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Paliperidone palmitate maintenance treatment in delaying the time-to-relapse in patients with schizophrenia: A randomized, double-blind, placebo-controlled study ☆

David Hough [a,*], Srihari Gopal [a], Ujjwala Vijapurkar [a], Pilar Lim [a], Margarita Morozova [b], Mariëlle Eerdekens [c]

[a] Johnson & Johnson Pharmaceutical Research & Development, L.L.C., Raritan, New Jersey, USA
[b] Mental Health Research Center, Moscow, Russia
[c] Johnson & Johnson Pharmaceutical Research and Development, Division of Janssen Pharmaceutica N.V., Beerse, Belgium

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ABSTRACT

Objective: We assessed efficacy and tolerability of the injectable atypical antipsychotic paliperidone palmitate in delaying time-to-relapse in adults with schizophrenia.
Methods: Eligible patients (Positive and Negative Syndrome Scale [PANSS] total score<120) were transitioned from previous antipsychotics to paliperidone palmitate during a 9-week, open-label phase. Patients received the first 2 intramuscular injections of paliperidone palmitate (50 mg eq) one-week apart, then subsequent injections (25, 50, or 100 mg eq, flexibly-dosed), once-monthly. Stable patients (PANSS total score ≤75) continued into the 24-week maintenance phase. At maintenance phase endpoint, stabilized patients were randomized (1:1 ratio) to either continue paliperidone palmitate (at stabilized dose) or begin placebo in the variable-duration, double-blind phase.
Results: The preplanned interim analysis (conducted after 68 relapse events) included 312 patients: mean age = 40 years, 55% men, 66% white, and mean transition baseline PANSS total score (SD): placebo, 69.5 (16.89); paliperidone palmitate, 69.3 (17.39). Time-to-relapse (primary endpoint) favored paliperidone palmitate ($p<0.0001$, log-rank test) at interim and final analysis ($n=408$). The hazard ratio (placebo/paliperidone palmitate) at the final analysis was 3.60 (95% CI: 2.45, 5.28). Treatment-emergent adverse event rates (final analysis set) were: 67% for transition and maintenance phases, and 45% (placebo) and 44% (paliperidone palmitate) for the double-blind phase. Across phases, the incidence of glucose-related adverse events was low (≤4%), while mean weight increased by 1.9 kg for paliperidone palmitate and remained unchanged for placebo patients. Injection site tolerability was comparable between groups.
Conclusion: Paliperidone palmitate significantly delayed time-to-relapse compared with placebo and presented no new safety signals.

1. Introduction

The chronic nature of schizophrenia, coupled with cognitive impairment, lack of insight, and frequent relapse of acute psychotic symptoms results in an illness that offers significant treatment challenges. Poor adherence to, or discontinuation of, potentially effective antipsychotic therapy substantially increases the risk for relapse in patients with schizophrenia (Keith et al., 2004). Long-acting injectable (LAI) antipsychotics offer the opportunity to establish long-

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* Corresponding author. Johnson & Johnson Pharmaceutical Research & Development, L.L.C., 1125 Trenton–Harbourton Road, Titusville, New Jersey 08560, USA. Tel.: +1 609 730 4415; fax: +1 609 730 2291.
E-mail address: DHough2@its.jnj.com (D. Hough).

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term control in patients (Kucukalic et al., 2007; Nasrallah and Lasser, 2006). They provide consistent drug levels that are sustained over weeks and missed injections are immediately known, permitting the medical team the opportunity for intervention (Kane, 2007; Nasrallah and Lasser, 2006).

Paliperidone palmitate, an atypical antipsychotic agent, is the palmitate ester of paliperidone and is designed to be administered as a once-monthly intramuscular injection. The efficacy and safety of the oral extended-release formulation in the acute and maintenance treatment of schizophrenia have been demonstrated (Marder et al., 2007; Kane, 2007; Kramer et al., 2007). Several studies have also demonstrated efficacy and safety of paliperidone palmitate in patients with acute schizophrenia (Nasrallah et al., 2008a; Pandina et al., submitted for publication). Following an initial dosing regimen administered in the deltoid, patients rapidly and consistently obtain therapeutic plasma levels (Samtani et al., 2009a,b) and plasma concentrations can be subsequently maintained using either deltoid or gluteal injections (Hough et al., 2009; Samtani et al., 2009c). Oral supplementation is not required during dosing (Samtani et al., 2009a,b). Paliperidone palmitate was recently approved in the United States for the acute and maintenance treatment of schizophrenia. The current double-blind randomized study evaluated its efficacy and safety in delaying time-to-relapse in patients with schizophrenia and supports the maintenance indication.

2. Materials and methods

2.1. Patients

Men and women, aged 18–65 years (inclusive), with a diagnosis of schizophrenia (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition [DSM-IV], criteria) for at least 1 year before screening, and a Positive and Negative Syndrome Scale (PANSS) total score below 120, at screening and baseline were enrolled. Both symptomatic and stable patients were eligible.

Major exclusion criteria were: primary, active DSM-IV (American Psychiatric Association, 1994) diagnosis other than schizophrenia; significant risk of suicidal or aggressive behavior; history of substance dependence within 3 months before screening; significant medical conditions, or treatment resistance (failure to respond to 2 adequate trials, minimum 4 weeks of antipsychotic medications); use of any 4-week depot antipsychotic within 28 days or risperidone LAI within 5 weeks before screening; use of oral antipsychotics, mood stabilizers, or other prescription or over-the-counter drugs within 2 days before baseline; or involuntary admission to a psychiatric hospital. Women were excluded if pregnant, nursing, or planning to become pregnant.

The independent ethics committee or institutional review board at each study site approved the protocol and the study was conducted in accordance with the ethical principles in the Declaration of Helsinki, consistent Good Clinical Practices and applicable regulatory requirements. All participants provided written informed consent.

2.2. Study medication

Doses of paliperidone palmitate can be expressed both in terms of milligram equivalents (mg eq) of the pharmacologically active fraction, paliperidone, and in milligrams (mg) of paliperidone palmitate. Thus, the doses expressed as "paliperidone palmitate 25, 50, or 100 mg eq" equate to 39, 78, and 156 mg, respectively, of paliperidone palmitate.

Paliperidone palmitate was provided as prefilled syringes containing 25, 50, or 100 mg eq paliperidone palmitate (or matching placebo [Intralipid® 20% injectable emulsion]). Injections were administered in the gluteal muscle, alternating the location side (left or right) at each injection.

Oral tolerability medication (paliperidone extended release [ER], 3 mg) was administered for 4 days during the screening period to patients without previous documented exposure to risperidone or paliperidone.

2.3. Study design, randomization, and blinding

This study, conducted from March 4, 2005 to February 16, 2007 (up through the double-blind phase), included patients from 56 centers in 9 countries. There were 5 phases (Fig. 1): screening and oral tolerability testing phase (up to 7 days), a 9-week open-label transition phase during which eligible patients (PANSS total score <120) were switched from their previous antipsychotic and received once-monthly injections of flexibly-dosed paliperidone palmitate (25, 50, or 100 mg eq) after an initial regimen of paliperidone palmitate 50 mg eq on days 1 and 8; a 24-week open-label maintenance phase during which stable patients (PANSS score ≤ 75 at week 9) received flexibly-dosed paliperidone palmitate (25, 50, or 100 mg eq) for the first 12 weeks, with dose adjustments based on patient's clinical need, followed by 12-weeks of treatment at the established maintenance dose; a variable-duration, event-driven double-blind phase, when stabilized patients with PANSS total score ≤ 75 and selected PANSS item scores ≤ 4 (P1 [delusions], P2 [conceptual disorganization], P3 [(hallucinatory behavior)], P6 [suspiciousness/persecution], P7 [hostility], G8 [uncooperativeness] and G14 [poor impulse control]) were randomized in a 1:1 ratio (via a sponsor-prepared computer-generated randomization scheme; assigned by an interactive voice-response system) to receive either paliperidone palmitate (at the previously stabilized dose), or placebo; and an optional 52-week open-label extension phase.

Patients remained in the double-blind phase until they experienced a relapse, withdrew from the study, or until the study was completed. An interim analysis for efficacy was preplanned to occur after 68 relapse events (as defined in Section 2.5). We report here the results through the end of the double-blind phase.

An Independent Data Monitoring Committee (IDMC) performed ongoing safety monitoring, evaluated efficacy at the interim analysis, and provided recommendations about modifying, stopping, or continuing the study.

2.4. Assessments

The primary efficacy variable was the time-to-first relapse during the double-blind phase. Relapse was defined as one or more of the following: (1) hospitalization for symptoms of schizophrenia (involuntary or voluntary admission), (2) 25% increase in PANSS total score for two consecutive assessments for patients who scored >40 at randomization, or a 10-point increase for patients who scored ≤ 40 at randomization,