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Paliperidone palmitate once-monthly maintains improvement in functioning domains of the Personal and Social Performance scale compared with placebo in subjects with schizoaffective disorder

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ABSTRACT

Objective: Evaluate the effect of paliperidone palmitate once-monthly (PP1M) injectable on the specific functioning domains of the Personal and Social Performance (PSP) scale in patients with schizoaffective disorder (SCA) participating in a long-term study.
Methods: This study (NCT01193153) included both in- and outpatient subjects with SCA experiencing an acute exacerbation of psychotic and mood symptoms. Subjects were treated with PP1M either as monotherapy or in combination with antidepressants or mood stabilizers during a 25-week open-label (OL) phase. Stabilized subjects were randomly assigned 1:1 (PP1M or placebo) into a 15-month double-blind (DB) relapse-prevention period. Functioning of the randomized subjects during OL and DB phases was evaluated using the PSP scale (four domains: socially useful activities, personal/social relationships, self-care, and disturbing/aggressive behaviors). Three statistical approaches were utilized to analyze PSP scores to assess robustness and consistency of findings. No adjustments were made for multiplicity.
Results: 334 of 667 enrolled subjects were stabilized with PP1M, randomly assigned to PP1M ($n = 164$) or placebo ($n = 170$) in the DB phase, and included in this analysis. Improvements in all PSP domain scores were observed during the OL phase and were maintained during the DB phase with PP1M, but decreased with placebo. Differences compared to placebo were significant in all four PSP domains during the DB phase ($P \le 0.008$).
Conclusion: The analysis in this study showed that PP1M improves functioning, as measured by the four PSP domain scores, in symptomatic subjects with SCA. Functioning was maintained compared with placebo.

1. Introduction

Schizoaffective disorder (SCA) is a serious mental illness characterized by mixed symptoms of schizophrenia and affective disorders (American Psychiatric Association, 2013; Malaspina et al., 2013). Functional impairment, though not a diagnostic criterion, is commonly observed and is a major adverse outcome for patients and public health (Nasrallah et al., 2010; Marneros et al., 1990). Consequently, improving and preserving functioning is an important long-term treatment goal for better prognosis, recovery, and community adjustment (Nasrallah et al., 2010; Marneros et al., 1990). According to consensus statements formulated by the Schizoaffective Disorder Working Group, longitudinal assessment of functioning in response to treatment should be performed using appropriate tools, such as the Personal and Social Performance (PSP) scale (Nasrallah et al., 2010). The PSP scale is a validated clinician-reported instrument that has been widely used in clinical trials to assess personal and social functioning of patients with psychiatric disorders based on four distinct domains: (A) socially useful activities, (B) personal/social relationships, (C) self-care, and (D) disturbing/aggressive behavior (Morosini et al., 2000; Nasrallah et al., 2008). Domains A, B, and C represent the functional assessments in Criterion B of schizophrenia in the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5). The PSP scale provides quantitative measures of patient functioning that are separate from disease-specific symptoms (Morosini et al., 2000).

Pharmacologic regimens, including antipsychotics, mood stabilizers, and antidepressants, are a mainstay of treatment for patients with SCA

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(McElroy et al., 1999; Flynn et al., 2002; Lerner et al., 2004). However, adherence to a daily oral treatment regimen is often difficult (Karve et al., 2014; Alphs et al., 2016), and medication gaps may contribute to suboptimal treatment response and poorer long-term outcomes (Lindenmayer et al., 2009; Boden et al., 2011). Advances and innovations in treatment options over the past decade have improved the outlook for patients with SCA (Canuso et al., 2010) or schizophrenia, particularly the development of long-acting injectable (LAI) antipsychotic therapies (Fu et al., 2015; Lindenmayer and Kaur, 2016; Alphs et al., 2016; Parellada and Bioque, 2016; Potkin and Preda, 2016; Citrome, 2016; McDonnell et al., 2014). LAIs provide therapeutic plasma concentrations over several weeks, thereby eliminating the need for daily oral antipsychotic therapy. LAIs allow clinicians to directly monitor adherence (Pandina et al., 2010; Pandina et al., 2011), and thereby potentially reduce risk of relapse and improve and/or maintain functioning. A 15-month, randomized, double-blind (DB), placebo-controlled relapse-prevention trial of subjects with SCA evaluated the long-term efficacy and safety of once-monthly paliperidone palmitate (PP1M) given either as monotherapy or in combination with antidepressants or mood stabilizers (Fu et al., 2015). Results demonstrated that PP1M significantly delayed time to relapse and reduced the risk of psychotic, depressive, and manic relapses compared with placebo, resulting in regulatory approval for PP1M in the treatment of SCA (Janssen Pharmaceuticals, Inc., 2014). Furthermore, functioning, as measured by the PSP scale (Morosini et al., 2000), was better maintained in subjects who received PP1M compared with placebo.

Because personal, social, and occupational functioning are widely recognized as important long-term outcomes in patients with serious mental illness (Burns and Patrick, 2007), additional PSP analyses from this trial were conducted to examine the dimensions of functioning that were impacted by PP1M treatment (Fu et al., 2015). The specific objectives of these analyses were twofold: first, to evaluate the effects of treatment with PP1M on each PSP functioning domain during open-label (OL) treatment of acutely ill patients and, second, to evaluate the ability of PP1M to maintain functioning of stable patients during the DB phase as compared with placebo (i.e., withdrawal of PP1M treatment). The analyses were designed to determine whether the overall functioning observed with the total score is reflected in one, some, or all four PSP domains.

2. Methods

2.1. Study design

This analysis was based on PSP data from a long-term, randomized, DB, placebo-controlled, relapse-prevention international study (NCT01193153) in SCA patients. Study design details have been described (Fu et al., 2015). Briefly, the study comprised a 25-week OL acute treatment phase and a 15-month DB relapse-prevention phase. The OL phase included a 13-week flexible-dose lead-in period and a 12-week fixed-dose stabilization period. During the lead-in period, all subjects received monthly intramuscular injections of PP1M 234 mg on day 1 and 156 mg on day 8, then flexible doses (78–234 mg) on day 36 and onward as monotherapy or in combination with mood stabilizers or antidepressants (i.e., adjunctive therapy). Subjects who completed the lead-in period and met stabilization criteria (i.e., Positive and Negative Syndrome Scale [PANSS] total score ≤ 70; Young Mania Rating Scale [YMRS] score ≤ 12; and Hamilton Rating Scale for Depression, 21-item version [HAM-D-21], score ≤ 12) entered the 12-week stabilization period and received PP1M once every 4 weeks at the final dose received during the lead-in period. Subjects who completed the stabilization period and maintained the stabilization criteria throughout the 12-week treatment were eligible to enter the DB phase, and were randomized 1:1 to fixed-dose PP1M or matching placebo injections. Subjects continued to receive PP1M or placebo once every 4 weeks until relapse of SCA symptoms (as defined in Fu et al., 2015), discontinuation or withdrawal, or until completion of the 15-month DB phase.

The current analysis included the randomized subjects of this multiphase study, whose functioning was evaluated during the 25-week OL acute treatment phase and 15-month DB maintenance treatment phase.

2.2. Study population

Men and women aged ≥ 18 years with a lifetime and current diagnosis of SCA, confirmed with the Structured Clinical Interview for DSM-IV, were eligible. Subjects must have had an acute exacerbation of psychotic symptoms of ≥4 days and ≤4 weeks before screening; prominent mood symptoms (scores ≥ 16 on YMRS and/or HAM-D-21), and a score of ≥4 on ≥3 of the PANSS items: P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), P4 (excitement), P6

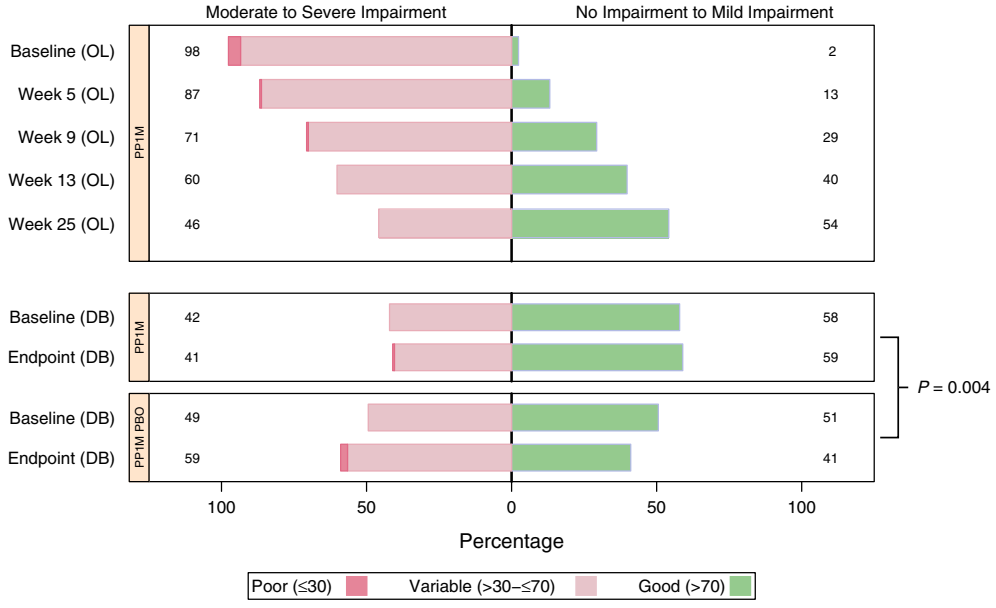

Fig. 1. Categorical changes in PSP total scores by study phase. DB, double-blind; OL, open label; PBO, placebo; PSP, Personal and Social Performance; PP1M, once-monthly paliperidone palmitate.