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Intramuscular long-acting paliperidone palmitate in acute patients with schizophrenia unsuccessfully treated with oral antipsychotics

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ABSTRACT

In this prospective multicentre, open-label, 6-month study (Paliperidone Palmitate Flexible Dosing in Schizophrenia [PALMFlexS]), tolerability, safety and treatment response with paliperidone palmitate (PP) were explored in patients with acute symptoms of schizophrenia following switching from previously unsuccessful treatment with oral antipsychotics. This pragmatic study was conducted in a large, more representative sample of the general schizophrenia population compared to randomized controlled pivotal trials, to specifically mimic real-world clinical situations. After initiation on Day 1 and Day 8, patients received PP once monthly at flexible doses (50–150 mg eq.) intramuscularly. The primary efficacy outcome was defined as the percentage of patients achieving ≥30% improvement in PANSS total score from baseline (BL) to last-observation-carried-forward (LOCF) endpoint (EP). Safety and tolerability assessments included Extrapyramidal Symptom Rating Scale (ESRS) total score and treatment-emergent adverse events (TEAEs). Overall, 212 patients received PP at least once after switching from oral antipsychotics, primarily due to lack of efficacy (45.8%). Significant improvements from BL in mean (SD) PANSS total score were observed from Day 8 onwards (BL to LOCF EP: −31.0 [29.0]; $p < 0.0001$). At endpoint, two-thirds (66.7%) and 43.5% of patients achieved a ≥30% and ≥50% improvement in mean PANSS total score, respectively. PP was associated with significant improvements across secondary measures of symptom severity, subjective well-being, medication satisfaction, illness-related disorders of activity and participation, and patient functioning ($p < 0.0001$; BL to LOCF EP). PP was generally well tolerated, with significant reductions in ESRS total score ($p < 0.0001$) and mainly mild-to-moderate TEAEs. TEAEs reported in ≥5% of patients were injection-site pain (13.7%), insomnia (10.8%), psychotic disorder (10.4%), headache and anxiety (both 6.1%). The PALMFlexS study findings provide valuable pragmatic clinical data on PP treatment in patients with acute schizophrenia previously unsuccessfully treated with oral antipsychotics.

Abbreviations: AE, adverse event; BL, baseline; BMI, body mass index; CGI-C, clinical global impression-change; CGI-S, clinical global impression-severity; CI, confidence interval; DSM-IV, diagnostic and statistical manual of mental disorders-IV; EP, endpoint; EPMS, extrapyramidal motor symptoms; ESRS, extrapyramidal symptom rating scale; IEQ, involvement evaluation questionnaire; IM, intramuscular; ITT, intent-to-treat; LAT, long-acting antipsychotic therapy; LOCF, last-observation-carried-forward; MedDRA, medical dictionary for regulatory activities; Mini-ICF-APP, mini-international classification of functionality, disability and health (ICF) rating for activity and participation disorders in psychological illnesses; PALMFlexS, paliperidone palmitate flexible dosing in schizophrenia; PANSS, positive and negative syndrome scale; PP, paliperidone palmitate; PSP, personal and social performance; RCT, randomized controlled trial; SD, standard deviation; SWN-S, subjective well-being under neuroleptics-scale (short form); TEAE, treatment-emergent adverse event; TSQM, treatment satisfaction questionnaire for medication.

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1. Introduction

Many people with schizophrenia have the potential to achieve long-term remission and functional recovery (Zipursky et al., 2013), but only a small proportion realize this goal (Kane, 2013). One study of previously stabilized patients reported remission rates of 39.2% before relapse and 35.9% post-relapse (Emsley et al., 2012), while a recent metaanalysis of 50 studies highlighted that only 13.5% of patients met recovery criteria (Jaaskelainen et al., 2013).

Although a first step towards achieving remission is to elicit a response to treatment and bring symptoms under control following an acute psychotic episode, this goal is frequently disrupted by relapse, often leading to rehospitalization, poor treatment response and loss of functional gains (Kane, 2013). The response to antipsychotic treatment after relapse varies, with a subset of patients displaying emergent refractoriness, independent of the relapse event (ie first or subsequent relapse). Furthermore, this trajectory is unaltered even when the interval between first signs of relapse and initiation of treatment is brief (Emsley et al., 2013a). In addition, an earlier 15-year prospective follow-up of a Dutch cohort of patients with schizophrenia found that, following a relapse, one in six patients did not subsequently respond to treatment and one in ten committed suicide, supporting the need for adequate relapse prevention (Wiersma et al., 1998). Recurrent relapse may also be associated with structural brain changes, cognitive deterioration, reduced quality of life and overall poor prognosis (Andreasen et al., 2013; Taylor et al., 2005; van Haren et al., 2007).

Relapses and acute exacerbations in patients with schizophrenia are common (Emsley et al., 2013b). Notably, a relapse rate of 27% over 7–12 months was reported in a recent metaanalysis of randomized clinical trials of patients continuing antipsychotic medication after stabilization (Leucht et al., 2012). Many patients relapse soon after treatment discontinuation, sometimes with the transition from remission to relapse being abrupt and occurring without warning (Emsley et al., 2013b), suggesting efficient relapse prevention strategies after initial disease onset may convey a significant clinical benefit (Andreasen et al., 2013). The most frequent reason for relapse is discontinuation of oral antipsychotic treatment, with the risk of relapse being five times greater among those patients who discontinue their treatment (Robinson et al., 1999), which is highly relevant given, for example, that less than half of patients were found to adhere to their initial antipsychotic treatment during the first 30 days after discharge from their first hospitalization for schizophrenia (Tiihonen et al., 2011). Moreover, it has been shown that healthcare providers consistently overestimate patient adherence to antipsychotic medication (Byerly et al., 2012).

Long-acting injectable antipsychotic therapy (LAT) has been shown to reduce relapse rates significantly (Kishimoto et al., 2013; Leucht et al., 2012), and may enhance adherence to treatment in patients with schizophrenia (Cañas et al., 2013). However, LAT use has generally been reserved for patients with difficulties in complying with oral regimens during maintenance treatment (Ascher-Svanum et al., 2009; Heres et al., 2006) and their use in the acute hospital setting has largely been avoided due to their slow-release profiles and delayed onset of effect. Therefore, little is known about use of LATs in patients with acute symptoms of schizophrenia compared with stabilized patients (Burns, 2009). Given the frequency and early onset of medication non-adherence among patients with schizophrenia (Tiihonen et al., 2011; Velligan et al., 2009) and the role of LATs in addressing this problem as well as in improving broader patient outcomes (Kaplan et al., 2013), evaluation of the impact of LATs during an acute exacerbation of schizophrenia is warranted.

Paliperidone palmitate (PP) is an LAT, designed for once-monthly intramuscular (IM) administration for the maintenance treatment of schizophrenia (Xeplion SmPC, 2013). PP has been developed as an aqueous suspension that can be delivered intramuscularly and which has pharmacokinetic properties that facilitate rapid achievement of therapeutic plasma concentrations (Meyer, 2013). Using the initiation regimen of PP (150 mg eq. on Day 1 and 100 mg eq. on Day 8, both administered into the deltoid muscle), an early onset of effect was observed as of Day 8 of treatment (Pandina et al., 2010) and even from Day 4, in markedly to severely ill patients (Alphs et al., 2011). The efficacy of PP in the acute treatment of schizophrenia has been demonstrated in fixed-dose short-term trials (Alphs et al., 2011; Pandina et al., 2010); however, information and guidance on flexible dosing, dose–response relationships, strategies for direct transition from other antipsychotics to PP and use of relevant concomitant medication in routine clinical practice are lacking. The pivotal studies for PP in patients with an acute exacerbation of schizophrenia included an initial washout period, used fixed doses (without the option of dosage adjustment), and were conducted in selected, relatively homogenous groups of patients (Gopal et al., 2010; Nasrallah et al., 2010; Pandina et al., 2010). Therefore, there is a need to assess PP in a less restrictive setting, such as a more diverse population of patients, with higher rates of comorbidities, substance abuse and/or comedications, to better reflect those normally seen in daily clinical practice.

The Paliperidone Palmitate Flexible Dosing in Schizophrenia (PALMFlexS) trial is a pragmatic prospective interventional study that was conducted in a large, more representative sample of patients with schizophrenia (Schreiner et al., 2014) and was designed to explore how treatment outcomes may guide recommendations for use of, and transition to, PP in acutely ill patients with schizophrenia.

2. Materials and methods

2.1. Study design

This was a non-randomized, single-arm, multicentre, open-label, 6-month, prospective interventional study in patients with acute schizophrenia previously unsuccessfully treated with oral antipsychotics (Clinical trials.gov number: NCT01281527). A total of 160 sites in 21 countries took part in the study (see Appendix). Prior to trial initiation, the protocol was reviewed and approved by an independent ethics committee in all participating countries. The trial was performed in accordance with the Declaration of Helsinki. Patients were informed of the risks and benefits of the trial and written informed consent was obtained before commencement of any trial-related activities.

The study consisted of a screening period, a 6-month study period, and an optional extension phase. This manuscript reports results from the 6-month study period. The screening period included a 2-day oral tolerability test with paliperidone ER for patients without source documentation of previous risperidone or paliperidone exposure. Only patients demonstrating an ability to tolerate the drug, as judged by the treating physician, were eligible to enter the 6-month study period. The start of the 6-month study period was defined as the day of the first PP injection.

2.2. Patients

Eligible participants were males and females aged ≥18 years, with acute symptoms of schizophrenia (Diagnostic and Statistical Manual of Mental Disorder [DSM]-IV), defined as having a baseline [BL] Positive and Negative Syndrome Scale [PANSS] total score of ≥80 and a BL Clinical Global Impression — Severity [CGI-S] score of ≥4, and who had been previously unsuccessfully treated with an oral antipsychotic in the 4 weeks prior to enrolment. Prior treatment was considered to have been unsuccessful due to one or more of the following: lack of efficacy (BL PANSS ≥70 or ≥2 items scoring ≥4 in the PANSS positive or negative subscale or ≥3 items scoring ≥4 in the PANSS general psychopathology subscale, as judged by the investigator), lack of tolerability or safety (the presence of clinically relevant side effects), lack of compliance, or the patient's wish. Additionally, patients were eligible, if, at the discretion of the investigator, the patient may benefit from a switch of oral antipsychotic medication to PP.