia and functionality indicated maintenance of effect.

Numerical maintenance of effect from the short-term studies was also shown for subjects with bipolar depression and subjects with autistic disorder continued from study D1050326 and D1050325 respectively.

The MAH planes to submit a type II C.I.4 variation on November 2019 to register a new indication – schizophrenia in adolescents – after the outcome of the PIP modification that will be submitted in July 2019. With this variation the MAH will also submit the CSR of the study D1050302.

Further evaluation to support any proposed changes in the product information will be assessed in the coming variation.

3. **Rapporteur's overall conclusion and recommendation**

The MAH has provide long-term data safety, tolerability and efficacy of lurasidone flexibly dosed. Maintenance of efficacy in schizophrenia was demonstrated for treatment with lurasidone for periods up to two years. Lurasidone appears tolerable with a safety profile in line with what is known for the adult population in the dose range investigated. Update of the product information should be discussed when the applicant submits the variation to register a new indication as stated by the applicant.

☒ **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: Active substance:

Study title	Study number	Date of completion	Date of submission of final study report
Open-label, multicentre, single and multiple fixed ascending dose study to evaluate pharmacokinetics, safety, and tolerability of lurasidone in the paediatric population	D1050300	Last visit: 06 May 2013 CSR: 23 October 2013	Article 46 May 2014
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	Last visit: 29 December 2015 CSR: 06 June 2016	Article 46 August 2016
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	Last visit: 17 October 2018 CSR: 16 April 2019	Article 46 May 2019
Study 4, *Deleted in procedure EMEA-001230-PIP01-11-M04*	n.a	n.a	n.a