A Randomized, Double-Blind Study of Paliperidone Extended-Release in Treatment of Acute Schizophrenia in Adolescents

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Background: Paliperidone extended-release (ER) is approved for treatment of schizophrenia in adults but has not been evaluated in adolescents.

Methods: In this 6-week, double-blind, parallel-group study, participants ($n = 201$) aged 12 to 17 years, with a Positive and Negative Syndrome Scale (PANSS) total score of 60 to 120 were randomly allocated (1:1:1:1) to receive either placebo or one of three weight-based, fixed doses of paliperidone ER, once-daily (patients weighing 29 to $<$ 51 kg at baseline: 1.5 mg [Low], 3 mg [Medium], or 6 mg [High]; patients weighing $\geq$ 51 kg: 1.5 mg [Low], 6 mg [Medium], or 12 mg [High]).

Results: The mean (SD) change in PANSS total score from baseline to endpoint (primary efficacy variable) was significant for the paliperidone ER Medium-treatment (−17.3 [14.33]; $p < .05$; $n = 54$) but not for Low- (−9.8 [16.31]; $n = 48$) or High-treatment groups (−13.8 [15.74]; $n = 47$) versus placebo (−7.9 [20.15]; $n = 51$). By actual dose, the mean (SD) change in PANSS total score was significant for the 3-, 6-, and 12-mg doses (3 mg: −19.0 [15.45]), 6 mg: −13.8 [14.75], and 12 mg: −16.3 [15.41;] all $ps < .05$), compared with placebo (−7.9 [20.15]). The total percentages of treatment-emergent adverse events were dose-related for the three weight-based treatment groups.

Conclusions: With weight-based treatment, only paliperidone ER Medium-treatment (3–6 mg) resulted in significant improvement in symptoms of schizophrenia in adolescents, as did 3, 6, and 12 mg by actual dose strengths. Weight-based dosing of paliperidone ER in adolescents with schizophrenia does not appear to be necessary. Paliperidone ER (1.5–12 mg, once daily) was tolerable, and no new safety concerns were reported.

Key Words: Adolescents, atypical antipsychotics, paliperidone extended-release, schizophrenia

The incidence of schizophrenia increases in adolescents and is higher in boys than girls (1). In adolescent schizophrenia, patients often have worse premorbid functioning, greater duration of untreated symptoms, and, in some cases, a poorer outcome than the adult-onset form of the disorder.

Controlled studies with second-generation antipsychotics support the short-term efficacy of these drugs for treating schizophrenia in adolescents (2–5). Treatment choice is primarily guided by tolerability and safety considerations because adolescents appear to be at a higher risk than adults for developing extrapyramidal symptoms (EPS) and metabolic and endocrine abnormalities (6).

Paliperidone extended-release (ER) is an oral second-generation antipsychotic, approved for the treatment of schizophrenia and schizoaffective disorder in the United States and several countries of the European Union (7).

The primary objective of this 6-week, double-blind, placebo-controlled study was to evaluate efficacy, safety, and tolerability of three weight-based fixed doses of paliperidone ER in adolescents with acutely symptomatic schizophrenia.

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Methods and Materials

Study Population

Adolescents of either sex, aged between 12 and 17 years (inclusive), weighing at least 29 kg, diagnosed with schizophrenia (DSM-IV criteria) for at least 1 year before screening, having Positive and Negative Syndrome Scale (PANSS) total score (8,9) between 60 and 120 (inclusive) at screening and baseline (indicative of an acute, symptomatic episode of schizophrenia), with a history of at least one adequate antipsychotic trial were enrolled. The diagnosis of schizophrenia was confirmed by qualified raters who had prior experience and didactic training, provided at the investigator meeting and via online training modules, in using the Kiddie Schedule for Affective Disorders and Schizophrenia—Present and Lifetime Version, including all supplements (10). Patients should not have been a danger to themselves or others.

Exclusion criteria included DSM-IV diagnosis other than schizophrenia; substance dependence (DSM-IV criteria) in 3 months preceding screening; history of seizure, neuroleptic malignant syndrome, encephalopathic syndrome, tardive dyskinesia, insulin-dependent diabetes mellitus; and any significant or unstable systemic disease. In addition, patients with an increased risk for torsade de pointes or sudden death (investigator's assessment) and those who received either clozapine in the 2 months before, depot antipsychotic therapy within two treatment cycles before, or electroconvulsive therapy in the 3 months before baseline visit were excluded. Females who were pregnant, planning to become pregnant, or were nursing were also excluded. Prohibited concomitant medications included antidepressants, lithium, antipsychotics, psychostimulants, anticonvulsants, sedatives, β-adrenergic blockers except propranolol (for akathisia), antiparkinsonians (except benztropine and biperiden), and cholinesterase inhibitors.

An independent ethics committee or institutional review board at each study site approved the protocol. The study was conducted in accordance with the ethical principles that have their origin in the

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Declaration of Helsinki, consistent Good Clinical Practices, and applicable regulatory requirements. A Data Safety Monitoring Board monitored the safety of patients and ensured the study's integrity. All enrolled patients provided written assent, and their parents or legal guardians gave a written informed consent to permit the patient's participation.

Study Design

This parallel-group study was conducted from August 2007 to March 2009 at 35 centers in five countries. The study consisted of an up to 21-day screening and washout phase, a 6-week double-blind treatment phase with end-of-study or early-withdrawal visit and a follow-up phase for safety evaluations after 1 week.

During the double-blind treatment phase, patients were randomly assigned (1:1:1:1) to receive either placebo or one of three weight-based, fixed doses of paliperidone ER, once-daily (patients weighing 29 to $<$ 51 kg at baseline: 1.5 mg [Low], 3 mg [Medium], or 6 mg [High]; patients weighing $\geq$ 51 kg: 1.5 mg [Low], 6 mg [Medium], or 12 mg [High]). Randomization was based on a computer-generated randomization schedule balanced by using permuted blocks of treatments and was stratified by center. Randomization and treatment code were assigned by an interactive voice response system. Patients and study investigators remained blinded to the study drug during double-blind treatment phase until all patients had completed the study.

Hospitalization was optional, at investigator's discretion, for the first 3 weeks of the study. Patients who required hospitalization for longer than 3 weeks and had a Clinical Global Impression—Severity (CGI-S) scale score greater than 4, were discontinued from the study at the discretion of the investigator.

Patients who did not respond to treatment or whose symptoms worsened (defined as 20% or greater increase in PANSS total score from baseline) were discontinued on the basis of the clinical judgment of the investigator. Patients could also be withdrawn for safety reasons.

Paliperidone ER tablets were supplied in 1.5-, 3-, 6-, and 12-mg dose strengths. To maintain the study blind, all study drugs were overencapsulated for identical appearance.

Concomitant Medications

Benzodiazepines (lorazepam up to 3 mg/day or equivalent) were allowed as rescue medication, when clinically indicated (except for 8 hours before any behavioral assessment), during the screening and washout phase, and up to Day 21 of double-blind treatment phase. Beta-adrenergic blocker (only propranolol) and antiparkinsonian drugs (only benztropine 1–2 mg twice daily or biperiden 2 mg three times daily) were allowed throughout the double-blind phase for the relief of treatment-emergent akathisia and EPS. Other concomitant medications were allowed, if required to address other medical conditions (headache, constipation, upset stomach, etc.).

Efficacy Assessments

The primary efficacy variable was the change in PANSS total score from baseline to endpoint (Day 43 or last postbaseline assessment). Key secondary variables included the change from baseline to endpoint in CGI-S and Children's Global Assessment Scale (CGAS) scores. The PANSS, CGI-S, and CGAS scores were evaluated at baseline, weekly thereafter until endpoint, and at follow-up visit by qualified investigators who achieved a high interrater reliability coefficient (.874 on PANSS).

Other efficacy variables included responder rate (defined as percentage of patients with 20% or greater reduction in PANSS total score from baseline to endpoint) and change from baseline to endpoint in PANSS Marder factor scores (positive symptoms, negative symptoms, disorganized thoughts, uncontrolled hostility/excitement, and anxiety/depression) (11).

Safety Assessments

Treatment-emergent adverse events (TEAEs), vital signs, clinical laboratory tests (hematology, serum chemistry, urinalysis), electrocardiograms and height and weight were monitored. In addition, EPS were assessed using Abnormal Involuntary Movement Scale (AIMS) (12), Barnes Akathisia Rating Scale (13), and Simpson–Angus Scale (SAS) (14).

Statistical Analysis

Efficacy variables were analyzed using the last-observation-carried-forward approach in the intent-to-treat (ITT) analysis set (all randomized patients who received at least one dose of study medication and had both a baseline and at least one postbaseline assessment for any of the efficacy variables).

Planned Analyses

The primary efficacy variable was assessed using an analysis of covariance (ANCOVA) model with weight-based treatment groups and country as factors and baseline PANSS total score as a covariate. A closed testing procedure using Dunnett's test was used for the primary efficacy variable to adjust for multiple comparisons in testing paliperidone ER groups against placebo. A sensitivity analysis was performed for the primary efficacy variable using the mixed-model repeated-measures method, with an unstructured variance–covariance matrix and fixed effect for treatment group (four groups), country (five groups), baseline PANSS total score, time (Days 8, 15, 22, 29, 36, 43) and treatment-by-time interaction. CGI-S (ranked data) scale scores, CGAS scores, and the PANSS factor scores were analyzed using a similar ANCOVA model as that of primary efficacy variable. A Cochran–Mantel–Haenszel test controlling for country was used to analyze the percentages of PANSS responders. No multiplicity adjustment was performed for secondary and other efficacy analyses.

Safety was analyzed using descriptive statistics and frequency distributions for the safety variables in the safety analysis set (all randomized patients who received at least one dose of study medication). A study-specific, linear-derived QT correction formula (QTcLD) was the primary method for calculation of heart-rate-corrected QTc interval (15).

Additional and Exploratory Analyses

PANSS total scores, CGI-S scale scores, and CGAS scores were additionally analyzed by "actual dose strengths" (1.5, 3, 6, or 12 mg) of paliperidone ER received versus placebo, using ANCOVA, with "actual dose strengths" and country as factors and baseline value as a covariate, with no adjustment for multiplicity. Treatment-by-baseline body weight category ($<$ 51 kg and $\geq$ 51 kg) interaction was explored for weight-based treatment groups, using an ANCOVA model for change from baseline in PANSS total score at endpoint with treatment, country, and baseline body weight category as the fixed-effects, and treatment-by-baseline body weight category interaction, and baseline PANSS total score as a covariate.

Post Hoc Analyses

Suicidality was assessed using the Columbia Classification Algorithm of Suicide Assessment code (16), assigned to each potentially treatment-emergent suicide-related event, by blinded clinicians. Effect of paliperidone ER on glucose homeostasis was assessed using homeostatic model assessments (HOMA) (17).