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A double-blind study of paliperidone palmitate and risperidone long-acting injectable in adults with schizophrenia

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ABSTRACT

This 13-week double-blind study was designed to assess noninferiority of the recently approved (in the U.S.) injectable atypical antipsychotic paliperidone palmitate (PP) versus risperidone long-acting injectable (RIS-LAI) in adult patients with schizophrenia. Patients (N = 1220) were randomized (1:1) to either a) PP: deltoid injections on day 1 (150 mg eq.), day 8 (100 mg eq.), and once-monthly flexible dosing as deltoid or gluteal injections on day 36 (50 mg eq. or 100 mg eq.) and day 64 (50 mg eq. or 100 mg eq. or 150 mg eq.) or b) RIS-LAI: gluteal injections days 8 and 22 (25 mg), days 36, 50 (25 or 37.5 mg) and days 64, 78 (25, 37.5 or 50 mg). RIS-LAI-treated patients received oral supplementation with RIS 1–6 mg/day (days 1 to 28), and PP-treated patients received oral placebo. The safety analysis set (n = 1214) included 58% men, 78% white, with mean (SD) baseline PANSS total score: PP, 84.1 (12.09); and RIS-LAI, 83.6 (11.28). Mean (SD) change from baseline to endpoint in PANSS total score decreased similarly in both groups; PP (−18.6 [15.45]) and RIS-LAI (−17.9 [14.24]). PP treatment was noninferior to RIS-LAI (point estimate [95% CI]: 0.4 [−1.62;2.38], per-protocol analysis set [primary analysis]). The tolerability and safety of PP was generally similar to RIS-LAI with no new safety or tolerability findings.

1. Introduction

The intramuscular (i.m.) long-acting injectable (LAI) formulations of antipsychotic medications were developed to enhance treatment adherence and improve the long-term management of schizophrenia (Keith et al., 2004; Nasrallah, 2007). Due to their sustained delivery, LAIs help reduce relapse secondary to non-adherence and provide clinical stability necessary for psychosocial interventions (Kane et al., 2003; Nasrallah, 2007). Despite frequent non-adherence to oral medications and subsequent relapse, LAIs are not commonly used. The rates vary across countries but only 30% or fewer patients are prescribed an LAI (Patel et al., 2009; Barnes et al., 2009). Suboptimal knowledge of the antipsychotic LAIs is possibly associated with the underutilization of these formulations in many countries, highlighting the role of stigma and the need for more research (Kane and Garcia-Ribera, 2009; Patel et al., 2009).

Risperidone-LAI (RIS-LAI) was the first atypical antipsychotic available as an injectable formulation. The recommended dosage for patients with schizophrenia is 25 to 50 mg every 2 weeks (RISPERDAL® CONSTA® Prescribing Information), with oral supplementation for first 3 weeks of treatment. Paliperidone palmitate (PP) is the palmitate ester of paliperidone (9-hydroxy-risperidone), the active metabolite of risperidone. PP is a once-monthly atypical antipsychotic LAI approved in the US for the acute and maintenance treatment of schizophrenia in adults and is formulated to provide sustained plasma concentrations of paliperidone, the pharmacologically active fraction (Invega® Sustenna™ Prescribing Information). The deltoid initiation regimen for PP allows rapid attainment of therapeutic concentrations (Samtani et al., 2009), precluding any need for oral supplementation. PP at doses of 25–150 mg eq. demonstrated efficacy and was generally safe and tolerable in previous double-blind, placebo-controlled studies in adult patients with schizophrenia (Hough et al., 2009; Pandina et al., 2010; Gopal et al., 2010).

Both PP and RIS-LAI are effective and tolerated in the treatment of schizophrenia (Hough et al., 2009, 2010; Kane et al., 2003; Keks et al.,

Abbreviations: AIMS, Abnormal Involuntary Movement Scale; ANCOVA, analysis of covariance; BMI, body mass index; CGI-S, Clinical Global Impression—Severity; CI, confidence interval; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; EPS, extrapyramidal symptoms; IEC, Independent Ethics Committee; IRB, Institutional Review Board; ITT, intent-to-treat; LAI, long-acting injectable; PANSS, Positive and Negative Syndrome Scale; PK, pharmacokinetic; PP, paliperidone palmitate; PSP, Personal and Social Performance Scale; RIS, risperidone; SDS, Schedule for Deficit Syndrome; TEAEs, treatment-emergent adverse events; VAS, Visual Analog Scale.

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2007; Kramer et al., 2010; Pandina et al., 2010). In an earlier study (Fleischhacker et al., 2009) that compared efficacy of these two LAIs, adequate plasma levels of paliperidone were not achieved for PP as a result of an inadequate initiation dosing regimen with PP (initiated as gluteal injections of 50 mg eq. on days 1 and 8). Hence, PP did not demonstrate noninferiority to RIS-LAI in that study.

A direct comparison between PP and an already approved LAI atypical antipsychotic provides valuable comparative information on efficacy, safety, and tolerability of the agents in the treatment of schizophrenia. The present 13-week study was also conducted to address European Medicines Agency guidelines to demonstrate noninferiority of new injectable antipsychotics to approved formulations. The study included a modified dosing initiation regimen and was designed to demonstrate that PP (without oral supplementation) initiated as deltoid injections (day 1 [150 mg eq.], day 8 [100 mg eq.]) and subsequent flexible dosing (50, 100, or 150 mg eq.) once-monthly was not less efficacious than RIS-LAI (25, 37.5, or 50 mg) administered every 2 weeks with oral supplementation. The safety and tolerability of PP in the treatment of schizophrenia was also assessed.

2. Materials and methods

2.1. Patients

Consenting men and women (18 years or older) with an established Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnosis of schizophrenia for at least one year before screening, a Positive and Negative Syndrome Scale [PANSS] total score at screening between 60 and 120 (inclusive), and with a body mass index $\geq$17.0 kg/m^2 and $<$40 kg/m^2, were enrolled.

Main exclusion criteria included a history of: primary active DSM-IV Axis I diagnosis other than schizophrenia, decrease of at least 25% in the PANSS total score between screening and baseline, DSM-IV diagnosis of active substance dependence within 3 months before screening, history of treatment resistance (failure to respond to two adequate treatments with different antipsychotic medications; a minimum of 6 weeks at a clinically efficacious tolerated dose), and a relevant history of, or current presence of, any significant or unstable systemic disease. Other exclusion criteria were: significant risk of suicidal, or violent behavior, having previously received an injection of PP and treatment with any of the disallowed medications (mood stabilizers, including lithium and all anticonvulsants), and exposure to an experimental drug, biologic, or medical device within 6 months before screening. Women were excluded if pregnant, nursing, or planning to become pregnant.

The Independent Ethics Committee (IEC) or Institutional Review Board (IRB) at each study site approved the protocol and the amended protocol. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. All patients provided written informed consent before entering the study.

2.2. Study medication

Because doses of PP can be expressed both in terms of milligram equivalents (mg eq.) of the pharmacologically active fraction, i.e., paliperidone, and in milligrams of PP, the doses expressed as PP 50, 100 and 150 mg eq. equate to 78, 156 and 234 mg respectively, of PP. The study medication PP does not require refrigeration or reconstitution and was provided as 50, 100, and 150 mg eq. injectable suspensions (supplied as 156 mg/mL), or matching placebos (20% Intralipid™ 200 mg/mL, Fresenius Kabi AB, Uppsala, Sweden). RIS-LAI was supplied as risperidone depot microspheres in strengths of 25, 37.5, and 50 mg. Matching placebo injections for RIS-LAI were supplied as 2-mL prefilled syringes of diluents. Oral risperidone tablets were supplied as 1 mg tablets. Matching oral placebo tablets were supplied to patients in the PP treatment group.

2.3. Study design, randomization, and blinding

This study was a randomized, double-blind, double-dummy, active-controlled, parallel-group, multicenter noninferiority comparative study conducted from March 2007 through July 2009. A total of 89 centers (sites) in 14 countries participated in this study: 57 centers in Eastern Europe (Bulgaria [29 patients], Czech Republic [98 patients], Estonia [66 patients], Hungary [65 patients], Lithuania [37 patients], Poland [44 patients], Russia [318 patients], and Ukraine [168 patients]), 14 centers in North America (United States [273 patients]), 12 centers in Western Europe (Austria [7 patients], France [10 patients], Germany [8 patients], Spain [35 patients]), and 6 centers in Asia (India [62 patients]). The study consisted of a screening period of up to 7 days for washout of disallowed psychotropic medications and for oral tolerability testing (patients without documented previous exposure to oral risperidone, oral paliperidone or those patients who were not currently receiving another antipsychotic were administered paliperidone ER 6 mg/day for 4 to 6 consecutive days), followed by a 13-week double-blind treatment period. Eligible patients were randomly assigned (1:1) to either of two double-blind treatment groups: PP without oral supplementation or RIS-LAI, with oral risperidone based on a computer-generated randomization scheme stratified by center, and implemented by an interactive voice response system. A double-dummy design was used to preserve the blind because the two study drugs are different in appearance (syringe and needle sizes), method of preparation of the injection (PP does not require reconstitution and RIS-LAI does), and injection schedules. Additional measures were undertaken to ensure the study blind was not broken. The study drug administrator was the only person to contact IVRS to receive the patient's medication number. The study drug administrator was not allowed to communicate patient-related information (including IVRS information) to study site personnel (including the investigator) or to perform any efficacy and safety assessments. Also, the patient and staff performing study-related procedures were to be precluded from seeing the contents of the syringe or observing the injection (since active and placebo drugs differ slightly in appearance) and the study drug was to be stored and administered in such a way as to maintain the blind. At the time of randomization, patients could either be (voluntarily hospitalized) inpatients or outpatients. Hospitalization was not required during any period of the study, but was allowed if deemed necessary by the investigator.

Patients in the PP group received the initiation regimen, monthly PP injections, placebo injections (matched to RIS), and placebo oral supplementation (Table 1). Patients on RIS-LAI received biweekly RIS-LAI injections from day 8 onwards, oral supplementation, and placebo injections (matched to PP) (Table 1). On the days when there were dual injections (days 8, 36, and 64), the injections were not to be administered into the same muscle. The side or muscle site was alternated for each injection. Deltoid injections of PP were administered with a 1-inch needle to patients weighing less than 90 kg, and with a 1.5-inch needle to patients weighing 90 kg or greater. All gluteal injections of PP were administered with a 1.5-inch needle; RIS-LAI or matched placebo injections were administered using a 2-inch needle.

The protocol was amended so that the oral supplementation with dose increases of RIS-LAI was made optional and was limited to 1 to 2 mg doses. The protocol was also amended to include the interim analysis for sample size re-estimation and to include an enhanced dosing regimen of PP [or matching placebo] injection of 100 mg eq. (initially 50 mg eq.) on day 8 to be mandatorily given in the deltoid, after it was discovered in earlier studies that there was heterogeneity