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Relapse prevention study of paliperidone extended-release tablets in Chinese patients with schizophrenia☆,☆☆,★

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ABSTRACT

Objectives: The objective of this study was to evaluate the long-term efficacy, safety, and tolerability of paliperidone extended-release (pali ER), in Chinese patients with schizophrenia.
Methods: In this parallel-group, relapse prevention, phase-3 study (screening [14-day], pali ER open-label run-in [8-week] and stabilization [6-week] phases, and double-blind (DB) treatment [variable duration], and open-label extension phases [24-week]), 136/201 patients with schizophrenia were randomized (1:1) to pali ER (3–12 mg) or placebo during the DB phase.
Results: Final analysis showed that, out of 135 patients in ITT (DB) population, 71 (52.6%) had a relapse event, 45 (33.3%) were ongoing at the time the study was stopped, and 19 (14.1%) discontinued from the DB phase. Time to relapse (primary endpoint) favored pali ER (hazard ratio = 5.23 [95% CI: 2.96, 9.25], $p < 0.0001$). Rate of relapses (55/71 [77.5%] placebo; 16/64 [25%] pali ER) and secondary endpoints (change from baseline in Positive And Negative Syndrome Scale [PANSS] and Clinical Global Impression — Severity Scores) were significantly lower ($p < 0.001$) in pali ER group vs placebo, in favor of pali ER. More psychiatric-related treatment-emergent adverse events (TEAEs) occurred in placebo- (21.1%) than pali ER group (10.9%). Most common (>3%) TEAEs in placebo group were insomnia and schizophrenia (8.5% each), while in pali ER group were aggression and akathisia (4.7% each), and schizophrenia, tremor, nausea, amenorrhea, and salivary hypersecretion (3.1% each). All serious TEAEs were psychiatric-related (schizophrenia, aggression, completed suicide, auditory hallucination, suicide attempt) and more frequent in placebo- (11.3%) versus pali ER group (3.1%). Death and tardive dyskinesia-related discontinuation (n = 1 each) occurred in placebo group. Body weight increase from run-in baseline was greater in pali ER group (mean increase: 3.90 kg) versus placebo (mean increase: 2.05 kg).
Conclusions: This study confirms the findings from earlier pali ER global relapse-prevention studies and demonstrates that pali ER treatment (3–12 mg) is efficacious over the long-term and significantly delays relapse in Chinese patients with schizophrenia. No new safety signals were detected in this population.

1. Introduction

Schizophrenia accounts for 55% of all psychotic disorders in the adult Chinese population (Li, 2011). Second generation antipsychotics (SGAs) are preferred as the primary treatment option in patients with schizophrenia, as they are effective in the treatment of both positive and negative symptoms (Csernansky et al., 2002; Kane et al., 2002; Lehman et al., 2004; Schooler et al., 2005; Taylor, 2003) and associated with fewer motor adverse effects. In China, the use of SGAs for the treatment of schizophrenia has increased from 53% in 1999 to 77% in 2008 and oral antipsychotics like olanzapine, quetiapine and risperidone are widely used (An et al., 2010).

Schizophrenia is a chronic condition requiring consistent, long-term treatment; it is common for patients to discontinue medication on their own (Kramer et al., 2007). Non-adherence to oral medications results in

Abbreviations: AE, Adverse event; AIMS, Abnormal involuntary movement scale; ANCOVA, Analysis of covariance; BARS, Barnes akathisia rating scale; BL, Baseline; BMI, Body mass index; CGI-S, Clinical global impression severity; CI, Confidence interval; C-SSRS, Columbia suicide severity rating scale; DB, Double blind; DSM-IV-TR, Diagnostic and statistical manual of mental disorders, 4th version; ECG, Electrocardiogram; EPS, Extrapyramidal symptom; ER, Extended release; HR, Hazards ratio; IDMC, Independent Data Monitoring Committee; ITT, Intent-to-treat; LOCF, Last observation carried forward; pali ER, Paliperidone extended-release; PANSS, Positive and negative syndrome scale; PSP, Personal and social performance scale; RI, Run in; SAS, Simpson–angus rating scale; SD, Standard deviation; SE, Standard error; SGAs, Second generation antipsychotics; ST, Stabilization; TEAEs, Treatment-emergent adverse events.

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increased relapse rates, which can subsequently lead to disease progression or even treatment failure (Emsley et al., 2008b). Thus, adherence to long-term treatment of schizophrenia remains a major treatment concern.

Paliperidone extended-release (pali ER), a SGA designed to deliver paliperidone at a relatively constant rate over a 24-hour period, is approved in the United States, European Union, and many other countries for the treatment of schizophrenia in adults (Invega product information, 2007). Pali ER is also approved in the United States and European Union as mono- and adjunctive therapy for the treatment of schizoaffective disorder (Invega product information, 2007). In completed clinical studies, pali ER 3 to 15 mg/day is efficacious and generally well-tolerated (Emsley et al., 2008a; Kane et al., 2007; Kramer et al., 2010). Asians generally accounted for a very small (≤5%) percentage of these study populations. It is well established that race and ethnic differences can influence treatment response, as well as the type and the extent of adverse events associated with antipsychotic treatment (Banerjee, 2012; Bhugra and Bhui, 1999; Coppola et al., 2012; Versola-Russo, 2006; Williams and Earl, 2007). Consequently, studies conducted in populations composed primarily of specific ethnic backgrounds or races are needed. The current study was hence conducted to confirm the efficacy of pali ER in delaying time to relapse and its overall safety in Chinese patients with schizophrenia.

2. Methods

2.1. Patients

The study was conducted at 18 sites within the People's Republic of China (from June 2011 to April 2013). Patients of either sex, aged ≥18 years, diagnosed with schizophrenia based on Diagnostic and Statistical Manual of Mental Disorders, 4th version (DSM-IV-TR) for at least 1 year before screening, and a Positive and Negative Syndrome Scale (PANSS) total score between 70 and 120 (inclusive), at screening and baseline were eligible for enrollment.

Major exclusion criteria for the study included: drug dependence (excluding nicotine and caffeine dependence) within 6 months before screening according to DSM-IV, history of cardiovascular, respiratory, neurologic, renal, hepatic, endocrine, or immunologic diseases, presence of circumstances that may increase the risk of the occurrence of torsade de pointes or sudden death, heart rate < 50 bpm, presence of congenital prolongation of the QT interval or demonstration of repeated prolonged QTc Fridericia interval > 450 ms in >1 electrocardiogram (ECG), neuroleptic malignant syndrome and hypersensitivity to risperidone, paliperidone, or their excipients. Patients treated with clozapine for treatment refractory or treatment resistant schizophrenia, monoamine oxidase inhibitor antidepressants within 4 weeks before screening, depot antipsychotic drugs within 120 days, paliperidone palmitate within 10 months or electroconvulsive therapy within 60 days before screening, and pregnant and lactating women were all excluded from the study.

The 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 Declaration of Helsinki, consistent Good Clinical Practices, and applicable regulatory requirements. All participants provided written informed consent.

2.2. Study design, randomization, and blinding

This phase 3, placebo-controlled, parallel-group study consisted of 5 phases (Fig. 1): screening phase of up to 14 days; 8-week open-label, run-in (RI) phase; 6-week open-label stabilization (ST) phase; double-blind (DB) treatment phase of variable length; and a 6-month open-label extension phase. Data from the open-label extension phase will be reported separately.

During the 8-week RI phase, eligible patients received flexibly-dosed pali ER once daily in a dose range of 3 to 12 mg: an initial dose of 6 mg was gradually increased by 3 mg/day after 5 days and decreased as deemed necessary by the investigator based on patient's tolerability. Patients were recommended to be hospitalized for 8 days from the start of this phase and followed as outpatients thereafter if the investigator judged them not to be of significant risk for suicidal or violent behavior and their Clinical Global Impression — Severity (CGI-S) score was 4 (moderately ill) or less. Only those patients capable of maintaining a stable dose regimen in the last week of this phase and with PANSS score <70, and prespecified individual PANSS scores (P1 [delusions], P2 [conceptual disorganization], P3 [hallucinatory behavior], P6 [suspiciousness/persecution], P7 [hostility], and G8 [uncooperativeness]) ≤4 were eligible to enter the ST phase during which they received the established fixed dose of pali ER.

Patients who completed the RI and ST phases of the study and met the following criteria, entered the DB phase: no changes in dose in ST phase, no deliberate self-injury or violent behavior resulting in clinically significant injury to self or another person or property damage, no psychiatric hospitalization (involuntary or voluntary admission to a psychiatric hospital for decompensation of the patient's schizophrenic symptoms, PANSS score < 70) and prespecified individual PANSS scores (P1, P2, P3, P6, P7 and G8) ≤4. Patients were randomized 1:1 to receive either pali ER (at the previously established dose) or placebo via an online interactive web-based response system and/or interactive voice response system.

2.3. Study medication

In the DB phase, pali ER or matching placebo tablets were overencapsulated; pali ER tablets were provided at once daily dose of 3, 6, 9 or 12 mg. These doses were derived from 3 or 6 mg tablets with 1 to 2 tablets depending on dose. In the RI and ST phases, pali ER tablets without overencapsulation were provided.

2.4. Efficacy

The primary efficacy endpoint was the time-to-first relapse during the DB phase. Relapse was defined as one or more of the following: (1) hospitalization for symptoms of schizophrenia (involuntary or voluntary admission), (2) deliberate self-injury or violent behavior, or suicidal or homicidal ideation that was clinically significant, (3) 25% increase in PANSS total score for patients who scored >40 at randomization, or a 10-point increase for patients who scored ≤40 at randomization for two consecutive assessments (within 1 week), and (4) increase in prespecified individual PANSS items scores (P1, P2, P3, P6, P7 and G8) to ≥5 for patients whose score was ≤3 at randomization, or to ≥6 for patients whose score was 4 at randomization for two consecutive assessments (within 1 week). Secondary efficacy endpoints included change from double-blind baseline to endpoint in PANSS total score, CGI-S and Personal and Social Performance Scale (PSP).

2.5. Safety

Safety assessments included extrapyramidal symptom (EPS) rating scales (Abnormal Involuntary Movement Scale [AIMS], Barnes Akathisia Rating Scale [BARS], the Simpson–Angus Rating Scale [SAS]), treatment-emergent adverse events (TEAEs), clinical laboratory tests, 12-lead electrocardiograms, vital signs measurement and physical examination findings.

The Columbia Suicide Severity Rating Scale (C-SSRS) was administered to assess for suicidal ideation and behavior.