Pharmacokinetics and Tolerability of Lurasidone in Children and Adolescents With Psychiatric Disorders

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ABSTRACT

Purpose: The aim of this study was to evaluate the pharmacokinetic (PK) profile and tolerability of lurasidone in children and adolescents with a range of psychiatric disorders.

Methods: This multicenter, open-label, single and multiple ascending-dose study of the PK profile of lurasidone (20, 40, 80, 120, and 160 mg/d) enrolled outpatients aged 6 to 17 years with a diagnosis of attention deficit/hyperactivity disorder, bipolar spectrum disorder, or other psychiatric disorder. Serial blood samples were collected for analysis of PK parameters, including Cmax, Tmax, and AUC0–24.

Findings: Exposure (Cmax and AUC0–24) to lurasidone and its active metabolites showed linear increases across the entire dose range. Slope estimates (95% CI) across the dose range studied was 0.90 ng·h/mL (0.74–1.06) for AUC0–24 and 0.70 ng/mL (0.52–0.87) for Cmax on day 10 or 12. Lurasidone exposure, after multiple-dose administration in this child and adolescent population, was similar to exposure observed at steady state in adults. The effects of dose on exposure to the 3 active metabolites of lurasidone were linear and similar after the administration of single and multiple doses. Adverse events were qualitatively similar to those reported in adults. Discontinuations due to adverse events were dose related, with doses <120 mg/d being better tolerated than higher doses, especially in younger children.

Implications: In this child and adolescent population, exposure parameters for lurasidone and its active metabolites were dose proportional in the range of 20 to 160 mg/d after the administration of single and multiple doses. These results suggest that lurasidone doses <120 mg/d were better tolerated compared with higher doses, especially in younger children. ClinicalTrials.gov identifier: NCT01620060.
hours and increased to 36 hours at steady state (day 9) in healthy volunteers. In adult subjects with schizophrenia administered single doses of 120 to 160 mg/d, the mean $t_{1/2}$ was 28.8 to 37.4 hours. In a study of multiple-dose lurasidone 120 mg/d in patients with schizophrenia or schizoaffective disorder, steady state was achieved by day 5.

Lurasidone is primarily metabolized by cytochrome P-450 (CYP) 3A4 and is not a substrate of CYP1A1, 1A2, 2A6, 4A11, 2B6, 2C8, 2C9, 2C19, 2D6, or 2E1 isozymes. The major biotransformation pathways are oxidative N-dealkylation, hydroxylation of norbornane ring, and $S$-oxidation. These pathways produce 2 pharmacologically active metabolites, ID-14283 (the exo-hydroxy metabolite) and ID-14326, which represent $\sim 25\%$ and 3% of the parent exposure, respectively, and a third minor active metabolite (ID-11614), accounting for 1%. Lurasidone does not induce or inhibit any CYP enzymes. The half-life of the primary active metabolite (ID-14283) is shorter than that of lurasidone, but ID-14283 otherwise has similar pharmacologic and in vivo characteristics.

Data on the PK profile of atypical antipsychotics in child and adolescent patients is important, especially in light of the notable increase in the rate antipsychotic medication use in this population over the past 20 years.

The primary objective of the present study was to characterize the PK and tolerability profile of single and multiple oral doses of lurasidone (20, 40, 80, 120, or 160 mg/d) in a child and adolescent population (aged 6–17 years). The secondary objective was to characterize the PK profile of lurasidone metabolites in this population.

**PATIENTS AND METHODS**

The study protocol was approved by a central institutional review board (Sterling IRB, Atlanta, Georgia), and the study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. Patients were enrolled at 8 clinical sites in the United States between June 2012 and May 2013. Before any study procedures were performed, informed consent from the parent or guardian of each child, as well as each patient’s assent (or informed consent from emancipated patients), were obtained.

**Study Participants**

Screening procedures/assessments to determine study eligibility included demographic characteristics and a complete medical history (including complete medication history), vital sign measurements (supine and standing blood pressure, heart rate, and body temperature), height and weight, complete physical examination (including a mental status examination), standard 12-lead ECG (the ECG was read by a central core laboratory, and the read results were used for determining eligibility), clinical laboratory tests (urine drug test and breath alcohol test; hepatitis B and C [only in patients without a documented history]; chemistry [including prolactin], hematology, and urinalysis; and serum pregnancy test [conducted only in female patients aged $\geq 8$ years]).

Eligible subjects were male or female outpatients between the ages of 6 and 17 years (inclusive) with a diagnosis of schizophrenia spectrum disorder, bipolar spectrum disorder, autism spectrum disorder, attention deficit/hyperactivity disorder with aggressive behavior (ie, comorbid conduct disorder or other disruptive behavior disorder), or Tourette’s syndrome. Patients were excluded if they had clinically significant alcohol or drug abuse/dependence within the previous 6 months or a positive breath alcohol test or urine screen for drugs of abuse at screening; severe cognitive impairment; clinical instability or an imminent risk for suicide or injury to self, others, or property; a clinically significant major medical condition or abnormal laboratory value or vital sign measurement; and/or pregnancy, breastfeeding, or sexual activity without the use of medically approved birth control. Psychotropic medications were tapered and discontinued at least 3 days before the administration of the first dose of lurasidone, with the exception of fluoxetine (discontinued for $\geq 28$ days) and monoamine oxidase inhibitors (discontinued for $\geq 14$ days). Inhibitors or inducers of CYP3A4 or any medication that could have significantly prolonged the QT/QTc interval was not to be taken within 28 days before study drug administration or at any point during the study and until study termination.

**Study Design**

In this multicenter, open-label, single and multiple ascending-dose study, patients were stratified into 1 of 4 age groups (6–9, 10–12, 13–15, and 16–17 years) (Figure 1). Dose cohorts were entered into the study sequentially, beginning with the 20-mg/d dose group. Sequentially escalated doses (40, 80, 120, or 160 mg/d) were administered to newly entered patients after PK and tolerability data from the previous dosing cohort

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had been reviewed. Dose escalation was stopped if a dose level was not well tolerated by a given age group. Enrollment of patients continued until a target of 12 completed patients per age group, per dose, was achieved.

All patients received a single dose of lurasidone followed by a 2-day washout period, and then once-daily dosing of lurasidone for 7 days (20- to 120-mg/d cohorts) or 9 days (160 mg/d cohort). Patients were started at the assigned dose, except for the 120 mg/d and 160 mg/d dosages, which were titrated to the assigned dose. The following dosing schemes were used: 120-mg/d cohort: day 1, 80 mg/d; days 4 and 5, 80 mg/d; and days 6 to 10, 120 mg/d; 160-mg/d cohort: day 1, 80 mg/d; days 4 and 5, 80 mg; days 6 and 7, 120 mg/d; and days 8 to 12, 160 mg/d.

In patients in the 20- to 120-mg/d cohorts, there was a screening period (from days –28 to –2), followed by a study period (from days –1 to 11), and a follow-up visit (on day 18 ± 3). During the study period, patients underwent 2 inpatient visits (between days –1 and 2, and between days 9 and 11) for dosing and study assessments, 3 outpatient visits (on days 3, 5, and 7), and a telephone contact (on day 6) for the assessment of tolerability and study drug adherence.

In the 160-mg/d cohort only, there was a screening period (from days –28 to –2), followed by a study period (from days –1 to 13), and a follow-up visit (on day 20 ± 3). During the study period, patients underwent 2 inpatient visits (between days –1 and 2, and between days 11 and 13) for dosing and study assessments, 3 outpatient visits (on days 3, 5, and 7), and a telephone contact (on day 6) for the assessment of tolerability and study drug adherence. In this cohort, patients were allowed to remain as inpatients from days –1 through 13. At the discretion of the investigator, patients were allowed to remain as inpatients from days –1 through 11.

Lurasidone was administered in the morning within 30 minutes after a breakfast of at least 350 kcal. A standardized breakfast was provided on days 1, 2, 10, and 11 (20- to 120-mg/d cohorts) or on days 1, 2, 12, and 13 (160-mg/d cohort). Ingestion of alcohol, caffeine, grapefruit or orange juice, and a total daily caloric intake in excess of 3000 kcal were prohibited during the course of the study.

Figure 1. Study design.
Sample Collection

Blood samples for PK analysis were collected predose on day 1 and over 48 hours postdose (at 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 hours) in the single-dose period, and predose on day 10 or 12 and at 0.5, 1, 2, 4, 6, 8, 12, and 24 hours postdose in the multiple-dose period of the study. Blood samples were collected from a forearm vein, primarily using an indwelling venous catheter (some samples were obtained by a single blood draw) into a 6.0-mL lavender-top Vacutainer (Becton, Dickinson and Company, Franklin Lakes, New Jersey) (or equivalent) collection tube containing EDTA as an anticoagulant. Samples were stored at −10°C to −30°C until analysis.

Determination of Plasma Concentrations of Lurasidone and Metabolites

All analyses were carried out at Covance Laboratories Inc (Madison, Wisconsin). Lurasidone and its active metabolites (ID-14283, ID-14326, and ID-11614) were extracted from the blood samples using a validated liquid–liquid extraction. After evaporation under nitrogen, the residue was reconstituted and analyzed using LC-MS/MS. The 2 inactive metabolites (ID-20219 and ID-20220) were extracted using protein precipitation. The supernatant was then diluted and analyzed using LC-MS/MS. For the measurement of the concentration of lurasidone and its active metabolites, overall assay precision (relative SD of quality-control samples) was in the range of 4.9% to 10.4%, and accuracy in terms of precision (relative SD of quality-control samples) was in the range of 4.9% to 9.4%, and accuracy in terms of relative error percentage was in the range of 4.9% to 10.4%, and accuracy in terms of relative error percentage was in the range of 4.9% to 9.4%. For the measurement of the concentrations of the 2 inactive metabolites, overall assay precision values (relative SD percentage of quality-control samples) were 4.3% to 8.6%, and accuracy values (relative error percentage) were −1.1% to 2.4%.

Pharmacokinetic Analysis

PK parameters were derived using noncompartmental methods with WinNonlin Professional version 5.2 (Pharsight Corp, Mountain View, California). All PK computations were performed using WinNonlin Professional version 5.2 or SAS version 9.2 (SAS Institute Inc, Cary, North Carolina). NONMEM version 7.1 was used for developing the population PK model and for simulating adult-population PK profiles.

The following PK parameters of lurasidone and its metabolites were estimated using actual elapsed time from dosing on days 1 and 10 (day 12 in the 160-mg/d cohort): Cmax; Tmax; Cmin at 24 hours postdose on day 10 (day 12 in the 160-mg/d cohort); AUC0–24, calculated by linear up/log down trapezoidal summation; AUClast on day 1 only, calculated by linear up/log down trapezoidal summation; AUC0–∞ on day 1 only, calculated by linear up/log down trapezoidal summation and extrapolated to infinity by the addition of the last quantifiable concentration divided by the terminal elimination rate constant (AUClast + Clast/λz); accumulation ratio of Cmax (RCmax), calculated as (Cmax on day 10)/(Cmax on day 1), when applicable; accumulation ratio of AUC0–24 (RAUC0–24), calculated as (AUC0–24 on day 10)/(AUC0–24 on day 1), when applicable; apparent terminal phase rate constant (λz) on day 1 only, determined by linear regression of the terminal points of the log-linear concentration–time curve; t1/2 on day 1 only, determined as ln2/λz; apparent oral clearance (CL/F), calculated for lurasidone only, as dose/AUC0–∞ on day 1 or dose/AUC0–24 on day 10 or 12; apparent volume of distribution at terminal phase (V/F), calculated for lurasidone only, as dose/(λz · AUC0–∞) on day 1 and dose/(λz · AUC0–24) on day 10 or 12.

Tolerability Assessments

Tolerability assessments included the frequency and intensity (mild, moderate, or severe) of spontaneously reported adverse events at all study visits. Laboratory assessments were obtained on days 1 and 10 (day 12 in the 16 mg/d cohort), and ECG was performed on day 1 (predose and 4 hours postdose) and day 10 (day 12 in the 16 mg/d cohort). In addition, vital sign measurements (body temperature, supine heart rate, and supine and standing systolic and diastolic blood pressure) were obtained in patients in the 20- to 120-mg/d cohorts at screening; on days 1, 1, 2, 3, 5, 7, 9, 10, and 11; and at follow-up (on day 18 ± 3). In patients in the 160-mg/d cohort, vital signs were obtained at screening; on days –1, 1, 2, 3, 5, 7, 11, 12, and 13; and at follow-up (on day 20 ± 3). A full physical examination was performed at screening; on day 11 (day 13 in the 160-mg/d cohort); and at follow-up (on day 18 or 20 ± 3).

Assessment of movement disorders was performed using the Abnormal Involuntary Movement Scale (AIMS),12 the Barnes Akathisia Rating Scale (BAS),13 and the Simpson–Angus Rating Scale.14 The Columbia–Suicide Severity Rating Scale15, used to systematically assess and track suicidal ideation and behavior, was
Statistical Analyses

The population for PK analysis consisted of all patients who received at least 1 dose of study drug and had at least 1 blood sample obtained for PK analysis. The sample for safety analyses included all patients who received at least 1 dose of study drug.

Lurasidone Cmax, AUClast, and AUC0–∞ (day 1), and Cmax and AUC0–24 (day 10 or 12) were the primary PK parameters; all other parameters were secondary. PK parameters were summarized by lurasidone dose using descriptive statistics. Concentrations below the lower limit of quantitation were treated as zero for the computation of descriptive statistics for days 1 and 10/12. The dose proportionality of lurasidone Cmax and AUC0–24 on day 10 (day 12 in the 160-mg/d cohort) was evaluated in all age groups combined, using a least-squares regression method. The pediatric data obtained in this study were compared with the adult-population PK data derived from a 3-compartment population PK model from several Phase I to III studies of lurasidone.

RESULTS

Patient Characteristics and Disposition

A total of 105 patients were enrolled in the study. All patients received at least 1 dose of study drug (safety population), and 102 patients underwent at least 1 complete PK assessment (PK population). Overall, 86% of patients (n = 90) completed all planned treatment periods. Fourteen subjects discontinued treatment before completing all periods, 9 (8.6%) because of adverse events. The safety sample overall was 65% male, with 78% white and 22% black patients and a mean age, weight, and body mass index of 12.7 years, 51 (18) kg, and 20.6 (4.1) kg/m², respectively. The most common diagnosis in the sample was attention deficit/hyperactivity disorder with aggressive behavior (78 patients [74%]), followed by bipolar spectrum disorder (19 [18%]), schizophrenia (5 [5%]), Tourette’s syndrome (2 [2%]), and pervasive developmental disorders/autistic spectrum disorder (1 [1%]).

Pharmacokinetic Parameters

Mean PK exposure (AUC0–∞, AUClast, and Cmax) on day 1 after single-dose lurasidone administration increased with dose from 20 to 80 mg/d (Table I). Other PK parameters (Tmax, t1/2, CL/F, and Vz/F) were not linearly increased across dose groups. Median Tmax was 2 hours. Mean CL/F and Vz/F values of lurasidone were similar across all dose groups and ranged from 317 to 346 L/h and from 6940 to 8700 L, respectively. Mean t1/2 on day 1 ranged from 16.2 to 21.3 hours across the 3 dose groups.

On day 10/12, after multiple lurasidone doses, AUC0–24 and Cmax values were linearly increased across doses from 20 to 160 mg/d. The slope estimate (95% CI) of AUC0–24 was 0.90 ng · h/mL (0.74–1.06) and of Cmax was 0.70 ng/mL (0.52–0.87) across the mean concentrations of the doses. The time courses for serum concentrations over 48 hours on day 1 and over 24 hours on day 10/12 were linearly increased across doses (Figure 2). However, the linear effect primarily occurred between the 20- and 80-mg/d doses and appeared attenuated between the 80- and 160-mg/d doses.

The median Tmax value on day 10/12 was independent of dose and was 1 to 2 hours across the 5 dose groups. Mean CL/F values of lurasidone on day 10/12 were similar across all dose groups and ranged from 256 to 323 L/h.

Median Tmax values of the 5 metabolites of lurasidone (ID-14283, ID-14326, ID-11614, ID-20219, and ID-20220) were generally similar to the lurasidone Tmax, indicating rapid metabolism. Minimal accumulations of ID-14283 and ID-14326 were observed after 10 days of lurasidone dosing over the dose range of 20 to 80 mg/d, and no obvious accumulations of ID-11614, ID-20219, or ID-20220 was observed, likely due to the relatively short t1/2 values of these metabolites. Mean PK exposure (AUC0–24, AUClast, and Cmax) of the 3 active metabolites of lurasidone (ID-14283, ID-14326, and ID-11614) were generally linearly increased across doses on days 1 and 10/12. Mean serum concentrations of metabolites ID-14283, ID-14326, ID-11614, and ID-20220 were generally lower than lurasidone concentrations on days 1 and 10/12, whereas mean serum ID-20219 concentrations were similar to lurasidone concentrations (data not shown).

The AUC0–24,ss (Figure 3) and Cmax (data not shown) values across the dose range studied (20–160 mg/d) were generally similar to values at steady state observed in the adult-population PK model; however, younger children (aged ≤9 years) appeared to have had slightly higher mean exposures, although this was not formally evaluated.
Tolerability

The most common adverse events across dose cohorts were somnolence (42%), sedation (18%), nausea (17%), and vomiting (15%) (Table II). Most (70%) adverse events were mild or moderate in intensity. The percentages of patients reporting severe adverse events were 0%, 4.0%, 15.8%, 4.0%, and 0% for the 20-, 40-, 80-, 120-, and 160-mg/d doses, respectively. All of the patients in the 120-mg/d dose cohort aged 6 to 9 years experienced moderate or severe vomiting and sedation or somnolence; therefore, after study team review, treatment in the 6- to 9-year-old patient group was not escalated to the 160-mg/d dose.

Adverse events leading to study discontinuation were vomiting (2 patients with the 40-mg/d dose; 1 with 80 mg/d), somnolence (1 with 40 mg/d; 1 with 80 mg/d), akathisia (1 with 80 mg/d), Parkinsonism (1 with 80 mg/d), blurred vision (1 with 80 mg/d), and dystonia (1 with 120 mg/d).

Two serious adverse events were reported. One patient (a 10-year-old boy) experienced Parkinsonism on day 6 of treatment with lurasidone 80 mg/d and was discontinued on day 6; the event resolved spontaneously. The second subject (a 13-year-old girl) experienced dystonia 4 days after the initiation of treatment with lurasidone 80 mg/d. The investigator assessed the event of dystonia as moderate in intensity, intermittent, and related to the study drug. At the family’s request, the patient was admitted to the hospital. On day 5, the patient was admitted to the clinical site to complete the study, and she remained an inpatient in the clinical site. While at the clinical site, the patient received a planned 120-mg/d dose of lurasidone on day 6. Study medication was discontinued on day 7 by the investigator. The subject received benztropine from days 5 through 8 for the treatment of dystonia, which resolved on day 8. No deaths during the study were reported.

A low frequency of movement disorder was reported (akathisia, 2%; Parkinsonism, 1%). At all doses and ages combined, the mean (SD) changes from baseline to day 10/12 were 0 (0.3) on the BAS and 0.1 (0.44) on the Simpson-Angus Rating Scale. On the AIMS scores for severity, incapacitation, and patient awareness of abnormal movements, the mean (SD) changes from baseline to day 10/12 were 0 (0.11), 0 (0.0), and 0 (0.11), respectively.

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<th>Table 1. Pharmacokinetic parameters for lurasidone on day 1 (single dose) and days 10 or 12 (multiple dose), mean (SD).</th>
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No clinically significant changes in laboratory test measurements, vital sign measurements, or ECG findings were reported. No clinically significant changes in weight were observed. No suicidal ideation or behavior was reported by any patient during the study.

**DISCUSSION**

Relatively few studies have reported on the PK profile of atypical antipsychotic agents in children and adolescents. The present study is the first to examine the PK profile of lurasidone in child and adolescent patients. The results suggest that lurasidone exposure, after the administration of single and multiple doses of 20 to 160 mg/d in patients aged 6 to 17 years, was generally similar to that observed in adults, although slightly higher exposure levels were observed in the 6–9-year cohort at some doses (eg, 120 mg). A linear dose effect on drug exposure was evident with lurasidone 20 to 80 mg/d on day 1 (AUC0–1, AUClast, and Cmax), and also at steady state with lurasidone 20 to 160 mg/d on day 10/12 (AUC0–24 and Cmax). Similar linear effects of dose on exposure to all 3 active metabolites of lurasidone were also generally seen after the administration of single and multiple doses.

The adverse event profile of lurasidone was qualitatively similar to that reported in adult patients; however, there was a higher frequency of somnolence in the current pediatric sample (42%; combined doses) compared with the rate reported in adults in short-term trials in schizophrenia (11%; pooled data, N = 1004). Higher rates of somnolence in children (vs adults) treated with atypical antipsychotic agents have previously been reported. There were few adverse events related to movement disorders, a finding consistent with those from the BAS, Simpson-Angus...
Rating Scale, and AIMS assessments. Adverse events were more frequent at the higher doses (120 and 160 mg/d), particularly in younger patients. In addition, discontinuations due to adverse events appeared to have been dose related; 75% of patients who discontinued treatment received lurasidone doses of ≥80 mg/d. Thus, the PK and tolerability results from this study suggest that the dose range of 20 to 80 mg/d provides adequate serum concentrations, but with improved tolerability compared with higher doses. These PK findings from a child and adolescent population suggest that the therapeutic dose range for lurasidone may be similar in this population compared to adults, although, doses ≥120 mg/d were less tolerated in the younger population. Based on these study results, the dose range of 20 to 80 mg/d has been studied in efficacy trials with lurasidone in child and adolescent populations.

Some limitations of the study design may limit the interpretation of the data. In particular, although sample sizes were sufficient for pharmacokinetic analyses, they were too small to allow for reliable conclusions about the tolerability of various doses of lurasidone in specific age groups. The diagnoses of the current patient population (74% with attention deficit/hyperactivity disorder with aggressive behavior) limit the generalizability of these results to other disorders. Finally, the study did not assess the effect of hepatic or renal impairment on lurasidone exposure in this child and adolescent population.

Figure 3. Lurasidone exposure (AUC₀-2₄,ss) in pediatric patients compared with adult patients, after multiple-dose administration of lurasidone 20 to 160 mg/d. The open circles represent the observed AUC₀-2₄,ss by age group in the present study in children. The boxplot represents the simulated distribution of AUC₀-2₄,ss values from 5000 patients using an adult population PK model. Demographic covariate vectors were sampled from the empirical distribution of the observed PK dataset in adults.
CONCLUSIONS
In the present single and multiple ascending-dose study, the first to examine the PK profile of lurasidone in a pediatric population, lurasidone and its 3 active metabolites exhibited dose-proportional exposure levels that were generally similar to what has been observed in adults. The adverse events profile was qualitatively similar to results reported in prior studies in adults. The results from this study suggest that lurasidone doses of <120 mg/d were better tolerated than were higher doses, especially in younger children.

ACKNOWLEDGMENTS
The authors thank the investigators and patients who participated in the clinical trial summarized herein. The study sponsor, with consultative input from Dr. Findling, designed the study; and the study sponsor supervised the collection, analysis, and interpretation of the data. All authors participated in the development of the manuscript, and contributed to the decision for publication. Editorial and medical writing support was provided by Edward Schweizer, MD, Paladin Consulting Group, and was funded by Sunovion Pharmaceuticals Inc. Dr. Raymond Mankoski, Sunovion Pharmaceuticals Inc, contributed to medical writing and editing.

The authors are responsible for the scientific content of this article. Dr. Jin analyzed the data for the manuscript.

CONFLICTS OF INTEREST
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<td>0</td>
<td>4 (16)</td>
<td>2 (13)</td>
<td>6 (6)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (12)</td>
<td>0</td>
<td>3 (3)</td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (12)</td>
<td>0</td>
<td>3 (3)</td>
<td></td>
</tr>
<tr>
<td>Vision blurred</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (8)</td>
<td>1 (6)</td>
<td>3 (3)</td>
<td></td>
</tr>
</tbody>
</table>

TEAE = treatment-emergent adverse event.
Lilly, Lundbeck, Merck & Co Inc, National Institutes of Health, Novartis, Noven, Otsuka, Oxford University Press, Pfizer Inc, Physicians Postgraduate Press, Rhodes Pharmaceuticals, Roche, Sage, Seaside Pharmaceuticals, Shire, Stanley Medical Research Institute, Sunovion Pharmaceuticals Inc, Supernus Pharmaceuticals, Transcept Pharmaceuticals, Validus, and WebMD. Drs. Chiu, Silva, Goldman, Jin, Pikalov, and Loebel are employees of Sunovion Pharmaceuticals Inc. The authors have indicated that they have no other conflicts of interest with regard to the content of this article.

REFERENCES

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