# Efficacy and Safety of Paliperidone Extended Release in Adolescents With Schizophrenia: A Randomized, Double-Blind Study

Adam J. Savitz, MD, PhD, Rosanne Lane, MAS, Isaac Nuamah, PhD, Srihari Gopal, MD, MHS, David Hough, MD

**Objective:** To evaluate the efficacy, safety, and tolerability of paliperidone extended release (ER) relative to aripiprazole in adolescent schizophrenia.

**Method:** In this multicenter, double-blind, phase 3 study (screening [≤3 weeks], with an acute treatment period [8 weeks] and a maintenance period [18 weeks]), adolescents (12–17 years old) with schizophrenia (*DSM-IV* diagnosis; Positive and Negative Symptom Score [PANSS] total score 60–120) were randomized (1:1) to once-daily paliperidone ER (6 mg per day [days 1–7], flexibly dosed 3, 6, or 9 mg per day from week 2 to end of study [EOS]), or to aripiprazole (2 mg per day [days 1 and 2], 5 mg per day [days 3 and 4], 10 mg per day [days 5–7], flexibly dosed 5, 10, or 15 mg per day [week 2 to EOS]).

**Results:** Overall, 76% of enrolled patients (174/228) completed the study (paliperidone ER, 75% [85/113]; aripiprazole, 77% [89/115]). There was no significant difference in change in PANSS total scores from baseline to day 56 (primary endpoint) (paliperidone ER versus aripiprazole, −19.3 [13.80] versus −19.8 [14.56], $p = .935$); responders, 67.9% versus 76.3%, $p = .119$) and day 182 (−25.6 [16.88] versus −26.8 [18.82], $p = .877$; responders, 76.8% versus 81.6%, $p = .444$). All secondary endpoints (maintenance of clinical stability, change in PANSS-negative symptoms, Clinical Global Impression–Severity, and Personal and Social Performance scores) were similar in both treatment groups. The most common (>10% patients) treatment-emergent adverse events for paliperidone ER were akathisia, headache, somnolence, tremor, and weight gain, and for aripiprazole were worsening of schizophrenia and somnolence. Extrapyramidal symptoms including dystonia and hyperkinesia occurred in >2% in paliperidone ER–treated versus aripiprazole-treated patients.

**Conclusion:** Paliperidone ER did not demonstrate superior efficacy to aripiprazole in treating adolescent schizophrenia. Both drugs showed clinically meaningful improvements in symptom and functional measurements and were generally tolerable.

**Clinical Trial Registration Information**—An Efficacy and Safety Study of Extended-Release (ER) Paliperidone in Adolescent Participants With Schizophrenia; http://clinicaltrials.gov; NCT01009047.

**Key Words:** aripiprazole, flexibly dosed, paliperidone extended-release, schizophrenia

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It is estimated that 1 in 10,000 children and adolescents worldwide develop schizophrenia according to *DSM-IV* criteria.[1] Within the pediatric age group, schizophrenia is most commonly diagnosed in adolescents with an estimated prevalence of 0.5% in the age group of 13 to 17 years[2,3] and symptoms generally similar to those in adults.[4] An earlier age of onset for schizophrenia, particularly prepubertal, is associated with a poorer prognosis and greater impact of the disease on personality and relationship development, cognitive functioning, educational and work attainment, and social functioning.[1,5] Moreover, adolescent-onset schizophrenia is a lifelong illness.

Newer second-generation antipsychotics, approved for the treatment of schizophrenia in adults, offer a potential new treatment option for adolescents. These atypical antipsychotic medications are as effective as typical antipsychotic medications with respect to clinical efficacy and have a preferred side effect profile and often a lower dropout rate from clinical trials, all of which is important, as treatment adherence is the key to successful remission of psychotic symptoms and may prevent relapse of illness.[6] However, numerous studies in adolescents have also shown clinically relevant adverse effects such as weight gain, metabolic disorders, prolactin changes, and extrapyramidal symptoms (EPS) with these therapeutic agents often at higher rates than seen in adults.[7-13] Hence, there is a need for rigorous and critical assessment of antipsychotic drugs used for treating schizophrenia in adolescents.

Paliperidone extended release (paliperidone ER), an active metabolite of risperidone, has been approved in the United States, European Union, and in many other countries for treating schizophrenia in adults and adolescents.[14] The efficacy and safety of paliperidone ER as well as risperidone in adolescents with schizophrenia compared to placebo has been demonstrated in 6-week placebo-controlled studies.[15,16]

Supplemental material cited in this article is available online.

Although the long-term efficacy and safety of risperidone are already established,[15] there have been few studies conducted to address the long-term efficacy and safety of paliperidone ER in adolescents or to directly compare other second-generation oral antipsychotics in this patient population.[17]

The objective of this study was to demonstrate the long-term efficacy and safety of paliperidone ER in adolescents with schizophrenia compared to a commonly prescribed atypical antipsychotic agent, aripiprazole, also approved to treat adolescents with schizophrenia in the United States and the European Union (Otsuka, Abilify product information, 2012). Studies conducted in adolescents with schizophrenia have found aripiprazole to be safe and generally well tolerated.[18,19] In contrast, other potential active comparators such as olanzapine, quetiapine, and ziprasidone are either not approved in the adolescent schizophrenia population or present unacceptable potential safety and tolerability problems. The hypothesis of the current study was that paliperidone was superior to aripiprazole in treating adolescents with schizophrenia.

# METHOD

## Study Population

Boys and girls (inpatients or outpatients at screening), aged 12 to 17 years (inclusive) with a body weight of ≥29 kg, diagnosed with symptoms of schizophrenia (*DSM-IV* criteria) for ≥1 year before screening, Positive and Negative Symptom Score (PANSS) total score of 60 to 120 (inclusive) at screening, and with ≥1 prior adequate treatment with antipsychotic medication, were enrolled. Diagnosis of schizophrenia was established using the Kiddie-Schedule for Affective Disorders and Schizophrenia–Present and Lifetime Version (K-SADS-PL) including all supplements.[20] Patients were required to have at least moderate symptoms (entry criteria of PANSS total score 60–120), and the clinician needed to believe that the patient was not receiving optimal treatment from his or her medication.

Exclusion criteria included a *DSM-IV* diagnosis of bipolar disorder (BD), major depressive disorder (MDD), schizoaffective disorder, schizophreniform disorder, autistic disorder, mental retardation, or primary substance-induced psychotic disorder; dissociative disorder or substance dependence (*DSM-IV* criteria) in 3 months before screening; history of seizure disorder, neuroleptic malignant syndrome, encephalopathic syndrome, tardive dyskinesia, or insulin-dependent diabetes mellitus; receiving clozapine (2 months before screening), depot antipsychotic therapy within 2 treatment cycles before screening, or electroconvulsive therapy (3 months before baseline visit); and sexually nonabstinent girls who were pregnant, nursing, or of childbearing capacity. Other comorbid disorders such as attention-deficit/hyperactivity disorder (ADHD) were allowed, as long as the diagnosis of schizophrenia was the primary diagnosis and the comorbid disorders did not require medications.

Prohibited medications included oral and injectable antipsychotics (except for the study drugs); psychostimulants or other dopamine agonists (e.g., dextroamphetamine, methylphenidate); certain sedatives (including barbiturates), hypnotics, or anxiolytics; mood stabilizers or anticonvulsants (e.g. lithium, phenytoin) used for any indication; electroconvulsive therapy; and any medications known to be a moderate or potent inhibitor or inducer of CYP3A4 or CYP2D6 that may cause a substantial increase or decrease in plasma concentrations of either aripiprazole or paliperidone (including but not limited to carbamazepine, valproic acid, paroxetine, fluoxetine, fluvoxamine, nefazodone, ketoconazole, itraconazole, or quinidine).

Allowed medications included psychotropic medications such as antidepressants (except enzyme inhibitors); certain benzodiazepines (up to pre-specified limits depending on the stage of the trial); and non-benzodiazepine hypnotics, anticholinergics, topical antifungal agents, antihistamines, anti-inflammatory drugs except systemic corticosteroids, histamine-2 ($H_2$) blockers, and rescue medications for the treatment of restlessness, agitation, insomnia, or extrapyramidal symptoms.

During the screening period, all antipsychotic medications were required to be stopped at least 5 half-lives before the baseline assessment. Benzodiazepines and other allowed medications could be used during the screening period for agitation.

An independent ethics committee or institutional review board at all sites approved the protocol. The study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki, consistent Good Clinical Practices, and applicable regulatory requirements. All patients provided written assent, and their parents/guardians gave written informed consent to participate in the study.

## Study Design

This double-blind (DB) phase 3 study was conducted from November 2009 to June 2012 at 41 centers in 7 countries (India, Romania, Russia, Slovakia, Spain, Ukraine, and the United States). It consisted of a 3-week or less screening and washout period, followed by an 8-week DB acute treatment period and an 18-week DB maintenance period (total duration, 26 weeks). The washout period was flexible to minimize adverse consequences to the patient. The actual duration of the washout period for any given patient was such that at baseline, the patient would not have received any prohibited drugs for 5 half-lives and would not have been intoxicated with alcohol or other substance of abuse for at least 5 days. All patients active at the end of the acute treatment period were directly transitioned to the DB maintenance period regardless of response during the DB acute treatment period. There was no change of antipsychotic medications from the DB acute treatment period to the DB maintenance period. Investigators were able to withdraw patients at any point due to lack of response and were encouraged to consider doing so if the PANSS total score increased >20% from baseline. No response criterion was required to continue to the maintenance phase. Investigators were to follow routine clinical practice and to allow partial responders to continue in the study.

During the DB acute treatment period, patients were randomized (1:1 ratio) to receive once-daily paliperidone ER orally (6 mg per day [days 1–7], flexibly dosed 3, 6, or 9 mg per day from day 8 to end of study [EOS]) or aripiprazole (2 mg per day ([days 1 and 2], 5 mg per day [days 3 and 4], 10 mg per day [days 5–7], flexibly dosed 5, 10, or 15 mg per day from day 8 to EOS). The randomization was based on a computer-generated randomization schedule balanced by using permuted blocks of treatments and stratified by center. Since this was a flexibly dosed study, the mode dose for individual patients was calculated to determine the most commonly used doses.

## Efficacy Assessments

The primary endpoint was mean change in the PANSS total score (based on last-observation-carried-forward [LOCF]) from baseline to day 56. Secondary endpoints included maintenance of clinical stability (defined as ≥20% improvement from baseline in the PANSS total score and Clinical Global Impression–Severity [CGI-S] score ≤4 at days 56 and 182, with no hospitalizations due to psychiatric