Schizophrenia Research 240 (2022) 205–213

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Long-term safety and effectiveness of open-label lurasidone in antipsychotic-Naïve versus previously treated adolescents with Schizophrenia: A post-hoc analysis

Christoph U. Correll a,b,c,⁎, Michael Tocco d, Andrei Pikalov d, Jay Hsu d, Robert Goldman d

a Department of Psychiatry, Northwell Health, The Zucker Hillside Hospital, Glen Oaks, NY, USA
b Hofstra Northwell School of Medicine, Department of Psychiatry and Molecular Medicine, Hempstead, NY, USA
c Charité Universitätsmedizin, Department of Child and Adolescent Psychiatry, Berlin, Germany
d Sunovion Pharmaceuticals Inc, Fort Lee, NJ, and Marlborough, MA, USA

ARTICLE INFO

Keywords:
Atypical antipsychotic
Lurasidone
Schizophrenia
Adolescent
Treatment-naïve

ABSTRACT

Background: There is a relative lack of long-term, prospective data evaluating the safety and effectiveness of treatment in early-onset adolescent patients with schizophrenia who are treatment-naïve. The aim of this post-hoc analysis was to examine the long-term safety and effectiveness of lurasidone in adolescents with schizophrenia who were antipsychotic treatment-naïve (TN; at the time of enrolment in the initial study) compared to adolescents treated previously (TP) with an antipsychotic.

Methods: Patients aged 13–17 who completed 6 weeks of double-blind (DB), placebo-controlled treatment with lurasidone were enrolled in a 2-year, open-label (OL), flexible-dose (20–80 mg/day) lurasidone study.

Results: The long-term analysis sample consisted of 50 TN and 221 TP patients, of whom 40% and 43%, respectively, discontinued prematurely. The three most common adverse events for TN and TP patients, respectively, were headache (26.0%, 23.5%); schizophrenia (14.0%, 12.2%), dizziness (16.0%, 4.1%), and nausea (16.0%, 11.8%). At endpoint, mean increase in weight was similar to expected weight gain based on growth charts for both TN (+4.5 kg vs. +5.7 kg) and TP (+4.6 kg vs. +6.6 kg) patients. Minimal changes were observed for each group in metabolic parameters and prolactin. Mean improvement was consistently greater in the TN vs. TP group (-19.2 vs. -15.9; effect size of 0.33) for between-group change in PANSS total score at Week 104.

Conclusions: In both TN and TP adolescents with schizophrenia, long-term treatment with lurasidone was associated with minimal effects on body weight, lipids, glycemic indices, and prolactin, with generally small differences noted in rates of reported AEs. Continued improvement in symptoms of schizophrenia was evident for both the TN and TP groups. These data indicate that lurasidone is a safe and efficacious treatment option for treatment-naïve youth with schizophrenia, who are generally most sensitive to antipsychotic adverse effects.

1. Introduction

Among individuals diagnosed with schizophrenia, initial onset of psychotic symptoms occurs during adolescence: >25% of the time (Hafner et al., 1993; Thomsen, 1996; Thorup et al., 2007; McGrath et al., 2016). Early onset of schizophrenia is associated with a greater likelihood of negative symptoms, an increased probability of hospitalizations, greater risk of relapse, and poorer social and occupational functioning compared to adult onset of the disorder (Immonen et al., 2017). Early identification and treatment of schizophrenia in the adolescent population is particularly important in this at-risk developmental period since treatment delay, which may be higher in adolescents than in adults (Stentebjerg-Olesen et al., 2016), has been associated with structural changes in the brain that may be related to poor long-term clinical outcome (Loebel et al., 1992; Crumlish et al., 2009; Owens et al., 2010; Guo et al., 2013; Zhang et al., 2017; Zhijao et al., 2019).

Several studies have examined the comparative efficacy of different antipsychotics among first-episode, treatment-naïve, patients (mostly adults) with schizophrenia (Sanger et al., 1999; Lieberman et al., 2003; Schooler et al., 2005; Green et al., 2006; Gaebel et al., 2007; Kahn et al., 1996).
Lurasidone is an atypical antipsychotic with high binding affinity for D2, 5-HT2A, and 5-HT2 receptors (antagonist); moderate affinity for 5-HT1A receptors (partial agonist); and no appreciable affinity for H1 and M1 receptors (Ishibashi et al., 2010). The short-term and long-term efficacy and safety of lurasidone in the dose range of 40–160 mg/day has been demonstrated in multiple studies of adult patients with schizophrenia (Nakamura et al., 2009; Meltzer et al., 2011; Citrome et al., 2012; Loebel et al., 2013a; Loebel et al., 2013b). Among adolescents (13–17 years old) with schizophrenia, lurasidone efficacy and safety has been demonstrated within the dose range of 40–80 mg/day in both short-term and long-term studies (Goldman et al., 2017; Correll et al., 2020). Importantly, lurasidone treatment in adolescents was associated with minimal effects on weight and metabolic parameters over a 2-year period.

Prior literature does not consistently find that first-episode and/or treatment-naive (TN) adolescents are more treatment responsive than previously treated (TP) adolescents (Zhu et al., 2017). However, TN adolescents appear to be at greater risk of antipsychotic adverse effects compared to TP adolescents, especially developmentally inappropriate weight gain (Correll et al., 2009; Jensen et al., 2017; De Hert et al., 2011; Correll, 2011; Carbon and Correll, 2014).

In a companion paper (Correll et al., 2019) we have reported results of a randomized, double-blind, placebo-controlled, 6-week trial of lurasidone demonstrating greater efficacy in TN vs. TP adolescents with a diagnosis of schizophrenia. However, side effect burden, and effects on weight and other safety parameters did not differ for the TN vs. TP groups in the acute treatment phase.

In this post-hoc analysis, we report long-term safety and effectiveness of lurasidone in the 2-year, open-label extension phase of the initial short-term, double-blind trial, which adds important safety information, i.e., weight gain and metabolic parameters over time. Based on the results of the initial double-blind trial, we hypothesized that open-label extension treatment with lurasidone would be associated with greater initial efficacy in TN vs. TP adolescents with schizophrenia and that safety would remain comparable in both groups during this 2-year study. We note that TN patients in the current extension phase were technically only treatment-naive at entry into the initial 6-week double-blind study, except for patients switching from placebo.

2. Methods

Data for this post-hoc analysis of the safety and effectiveness of lurasidone for treatment-naive and previously treated adolescents (aged 13–17) with schizophrenia were drawn from a 104-week, open-label extension study (clinicaltrials.gov identifier: NCT01914393) and an initial 6-week, double-blind, placebo-controlled trial evaluating the efficacy and safety of two fixed-doses of lurasidone (40 and 80 mg/d) for the treatment of schizophrenia (NCT01911429; Goldman et al., 2017).

The 2-year open-label study was conducted from November 2013 to October 2018 at 65 centers in 14 countries (Bulgaria, Columbia, Spain, France, Hungary, Korea, Mexico, Malaysia, Philippines, Poland, Romania, Russia, Ukraine, USA). An institutional review board/ethics committee at each investigational site approved the study, which was monitored by an independent Data and Safety Monitoring Board. Written informed consent was obtained from a parent or legal guardian and assent was obtained from each adolescent patient. The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practices guidelines and with the ethical principles of the Declaration of Helsinki.

2.1. Patients and study design

The initial 6-week double-blind, placebo-controlled, study enrolled patients with a DSM-IV-TR (American Psychiatric Association, 2000) diagnosis of schizophrenia who were experiencing an acute exacerbation (>2 months in duration), a Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) total score ≥70, and a Clinical Global Impression-Severity (CGI-S; Guy, 1976) score ≥4 (at least moderately ill). Key exclusion criteria included a history of intellectual disability or any neurologic disorder, or an alcohol or substance use disorder diagnosis in the previous 6 months. Prior treatment status was determined from self-report by caregiver and patient in response to standard questions during the screening visit for the 6-week double-blind study. To be enrolled in the subsequent open-label extension study, the protocol required a judgement by the investigator that the patient was suitable for participation in a 104-week study and was able to comply with the study procedures. Patients were excluded from the extension study if they were considered by the investigator to be at imminent risk of suicide or injury to self or others; if they exhibited evidence of moderate or severe extrapyramidal symptoms, dystonia, tardive dyskinesia, or any other movement disorder; and if they were not willing to use medically appropriate contraception if sexually active.

The blind was maintained in the open-label extension study using a dose of 40 mg/d for the first week, regardless of their treatment group in the original double-blind study. Flexible dose adjustments of lurasidone in the range of 20–80 mg/day were permitted at each visit during the open-label study to optimize effectiveness and safety. Lurasidone was taken orally once daily in the evening with a meal or within 30 min after eating.

2.2. Concomitant medication

During both the 6-week double-blind study and 2-year open-label extension study, concomitant treatment with benzodiazepines, antidepressants, and stimulants (for ADHD) was permitted. Treatment with benzotropine (<6 mg/day), or alternative medications, as needed for movement disorders, and treatment with prannanol (<120 mg/day) as needed for akathisia was also allowed. However, prophylactic use of medications to treat movement disorders was not permitted. At the discretion of the investigator, concomitant use of lorzepam or equivalent benzodiazepine (<6 mg/day or equivalent dose) for intolerable anxiety/agitation was acceptable. On an as-needed basis, benzodiazepine and non-benzodiazepine sedative-hypnotic agents were also permitted for insomnia.

If a patient was hospitalized at the conclusion of the original double-blind study, continued hospitalization for up to 14 days in the current extension study was allowed. If a patient could not be transitioned to an outpatient setting within 14 days, they were discontinued from the study.

2.3. Safety assessments

Spontaneously reported adverse events were recorded throughout the open-label extension phase. In addition, adverse event reporting was supplemented by administration of the Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale, a clinician-rated scale consisting of 48 adverse events divided into four categories (psychic, neurologic, autonomic, and other; Lingeard et al., 1987). For each side effect category and the total score on the UKU, mean severity scores were calculated (1-mild to 4-severe). The Simpson-Angus Scale (SAS; Simpson and Angus, 1970), the Barnes Akathisia Rating Scale (BARS; Barnes, 1989), and the Abnormal Involuntary Movement Scale (AIMS; Guy, 1976; Munetz and Benjamin, 1988) were used to assess movement...
disorders. The Columbia Suicide Severity Rating Scale (C-SSRS; Posner et al., 2011) was used to measure suicidal ideation and behavior. Additional safety assessments included vital signs, weight and BMI, laboratory tests (metabolic parameters and other blood chemistry, hematologic parameters), 12-lead electrocardiogram (ECG), and physical examination. Adverse events, monitoring of concomitant medications, vital signs, SAS, BARS, and AIMS were conducted at OL baseline, weeks 2, 4, 6, and 8 (following OL baseline) and monthly thereafter up to week 104, while the UKU, weight, laboratory tests, and ECG were performed at OL baseline, weeks 6, 12, 28, and every 12 weeks thereafter.

2.4. Effectiveness assessments

Effectiveness measures consisted of the following: the PANSS Total Score and the PANSS Positive, Negative, General Psychopathology, and Excitability subscales (Kay et al., 1987); the CGI-S (Guy, 1976); the clinician-rated Children’s Global Assessment Scale (CGAS; Shaffer et al., 1983); and the Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q; Endicott et al., 2006). The CGAS measures global functional impairment on a scale of 0–100 with higher scores indicating better functioning. Effectiveness and safety assessments were performed by qualified site-based raters. During the 2-year OL study, the PANSS and CGI-S were performed at OL baseline, weeks 2, 4, 6, and 8 (following OL baseline) and monthly thereafter up to week 104, with a follow-up visit at week 105. The CGAS and PQ-LES-Q were conducted at OL baseline, weeks 6, 12, 28, and every 12 weeks thereafter.

2.5. Statistical analysis

The safety sample consisted of all patients who completed the double-blind, acute-phase trial, continued into the current extension study, and received at least one dose of open-label lurasidone during the extension study. Descriptive analyses of safety outcomes included the number (% of treatment-emergent adverse events, serious adverse events, and discontinuations due to adverse events for both the TN and TP patient groups. Observed case analyses were calculated for mean (standard deviation [SD] or 95% confidence interval [95% CI]) change from double-blind acute study baseline in the PANSS total and baseline score as fixed effects. MMRM analyses were performed for mean (±standard deviation [SD]) change from double-blind acute study baseline in the PANSS total and subscale scores (Positive, Negative, General Psychopathology, Excitability); the CGI-S score; the CGAS and the PQ-LES-Q. All significance tests were two-tailed with alpha = 0.05; none of the P-values were a priori responder criterion of ≥ 50% reduction in PANSS total score was also used. Remission was defined as a PANSS item scores of ≤ 3 on the following PANSS items (N = 8 items): P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), G5 (mannerisms/posturing), G9 (unusual thought content), N1 (blunted affect), N4 (social withdrawal), N6 (lack of spontaneity; Andreasen et al., 2005).

3. Results

3.1. Patient disposition and characteristics

There were 327 patients who were randomized to treatment in the 6-week DB placebo-controlled study. Of these, 271 completed the 6-week study and continued into the 2-year open-label extension study, including 181 patients initially randomized to lurasidone (40 mg/d or 80 mg/d) and 90 patients initially randomized to placebo (Fig. 1). The 271 patients consisted of 50 who were TN (70% received lurasidone in the double-blind phase) and 221 who had received an antipsychotic prior to participating in the 6-week DB trial (TP: 66.1% received lurasidone in the double-blind phase; Table 1). Of the 50 TN patients, 30 (60.0%) completed the 2-year OL study. Of the 221 TP patients, 126 (57.0%) completed the OL study. The most common reason for discontinuation was withdrawal of consent (14% for both the TN and TP groups) (Fig. 1). Discontinuation due to adverse events occurred in 3 (6.0%) TN patients and 26 (11.8%) TP patients. For the TN group, a slightly higher proportion of patients previously assigned to placebo in the double-blind phase (vs. lurasidone) discontinued prematurely (46.7% vs. 37.1%); the proportion was similar in the TP group (46.7% vs. 41.1%).

Demographic and clinical characteristics of the treatment-naïve and previously treated patients at open-label phase baseline are provided in Table 1.

3.2. Drug exposure

Across the 104-week OL treatment period, the mean daily dose of lurasidone averaged 55.0 mg/day and 57.6 mg/day for the TN and TP groups, respectively. The modal daily dose of lurasidone during open-label treatment was 20 mg (in 2% of patients), 40 mg (46%), 60 mg (28%), and 80 mg (24%) for TN patients; for TP patients, the modal daily dose was 20 mg (in 3.6% of patients), 40 mg (33%), 60 mg (23.5%), and 80 mg (39.8%). Adherence was high, as indicated by pill counts. Median adherence (total tablets taken divided by total tablets should have taken) was 100% for both groups. Within the TN group, the most frequently used, as-needed, concomitant medications were anxiolytics (16%) and anticholinergic medications (10%). Within the TP group, anxiolytics were used by 24.9% of patients and anticholinergic medications by 9.5% of patients.

3.3. Safety

In general, the profile of adverse events was similar for the TN and TP patients (Table 2). Relative to the TP group, three adverse events in the TN group had NNH values <20: nasopharyngitis (NNH = 6), dizziness (NNH = 9), and akathisia (NNH = 14). The incidence rate of extrapyramidal events (including parkinsonism, dyskinesia, dystonia, extrapyramidal disorder, salivary hypersecretion, and tardive dyskinesia) was comparable in the TN and TP groups (18.0% vs. 15.8%). Overall side effect burden, as measured by the UKU side effect total score, was somewhat higher at OL baseline in the TP vs TN group (4.2 vs. 3.6; Table 3). Both groups showed reductions at endpoint in the UKU side effects score, but the reduction was greater in the TP group (-1.9 vs. -0.3; Table 3).

Serious adverse events occurred in 8% (n = 4) of TN patients and 10.9% (n = 24) of TP patients over the course of the 104-week extension phase. In the TN group, the following serious adverse events occurred: appendicitis (n = 1), depressive symptoms (n = 1), exacerbation of schizophrenia symptoms (n = 2), and suicidal ideation (n = 1); in the TP group, the serious adverse events were pyrexia (n = 1), injury (n = 4), diabetes (n = 1), psychiatric symptoms (n = 23), and hematuria (n = 1). No deaths occurred in either group.

On the Columbia Suicide Severity Rating Scale, the proportion of TN patients with emergent or worsening (relative to the double-blind
treatment period) suicidal ideation was 10.0% (n = 5) and the proportion with emergent or worsening suicidal behavior was 0% over the course of the 104-week extension study. The proportion of TP patients with emergent or worsening (relative to the double-blind treatment period) suicidal ideation was 5% (n = 11) and the proportion with emergent or worsening suicidal behavior was 1.4% (n = 3).

On average, there was no evidence of increases in movement disorders over the 2-year extension study. For the TN group, least squares (LS) mean changes from open-label baseline to weeks 52 and 104, respectively, were small and not clinically meaningful for the SAS mean score (-0.01 and -0.03), BAS total score (-0.3 and -0.4), and AIMS total score (0.03 and -0.23). Similarly, for the TP group, LS mean changes from open-label baseline to weeks 52 and 104, respectively, were small and not clinically meaningful for the SAS mean score (0.00 and -0.01), BAS total score (0.0 and -0.1), and AIMS total score (-0.03 and -0.01).

Both for TN and TP adolescents, mean change from extension phase baseline in actual weight and BMI during 104 weeks of open-label treatment with lurasidone was very similar to the expected changes based on CDC growth charts (Ogden et al., 2002) (Table 4).

For the TN group, lurasidone treatment was associated with small median changes from OL baseline to endpoint in total and LDL-cholesterol, triglycerides, glucose, hemoglobin A1C and insulin; and median changes in prolactin were minimal (≤1.2 ng/mL) in both male and female patients (Table 4). Similarly, in the TP group, only small changes in laboratory parameters were evident (Table 4).

During open-label treatment with lurasidone, no clinically meaningful changes were observed in heart rate, ECG, orthostatic blood pressure (systolic or diastolic), respiratory rate, or body temperature for either the TN or TP groups. On serial ECG assessments during up to 104 weeks of open-label treatment, no patient in either group had a QTcF value > 460 msec, and no patient in either group had an increase from open-label baseline in QTcF that was ≥ 60 msec.

3.4. Effectiveness

On all effectiveness measures, mean changes from OL baseline revealed continued improvement over the course of the 104-week extension phase for both TN and TP patients (Table 5). On the PANSS Total Score, mean improvement was numerically greater in the TN compared to the TP group at week 6 through week 104 (-19.2 vs. -15.9; effect size, 0.33; Fig. 2). A similar numerical improvement advantage was observed at week 104 for the TN vs. TP group on the PANSS Positive Symptom subscale (-5.4 vs. -4.5; effect size, 0.32), PANSS General Psychopathology subscale (-9.7 vs. -7.4; effect size, 0.45), and PANSS Excitability subscale (-2.2 vs. -1.7; effect size, 0.27); however, the improvement was similar at week 104 on the PANSS Negative Symptom subscale (-4.0 vs. -3.9; effect size, 0.02). On the CGI-Severity scale, significantly greater improvement was observed in the TN compared to the TP group at week 104 (-1.7 vs. -1.0; P < 0.05; effect size, 1.18; Table 5). A numerical advantage in favor of the TN vs. TP group was observed at week 104 on the CGAS (+19.8 vs. +16.1; effect size, 0.48) and the PQ-LES-Q (+11.8 vs. 10.7; effect size, 0.12).

Responder rates (≥20% reduction from OL baseline to endpoint in PANSS Total Score) were 57.1% (28/49) in the TN group and 58.3% (127/218) in the TP group; and responder rates using the ≥ 50% reduction criterion were 34.7% (17/49) in the TN group and 28.4% (62/218) in the TP group.

In an exploratory analysis, mean change from open-label baseline in PANSS total score was examined in two subgroups of the TN group by assignment during the six-week double-blind phase:

(1) patients initially randomized to placebo who were switched to open-label lurasidone, and (2) patients initially randomized to lurasidone who continued lurasidone in the open-label phase. Mean change in PANSS total score was greater for the double-blind placebo vs. lurasidone group at Week 52 (-25.2 vs. -14.4) and at Week 104 (-34.4 vs. -14.4).

4. Discussion

The results of this post-hoc analysis of data from a multicenter, open-label extension study in adolescents with schizophrenia indicate that lurasidone (20–80 mg/day) is generally well-tolerated for both TN and TP patients over the course of 2 years of maintenance treatment. The safety profile was similar for both patient groups and consistent with the

![Fig. 1. Patient disposition.](image-url)
previously reported safety profile based on short- and long-term studies of lurasidone in adult patients with schizophrenia (Nakamura et al., 2009; Meltzer et al., 2011; Citrome et al., 2012; Nasrallah et al., 2013; Ogasa et al., 2013; Tandon et al., 2016). However, the current finding that long-term treatment with lurasidone was associated with similar levels of safety in the TN versus TP patient groups differs from prior analyses of other antipsychotics where adverse effects were generally greater in youth vs. adults and in first-episode vs. more chronic patient populations (Correll, 2011; Correll et al., 2006; De Hert et al., 2011; De Hert et al., 2012). In this sample of adolescent patients, no new or unexpected adverse events were reported, no deaths occurred, and no serious drug-related effects were observed for both the TN and TP patient groups.

Study completion rates were comparable for TN and TP patients (60% vs. 57%); and were also comparable to the completion rate of 55% reported in a previous open-label, 2-year study of paliperidone in schizophrenia, n (%)

Table 1
Baseline Demographic and Clinical Characteristics at Open-Label Baseline (Safety Sample).

| Characteristic | Total(N = 271) | Treatment-Naive(N = 50) | Previously Treated(N = 221) |
|---------------|---------------|------------------------|-----------------------------|
| Male, n (%)   | 170           | 32 (64.0)              | 138 (62.4)                  |
| Age, years, mean (SD) | 15.5 (1.4) | 15.3 (1.5)              | 15.6 (1.4)                  |
| Race, n (%)   |               |                        |                             |
| White         | 197           | 34 (68.0)              | 163 (73.8)                  |
| Black         | 38 (14.0)     | 9 (18.0)               | 29 (13.1)                   |
| Asian         | 11 (4.1)      | 1 (2.0)                | 10 (4.5)                    |
| Other         | 25 (9.2)      | 6 (12.0)               | 19 (8.6)                    |
| Age at onset of psychotic symptoms, years, mean (SD) | 13.1 (2.8) | 13.7 (2.3)              | 13.0 (2.9)                  |
| Duration of onset of current episode of schizophrenia to screening for DB study (in years), mean (SD) | 0.12 (0.3) | 0.11 (0.18)             | 0.12 (0.35)                 |
| Prior hospitalizations for schizophrenia, n (%) |               |                        |                             |
| 0             |               |                        |                             |
| 1             |               |                        |                             |
| ≥2            |               |                        |                             |
| Treatment assignment during DB phase, n (%) |               |                        |                             |
| Lurasidone/Placebo | 181       | 35 (70.0)              | 146 (66.175)                |
| PANSS Total Score, mean (SD) baseline | 93.5        | 92.3 (9.5)             | 93.8 (11.3)                 |
| PANSS Positive, mean (SD) baseline | 23.7 (4.0) | 23.7 (3.0)             | 23.7 (4.182)                |
| PANSS Negative, mean (SD) baseline | 17.9 (5.5) | 16.7 (5.0)             | 17.5 (5.6)                  |
| PANSS Extraverted, mean (SD) baseline | 24.4 (4.3) | 23.0 (4.9)             | 24.7 (4.120.9)              |
| PANSS Psychopathological, mean (SD) baseline | 20.5 (4.9) | 18.7 (4.5)             | 18.7 (4.9)                  |
| PANSS Excitability, mean (SD) baseline | 45.4 (6.8) | 45.6 (6.1)             | 45.8 (6.937.9)              |
| PANSS Total Score, mean (SD) baseline | 37.5 (9.4) | 35.7 (8.2)             | 35.7 (9.6)                  |
| CGI-S score, mean (SD) baseline | 10.8 (3.1) | 10.7 (2.985)           | 10.8 (3.191)                |
| CGI-a score, mean (SD) baseline | 9.0 (3.7)  | 9.0 (3.7)              | 9.0 (3.7)                   |
| CGI-b score, mean (SD) baseline | 4.8 (0.6)  | 4.7 (0.738)            | 4.8 (0.640)                 |
| Weight, kg, mean (SD) baseline | 64.2        | 63.0 (11.2)            | 64.4 (12.6)                 |
| BMI, kg/m², mean (SD) baseline | 22.7 (3.5) | 22.4 (3.0)             | 22.7 (3.022.8)              |

BMI: body mass index; DB = double-blind; CGI-S: Clinical Global Impressions – Severity scale; OL: open-label; PANSS: Positive and Negative Syndrome Scale

Table 2
Number (%) of Treatment-Emergent Adverse Events (Safety Sample).

| Characteristic         | Treatment-Naive (N = 50) | Previously Treated (N = 221) | NNH |
|------------------------|--------------------------|------------------------------|-----|
| Nasopharyngitis        | 12 (24.0)                | 12 (5.4)                     | 6   |
| Dizziness              | 8 (16.0)                 | 9 (4.1)                      | 9   |
| Akathisia              | 7 (14.0)                 | 15 (6.8)                     | 14  |
| Nausea                 | 8 (16.0)                 | 26 (11.8)                    | 24  |
| Diarrhea               | 4 (8.0)                  | 9 (4.1)                      | 26  |
| Headache               | 13 (26.0)                | 52 (23.5)                    | 40  |
| Constipation           | 4 (8.0)                  | 10 (4.5)                     | 29  |
| Schizophrenia          | 7 (14.0)                 | 27 (12.2)                    | >50 |
| Toothache              | 4 (8.0)                  | 15 (6.8)                     | >50 |
| Weight increased       | 4 (8.0)                  | 17 (7.7)                     | >50 |
| Asthenia               | 4 (8.0)                  | 8 (3.6)                      | 23  |
| Abdominal pain         | 4 (8.0)                  | 7 (3.2)                      | >50 |
| Vomiting               | 3 (6.0)                  | 13 (5.9)                     | >50 |
| Somnolence             | 3 (6.0)                  | 21 (9.5)                     | TN  |
| Depression             | 3 (6.0)                  | 16 (7.2)                     | TN  |
| Influenza              | 3 (6.0)                  | 10 (4.5)                     | >50 |
| Insomnia               | 2 (4.0)                  | 20 (9.0)                     | TN  |
| Viral infection        | 2 (4.0)                  | 15 (6.8)                     | TN  |
| Anxiety                | 4 (8.0)                  | 30 (13.6)                    | TN  |
| Weight decreased       | 1 (2.0)                  | 12 (5.4)                     | TN  |
| Agitation              | 1 (2.0)                  | 20 (9.0)                     | TN  |
| Extrapyramidal events | 9 (18.0)                 | 35 (15.8)                    | 46  |
| Any Event              | 40 (80.0)                | 174 (78.7)                   | 77  |

NNH: number needed to harm; TN: treatment-naive; TP: previously treated

Table 3
Change From OL Baseline to LOCF-Endpoint in Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale Scores for Lurasidone (Safety Sample).

| Characteristic         | Treatment-Naive (N = 50) | Previously Treated (N = 221) |
|------------------------|--------------------------|------------------------------|
| Change from OL baseline, mean (SD) | 2.8 (2.7) | 2.1 (-1.6, 0.9)             | 3.3 (3.6)                     |
| Neurologic side effects score OL Baseline, mean (SD) | 0.3 (0.6) | 0.2 (0.0, 0.2)              | 0.1 (0.2, 0.0)                |
| Autonomic side effects score OL Baseline, mean (SD) | 0.4 (1.0) | 0.4 (0.2, 0.1)              | 0.5 (1.0)                     |
| Other side effects score OL Baseline, mean (SD) | 0.0 (0.2, 0.1) | 0.2 (0.3, 0.1) | 0.2 (0.3, 0.1) |
| UKU side effects total score OL Baseline, mean (SD) | 3.6 (3.4) | 4.2 (4.2)                   | 4.2 (4.2)                     |
| Change from OL baseline, mean (SD) | 0.3 (-1.7, 1.1) | 0.3 (-1.7, 1.1) | 0.3 (-1.7, 1.1) |

Higher baseline scores indicate greater severity; range of 0–30 for psychic, 0–24 for neurologic, 0–33 for autonomic, and 0–48 for other. OL: open-label; LOCF: last observation carried forward

a OL baseline means are shown for the subgroup available at OL endpoint.
adolescent schizophrenia (Savitz et al., 2015). Discontinuation due to adverse events was numerically lower in the TN vs. TP group (6% vs. 12%). The reason for this result is uncertain, although the difference may be partly attributable to the higher proportion of TP vs. TN patients who used a modal dose of 80 mg/day (40% vs 24%). The proportion of patients reporting extrapyramidal events was relatively low for both the TN and TP groups (10.0% and 10.9%). Two adverse events were notably higher in the TN group, nasopharyngitis (with a between-group difference of 2.6%) and dizziness (NNH = 9); clinically relevant between-group differences were not evident for other adverse events.

No clinically meaningful changes were observed in vital signs or ECG parameters for either the TN or TP group during long-term treatment with lurasidone. Importantly, weight gain did not differ from age- and developmentally appropriate levels during the 2-year follow-up, which was similar in both the TN and TP groups. Only minimal effects were also observed on lipids, glycemic indices, and prolactin during up to 2 years of treatment with lurasidone. The lack of excessive weight gain in the TN group is consistent with results from previous long-term studies in adults reporting that lurasidone has minimal effects on weight (Correll et al., 2009; Jensen et al., 2017), and in children and adolescents on selected antipsychotics (De Hert et al., 2011). The lower risk of weight gain for lurasidone compared to risperidone, quetiapine, olanzapine, clozapine, and paliperidone has been confirmed in a network meta-analysis of short-term treatment studies in children and adolescents with schizophrenia (Krause et al., 2018). Moreover, the favorable safety results for lurasidone observed in this study, including in the TN subgroup of adolescents with schizophrenia, are consistent with a recent review that compared up to 78 adverse effects of 15 antipsychotics used across different psychiatric disorders (Solmi et al., 2020). In that study, lurasidone was the antipsychotic with the lowest number of adverse effects that were significantly more frequent than with placebo (1.3%) among the 7 agents where ≥20% of the 78 potential adverse effects had been reported (asenapine, quetiapine, ziprasidone, paliperidone, risperidone, aripiprazole, olanzapine).

| Table 4 | Mean Change from Open-label Baseline in Laboratory Parameters and Weight (Safety Sample). |
|-----------------|-------------------------------------------------|
| Change from Open-label Baseline to Week 104 | Treatment-Naïve \((N = 50)\) | Previously Treated \((N = 221)\) |
| Metabolic labs, mg/dL, mean (95% CI) | Lurasidone | Placebo |
| Total cholesterol | +10.6 (1.5, 22.7) | +3.6 (1.7, 8.9) |
| LDL cholesterol | +16.9 (3.6, 30.2) | +5.2 (0.3, 10.2) |
| Triglycerides | +25.2 (5.5, 55.9) | +10.6 (0.4, 21.7) |
| Hemoglobin A1C (%), mean (95% CI) | 0.0 (-0.1, 0.1) | -0.1 (-0.1, 0.0) |
| Prolactin, (ng/mL), mean (95% CI) | +2.7 (12.8, 2.0) | -4.0 (-14.3, 6.3) |
| Male | +4.1 (2.7, 11.0) | -3.5 (-70.0, 0.0) |
| Change from Open-label Baseline to Weeks 52 and 104 | Treatment-Naïve** | Previously Treated \((N = 221)\) |
| Body weight, kg, mean (95% CI) | Lurasidone | Placebo |
| Week 52, Actual change | +3.4 (2.0, 4.9) | +2.7 (1.8, 3.6) |
| Week 52, Expected change* | +3.6 (3.1, 4.2) | +3.3 (3.0, 3.6) |
| Week 104, Actual change | +4.5 (2.4, 6.6) | +4.7 (3.3, 6.0) |
| Week 104, Expected change* | +6.0 (4.9, 7.1) | +5.7 (5.1, 6.2) |

* Age-and-gender adjusted weights are based on CDC growth charts for United States (Ogden et al., 2002); observed case analysis

** Week 52 and Week 104 mean change in weight, Actual/Expected by double-blind → open-label treatment assignment:

Placebo → Lurasidone group \((N = 15)\): Week 52: +4.0/+4.4; Week 104: +4.3/+6.7

Lurasidone → Lurasidone group \((N = 35)\): Week 52: +3.2/+3.4; Week 104: +4.5/+5.8

* sample sizes are very small for the treatment-naïve group \((n = 8)\)

Regarding long-term effectiveness, both TN and TP adolescents with schizophrenia showed clinically meaningful levels of improvement in symptoms as measured by the PANSS total and subscale scores over the course of 104 weeks of open-label treatment with lurasidone. The
magnitude of differential improvement, as measured by the between-group effect size, consistently favored the treatment-naïve group. The differential improvement advantage was especially notable in the exploratory subgroup that received placebo in the double-blind phase, and who therefore were truly treatment-naïve at entry into the open-label phase. The differentially greater reduction in PANSS total score in this double-blind placebo vs. double-blind lurasidone TN subgroups (13.4-point greater reduction at Week 52; 20.0-point greater reduction at Week 104) was only minimally attributable to a lower open-label baseline PANSS total score in patients treated with double-blind lurasidone vs. placebo (70.2 vs. 73.3). The effectiveness advantage in favor of the TN group supports the importance of prompt diagnosis and appropriate treatments of early onset schizophrenia in this sample, which might lead to better long-term outcomes.

There are several limitations of the current study that should be noted. First and foremost, this was a post-hoc analysis of an open-label extension study without a placebo or active control and P-values were not adjusted for multiplicity. Thus, the current findings should be considered exploratory and interpreted with caution. In addition, the stringent inclusion and exclusion criteria of the preceding DB trial may limit the generalizability of the current findings. Finally, the sample size for the TN group was relatively small, though it should be noted that this is the only long-term trial we are aware of to assess the safety and effectiveness of an antipsychotic in TN adolescent patients with schizophrenia over a 2-year period. Finally, the sample size for the TN group was relatively small and at OLE study baseline, patients randomized to lurasidone had up to 6 weeks of lurasidone exposure vs zero antipsychotic exposure in the patients rolling over from placebo. Nevertheless, this is the only long-term trial we are aware of to assess the safety and effectiveness of an antipsychotic in TN adolescent patients with schizophrenia over a 2-year period.

5. Conclusions

Long-term treatment with lurasidone (20–80 mg/day) was generally safe and well-tolerated among adolescents with schizophrenia who were either treatment-naïve or had received previous antipsychotic treatment. One main finding of this study is that with lurasidone, the safety was not reduced in TN vs TP patients. This important result makes lurasidone a viable treatment option for patients in the very early stages of the illness where adverse effects can negatively affect attitudes toward medication treatment and where cardiometabolic health can be worsened dramatically by most available antipsychotic agents. Minimal effects on weight and metabolic parameters were observed in both groups. Continued improvement in symptoms of schizophrenia was evident over the course of two years of open-label treatment. These results suggest that lurasidone has a favorable benefit-risk profile for both treatment-naïve and previously treated adolescents with schizophrenia and therefore may be considered as a potential first-line option for maintenance therapy in patients with as well as without previous exposure to antipsychotics. Comparative effectiveness and safety studies observing prospectively youth with early-onset schizophrenia treated with different antipsychotics in the same study long-term would be helpful for shedding light on relative advantages and disadvantages of individual agents and/or patient factors relevant for effectiveness and safety outcomes.

6. Contributors

All authors contributed to the analysis and interpretation of data, assisted in the drafting and revisions of the manuscript, and approved the submission.

7. Funding information

This work was supported by funding from Sunovion Pharmaceuticals Inc.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Correll has been a consultant and/or advisor to or has received honoraria from: Acadia, Alkermes, Allergan, Angelini, Axsome, Boehringer-Ingelheim, Gedeon Richter, Gerson Lehrman Group, Indivior, Intracellular Therapies, Janssen/J&J, LB Pharma, Lundbeck, MedAvante-ProPhase, Medscape, Merck, Mylan, Neurocrine, Noven, Otsuka, Pfizer, Recordati, Rovi, Servier, Sumitomo Dainippon, Sunovion, Supernus, Takeda, and Teva. He has provided expert testimony for Bristol-Myers Squibb, Janssen, and Otsuka. He served on a Data Safety Monitoring Board for Boehringer-Ingelheim, Lundbeck, Rovi, Supernus, and Teva. He received royalties from UpToDate and grant support from Janssen and Takeda. He is also a shareholder of LB Pharma. Dr. Tocco, Pikalov, Deng, and Goldman are employees of Sunovion Pharmaceuticals Inc.
Risperidone and haloperidol in first-episode psychosis: a long-term randomized trial. Am J Psychiatry 162 (5), 947–953.
Shaffer, D., Gould, M.S., Brasic, J., Ambrosini, P., Fisher, P., Bird, H., Aluwahlia, S., 1983. A children’s global assessment scale (CGAS). Arch Gen Psychiatry 40 (11), 1228–1231.
Simpson, G.M., Angus, J.W., 1970. A rating scale for extrapyramidal side effects. Acta Psychiatr. Scand. Suppl. 212, 11–19.
Solmi, M., Fornaro, M., Ostinelli, E.G., Zangani, C., Croatto, G., Monaco, F., Krinitski, D., Fusar-Poli, P., Correll, C.U., 2020. Safety of 80 antidepressants, antipsychotics, anti-attention-deficit/hyperactivity medications and mood stabilizers in children and adolescents with psychiatric disorders: a large scale systematic meta-review of 78 adverse effects. World Psychiatry 19 (2), 214–232.
Stentebjerg-Olesen, M., Pagsberg, A.K., Fink-Jensen, A., Correll, C.U., Jeppesen, P., 2016. Clinical Characteristics and Predictors of Outcome of Schizophrenia-Spectrum Psychosis in Children and Adolescents: A Systematic Review. J Child Adolesc Psychopharmacol 26 (5), 410–427.
Tandon, R., Cucchiaro, J., Phillips, D., Hernandez, D., Mao, Y., Pikalov, A., Loebel, A., 2016. A double-blind, placebo-controlled, randomized withdrawal study of lurasidone for the maintenance of efficacy in patients with schizophrenia. J Psychopharmacol 30 (1), 69–77.
Thornes, P.H., 1996. Schizophrenia with childhood and adolescent onset—a nationwide register-based study. Acta Psychiatr Scand 94 (3), 187–193.
Thorup, A., Waltoft, B.L., Pedersen, C.B., Mortensen, P.B., Nordentoft, M., 2007. Young males have a higher risk of developing schizophrenia: a Danish register study. Psychol Med 37 (4), 479–484.
Zhang, C., Wang, Q., Ni, P., Deng, W., Li, Y., Zhao, L., Ma, X., Wang, Y., Yu, H., Li, X., Zhang, P., Meng, Y., Liang, S., Li, M., Li, T., 2017. Differential Cortical Gray Matter Deficits in Adolescent- and Adult-Onset First-Episode Treatment-Naïve Patients with Schizophrenia. Sci Rep 7 (1), 10267.
Zhitao, G., Yuling, L., Suqin, G., Yanhong, X., 2019. Changes of brain gray matter volume in first-episode children and schizophrenia and its relationship with cognitive function. Chin Med J. 99, 3581–3586.
Zhu, Y., Krause, M., Huhn, M., Rothe, P., Schneider-Thoma, J., Chaimani, A., Li, C., Davis, J.M., Leucht, S., 2017. Antipsychotic drugs for the acute treatment of patients with a first episode of schizophrenia: a systematic review with pairwise and network meta-analyses. Lancet Psychiatry 4 (9), 694–706.