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

Ludger Hargarter [a,*], Pierre Cherubin [b], Paul Bergmans [c], Sofia Keim [d], Elmars Rancans [e], Yasin Bez [f], Eduard Parellada [g], Bernardo Carpiniello [h], Pierre Vidailhet [i], Andreas Schreiner [a]

[a] Medical & Scientific Affairs, Janssen Cilag EMEA, Neuss, Germany
[b] Medical Affairs, Janssen Cilag EMEA, Issy-les-Moulineaux, France
[c] Biometrics and Reporting, Janssen Cilag Benelux, Tilburg, The Netherlands
[d] Global Clinical Operations EMEA MAO, Janssen Cilag, Barcarena, Portugal
[e] Department of Psychiatry and Narcology, Riga Stradins University, Riga, Latvia
[f] Dicle University Medical Faculty, Diyarbakir, Turkey
[g] Barcelona Clinic Schizophrenia Unit (BCSU), Hospital Clínic de Barcelona, IDIBAPS, University of Barcelona, Barcelona, Spain
[h] Clinica Psichiatrica Università di Cagliari, Cagliari, Italy
[i] Centre Hospitalier Régional Universitaire de Strasbourg, Strasbourg, France

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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.

* Corresponding author at: Medical & Scientific Affairs, Janssen Cilag Europe, Middle East & Africa, Johnson & Johnson Platz 1, 41470 Neuss, Germany. Tel.: +49 2137 9551240.
E-mail address: lhargart@its.jnj.com (L. Hargarter).

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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.

A psychiatric diagnosis due to direct pharmacological effects of a substance or a general medical condition; a history of or current symptoms of tardive dyskinesia or neuroleptic malignant syndrome; or known allergies, hypersensitivity, or intolerance to risperidone or paliperidone or its excipients led to study exclusion. Patients who were antipsychotic treatment-naïve; receiving clozapine during the last 3 months prior to the start of the study; or considered to be at imminent risk of suicide were also excluded from the study, as were pregnant and breast-feeding female patients. Patients with a current substance use or abuse, with the exception of intravenous drug use, were eligible for enrolment and there were no exclusions based on body mass index (BMI).

2.3. Treatment

At initiation of PP, patients were tapered off their previous oral antipsychotic, preferably within a maximum of 4 weeks. PP was initiated at 150 mg eq. on Day 1 and 100 mg eq. on Day 8 (±2 days) IM, both given in the deltoid muscle. Subsequently, PP was administered once monthly in either the gluteal or deltoid muscle, on Days 38, 68, 98, 128 and 158 (±7 days) using flexible dosages, within the range of 50–150 mg eq., based upon the treating physician's clinical judgment of efficacy and tolerability.

Antipsychotics and other psychotropic medications that were administered prior to the start of the study for reasons other than the disease itself (e.g. sleep induction or sedation) could be continued during the study at a stable dose at the discretion of the treating physician. In the event of exacerbation of psychotic symptoms between visits requiring immediate intervention, oral antipsychotic medication, preferably paliperidone ER, could be given within the approved dose range. Benzodiazepines that were newly initiated during the study were allowed as rescue medication. The investigators re-evaluated the need for concomitant oral antipsychotic treatment, benzodiazepines and anticholinergic medication on an ongoing basis.

2.4. Efficacy assessments

The primary efficacy outcome was the percentage of patients achieving treatment response, defined as ≥30% improvement in PANSS total score from BL (Day 1) to last-observation-carried-forward (LOCF) endpoint (EP) (at 6 months or early discontinuation). PANSS was rated and scored by a trained and qualified rater (Kay et al., 1987).

Secondary outcomes included PANSS subscale and Marder factor scores (Marder et al., 1997), CGI-S score, Clinical Global Impression — Change (CGI-C) score, Personal and Social Performance (PSP) total score (range 0–100) and four PSP domain scores: socially useful activities, personal and social relationships, self-care, and disturbing and aggressive behavior, each rated on a 6-point scale (Morosini et al., 2000). The Mini-ICF (International Classification of Functionality, Disability and Health) rating for Activity and Participation Disorders in Psychological Illnesses (Mini-ICF-APP [Linden and Baron, 2005; Baron and Linden, 2009; Moldynski et al., 2013]) was used to quantify patients' abilities and disabilities on 13 dimensions on a 5-point scale and a total score that was calculated as the sum of the 13 dimension scores.

Additional secondary outcome measures encompassed the Subjective Well-being under Neuroleptics-Scale (SWN-S) (short form) (Naber et al., 2001); patient and physician satisfaction with the antipsychotic medication, as assessed using the 14-item Treatment Satisfaction Questionnaire for Medication (TSQM) scale (Atkinson et al., 2004) and a 7-point categorical scale, respectively; quality of sleep and daytime drowsiness, using an 11-point categorical rating scale; and carer burden, measured according to the Involvement Evaluation Questionnaire [IEQ] (van Wijngaarden et al., 2000).

2.5. Safety and tolerability

Evaluation of safety and tolerability included the measurement of extrapyramidal motor symptoms (EPMS) according to Extrapyramidal Symptom Rating Scale (ESRS) total score (Chouinard and Margolese, 2005) and adverse events (AEs), reported either directly by the patient or indirectly obtained by means of interviewing patients at study visits. All reported AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA version 13.0). Treatment-emergent adverse events (TEAEs) were defined as AEs that were new in onset or were aggravated in severity following initiation of PP. Recording of body weight and calculation of BMI were also performed. As this was a pragmatic study reflecting routine clinical practice, and data on prolactin plasma levels with PP have been extensively collected (in >3000 patients) during the clinical development program (Gopal et al., 2010; Nasrallah et al., 2010; Pandina et al., 2010), no regular laboratory tests were conducted in this study; however, investigators could measure laboratory values, including prolactin, at their own discretion at any time throughout the study.

2.6. Data analysis

The sample size estimation for patients with acute symptoms of schizophrenia switched from oral antipsychotics was based on the primary endpoint for this group. The proportion of patients with at least 30% improvement in PANSS total score was expected to be 40%. Using the large sample normal approximation, it was estimated at least 93

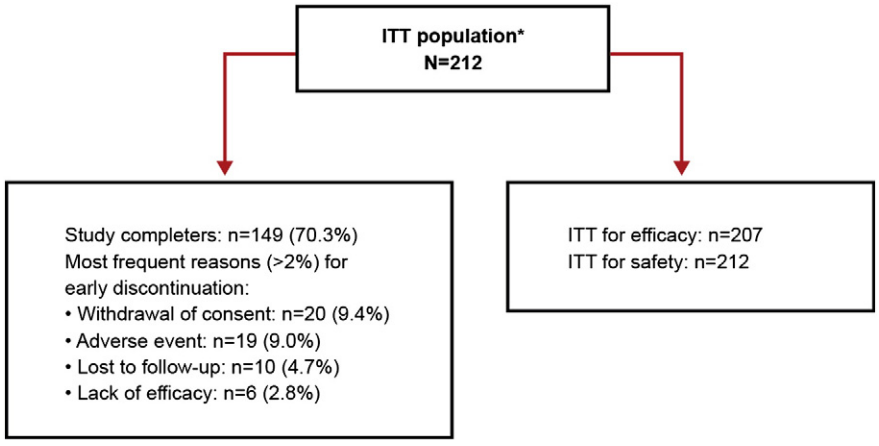

Fig. 1. Patient disposition. *The ITT population encompasses all patients who received at least one dose of PP; this includes two patients with a baseline CGI-S score of 3, thus violating the protocol inclusion criteria. ITT, intent-to-treat.

patients were required to reach a 95% confidence interval (CI) for a single proportion that maximally extends 10% from the observed proportion.

Efficacy analyses were undertaken in the intent-to-treat (ITT) population, which comprised all patients who received PP at least once, and had at least one post-BL efficacy assessment. Actual values and changes from BL were summarized descriptively at each assessment time point and at the patient's last evaluation (LOCF EP). Moreover, categorical variables were summarized with frequency and percentage. For secondary efficacy assessments, the change from BL at each visit and at LOCF EP was analyzed using the Wilcoxon signed-rank test.

Tolerability and safety data, evaluated throughout the study on the safety ITT population, were summarized descriptively.

Table 1
Patient demographics and dosing information.

Characteristic	N = 212
Mean age, years (SD)	36.4 (12.1)
Sex	
Male, %	59.0
Female, %	41.0
Type of schizophrenia, n (%)	
Paranoid	181 (85.4)
Disorganized	13 (6.1)
Catatonic	1 (0.5)
Undifferentiated	11 (5.2)
Residual	6 (2.8)
Baseline weight, kg (SD)	78.9 (18.7)
Baseline body mass index, kg/m^2 (SD)	27.3 (6.4)
Patients with ≥1 comorbidity, n (%)*	139 (65.6)
Body systems for which patients (≥10%) report ≥1 comorbidity, n (%)	
Psychiatric disorders	47 (22.2)
Nervous system disorders	36 (17.0)
Metabolism and nutrition disorders	28 (13.2)
Number of previous hospitalizations, n (%)	
None	36 (17.0)
1	41 (19.3)
≥2	135 (63.7)
PP dosage	
Patients receiving PP initiation regimen at Day 1 and Day 8 according to protocol,† n (%)	197 (92.9)
Mean modal PP maintenance dose mg eq. (SD)‡	107.7 (34.0)
Last PP maintenance dose received, n (%)§	
50 mg eq.	17 (9.3)
75 mg eq.	42 (23.1)
100 mg eq.	47 (25.8)
150 mg eq.	76 (41.8)
Relevant concomitant medications	
Number (%) of patients using benzodiazepines	
At baseline	80 (37.7)
Newly-initiated during study	83 (39.2)
At LOCF endpoint	74 (34.9)
At 6 months for completers¶	38 (25.5)
Number (%) of patients using anticholinergics	
At baseline	27 (12.7)
Newly-initiated during study	24 (11.3)
At LOCF endpoint	18 (8.5)
At 6 months for completers¶	10 (6.7)

CGI-S, Clinical Global Impression — Severity; PP, paliperidone palmitate; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.

*Individual patients can be labeled for >1 comorbidity.

†The recommended initiation regimen was PP 150 mg eq. on Day 1 and 100 mg eq. on Day 8 given in the deltoid muscle.

‡Excluding the initiation regimen (Day 1/Day 8).

§Last dose received by those patients who received the third dose (Month 1) onwards, n = 182.

¶Completers at 6 months n = 149.

3. Results

3.1. Demographics and patient disposition

Patient disposition is described in Fig. 1. A total of 212 patients received at least one dose of PP (ITT population). The main reason for transition from prior oral antipsychotic treatment to PP was lack of efficacy (97/212, 45.8%), followed by lack of compliance (74/212, 34.9%).

Baseline characteristics of the patient population are described in Table 1. Patients were predominantly male (59%) and most had a paranoid schizophrenia subtype diagnosis (85%). At BL 93 (43.9%) patients were hospitalized and 69.8% (n = 148) received at least one concomitant medication prior to enrolment.

Mean time on PP treatment was 136.9 days at a mean modal PP maintenance dose of 107.7 ± 34.0 mg eq. (Table 1). Nearly all patients (92.9%) received PP according to the recommended initiation regimen on Day 1 and Day 8. The majority of patients (n = 75, 41.4%) received 100 mg eq. for the third dose (50 mg eq.: n = 6 [3.3%], 75 mg eq.: n = 44 [24.3%], 150 mg eq.: n = 56 [30.9%]). From the third dose (Month 1) onwards, 33.0% of the patients had ≥1 dose decrease, while 34.1% of patients had ≥1 dose increase. The most common reason for the dose increases was 'suboptimal efficacy' (87.7% of the dose increases after the third dose); the most common reason for the dose decreases was 'subject responding well' (59.5% of the dose decreases after the third dose).

3.2. Efficacy outcomes

Results for primary and secondary efficacy outcomes are summarized in Table 2. After switching to PP, two-thirds (66.7%) of patients met the criteria for clinical response (≥30% improvement in mean PANSS total score) and almost half (43.5%) of patients achieved ≥50% improvement in mean PANSS total score. Mean PANSS total score was significantly improved (Fig. 2, Table 2), with significant reductions seen as early as Day 8 reflecting the first post-baseline assessment (mean reduction from BL [SD]: −9.4 [14.9]; 95% CI −11.4, −7.3; Wilcoxon signed-rank test, s = −9323.0, df = 199, $p < 0.0001$). Consistent with the total score, each of the PANSS Positive, Negative and General Psychopathology subscale and Marder factor scores showed a significant improvement (Supplementary Table 1).

PP was associated with a significant decrease in disease severity, as demonstrated by a reduction in CGI-S score (Wilcoxon signed-rank test, s = −6575.5, df = 165, $p < 0.0001$) (Table 2). Moreover, the proportion of patients rated markedly ill or worse based on the CGI-S scale decreased from 75.1% at BL to 20.5% at LOCF EP (Supplementary Fig. 1). The majority of patients who switched to PP improved from BL, with 82.1% of patients categorized in CGI-C as minimally (26.5%), much (41.3%) or very much (14.3%) improved.

Statistically significant improvements from BL to LOCF EP were observed in mean SWN-S total score and in mean TSQM global satisfaction score (Table 2). Additionally there were statistically significant improvements in TSQM satisfaction scores related to medication effectiveness (SD) (48.7 [20.2] to 62.0 [23.1]; Wilcoxon signed-rank test, $p < 0.0001$) and convenience (59.0 [21.7] to 72.5 [19.4]; Wilcoxon signed-rank test, $p < 0.0001$). A trend towards improvement in the side effects domain score was observed, although this did not reach statistical significance (73.3 [32.6] to 79.1 [30.4]; Wilcoxon signed-rank test, $p = 0.0555$ [BL to LOCF EP]). A statistically significant improvement in physician's satisfaction scores was observed for all aspects of treatment (Wilcoxon signed-rank test, all $p < 0.0001$ [BL to LOCF EP]).

3.3. Functioning outcomes

The mean PSP total score increased significantly from baseline to LOCF endpoint (Table 2). Improvement in patient functioning with PP was also reflected in the distribution of PSP category scores, with an

Table 2
Secondary efficacy outcomes*.

	Baseline (SD)	LOCF endpoint (SD)	Change from baseline to LOCF endpoint (SD)	95% CI, of mean change	p value†
Mean PANSS total score, (n = 207)	98.5 (20.1)	67.4 (24.0)	−31.0 (29.0)	−35.0, −27.1	<0.0001
Mean CGI-S score, (n = 205)	5.0 (0.8)	3.5 (1.3)	−1.5 (1.3)	−1.7, −1.3	<0.0001
Mean SWN-S score, (n = 207)	73.8 (15.5)	83.5 (17.9)	9.7 (20.6)	6.6, 12.7	<0.0001
Mean TSQM global satisfaction score, (n = 170)	48.7 (22.4)	61.9 (25.3)	13.2 (30.3)	8.6, 17.7	<0.0001
Mean quality of sleep score, (n = 203)‡	6.5 (2.6)	7.3 (2.5)	0.8 (3.1)	0.4, 1.2	<0.0001
Mean daytime drowsiness score, (n = 203)§	4.5 (2.9)	3.0 (2.7)	−1.5 (3.6)	−2.0, −1.0	<0.0001
Mean PSP total score, (n = 197)	43.9 (15.0)	62.9 (17.1)	19.0 (18.7)	16.4, 21.6	<0.0001
Mini-ICF-APP total score, (n = 207)	26.5 (8.5)	18.5 (9.8)	−8.0 (10.4)	−9.5, −6.5	<0.0001

CGI-S, Clinical Global Impression — Severity; CI, confidence interval; LOCF, last-observation-carried-forward; Mini-ICF-APP, mini International Classification of Functionality, Disability and Health (ICF) Rating for Activity and Participation Disorders in Psychological Illnesses; PANSS, Positive and Negative Syndrome Scale; PSP, Personal and Social Performance; SD, standard deviation; SWN-S, Subjective Well-being under Neuroleptics Scale; TSQM, Treatment Satisfaction Questionnaire for Medication.
*Only patients with a baseline measurement and at least one follow-up assessment were included.
†Wilcoxon signed-rank test.
‡A higher score indicates improvements in the quality of sleep.
§A lower score indicates improvements in the level of drowsiness.

increase in the number of patients with a PSP score >70 (defined as experiencing mild or no functional impairment) from 4.1% at BL to 37.1% at LOCF EP. Following PP treatment, all PSP domain scores showed a statistically significant increase (Wilcoxon signed-rank test, $p < 0.0001$) (Supplementary Fig. 2).

Illness-related disorders of activity and participation also improved significantly with PP, as measured by Mini-ICF-APP total scores (Table 2, Supplementary Fig. 3). Additionally, measures of quality of sleep and daytime drowsiness showed statistically significant improvements (Table 2).

3.4. Tolerability and safety

During the study, 63.7% of patients experienced at least one TEAE. The majority (89.1%) of TEAEs were rated as mild or moderate in intensity, and did not result in a PP dose change (69.7%). TEAEs reported in ≥5% of patients were injection-site pain (13.7%), insomnia (10.8%), psychotic disorder (10.4%), headache and anxiety (6.1% each).

Two cases of fatal outcome were reported, one due to acute myocardial infarction and one due to completed suicide, both of which were considered not related to the study drug by the investigator. Overall, 19 (9.0%) patients reported one or more AEs that led to early termination of the study. The most frequent AEs leading to premature study discontinuation were psychotic disorder (n = 4, 1.9%), schizophrenia (n = 2; 0.9%) and amenorrhoea (n = 2; 0.9%).

Among the total patient population, 12 (5.7%) had a potentially prolactin-related TEAE, two (0.9%) reported hyperprolactinemia, and one (0.5%) patient reported both. Reported potentially prolactin-related TEAEs included amenorrhoea (2.4%), amenorrhoea, galactorrhea (0.5%), erectile dysfunction (1.4%), galactorrhea (0.5%), gynecomastia (0.5%) and sexual dysfunction (1.4%).

The mean ESRS total score at BL was 3.8, indicating low levels of EPMS at the beginning of treatment with PP. Nevertheless there was a statistically significant further reduction in EPMS (ESRS total score 3.8 [6.3] to 2.3 [5.9]; Wilcoxon signed-rank test, $p < 0.0001$ [BL to LOCF EP]).

A mean (SD) increase of 0.9 (2.0) kg/m^2 in BMI was observed in patients and a mean weight change (SD) between BL and LOCF EP of 2.6 (5.6) kg (95% CI 1.8, 3.4). Overall, 40 (22.5%) patients had a ≥7% increase in body weight.

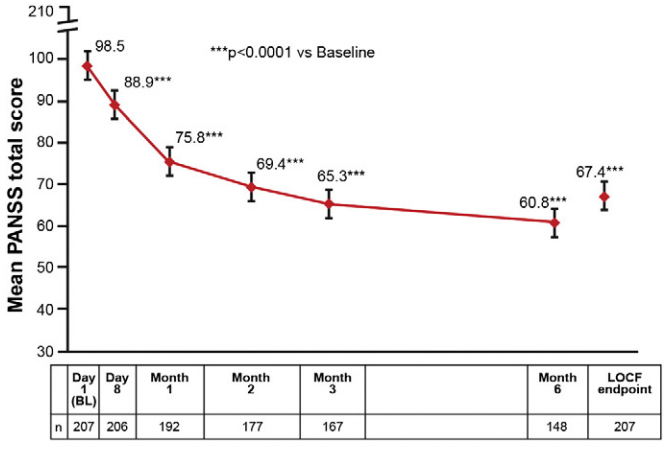

Fig. 2. Change in mean PANSS total score over time. Error bars represent 95% CI. BL, baseline; CI, confidence interval; LOCF, last observation carried forward; PANSS, Positive and Negative Syndrome Scale.

4. Discussion

The design of this study permitted optimization of PP and concomitant treatments to meet individual efficacy and tolerability needs of patients through flexible dosing within the recommended dose range. One advantage of this design is that treatment continuation is potentially higher than would be achieved otherwise, providing more meaningful data over a longer treatment period. Moreover, the patient population of the current sample was considerably different from that utilized in previously published PP RCTs. Based on inclusion criteria, patients had higher rates of comorbidities, comedications and substance abuse compared to the RCTs conducted with PP for regulatory purposes (Gopal et al., 2010; Nasrallah et al., 2010; Pandina et al., 2010). Taken together, the patient population and flexible-dose design of this study more closely resemble the situation encountered in routine clinical practice than that seen in RCTs, which are based on fixed-dose regimens and more selected patient samples. As such, this study can provide valuable guidance for use of, and transition to, PP in acutely ill patients with schizophrenia.

The level of psychotic symptoms experienced by patients at the outset of this study is indicative of a patient population with an acute exacerbation of schizophrenia, and the results suggest that PP is effective in improving symptoms of schizophrenia in these patients. Notably, psychotic symptoms significantly improved from Day 8 onwards in line with the early treatment response seen in other studies with PP (Alphs et al, 2011; Gopal et al., 2011; Pandina et al, 2010) as well as other reports suggesting that antipsychotic response starts within the first week of treatment and accumulates over time (Agid et al., 2003; Kapur et al., 2005; Suzuki et al., 2011). Outcomes particularly important in acutely ill patients with schizophrenia such as the rapid reduction of positive symptoms, anxiety, hostility and excitement were also achieved in this study. These findings are particularly important in patients with schizophrenia experiencing an acute exacerbation, where the primary treatment goal is rapid, optimal control of psychotic and associated symptoms.

Paliperidone as a molecule is associated with little or no sedation (Leucht et al., 2013). In this study of acute patients, there was a high level of concomitant sedating agent use at BL as well as during the study. However, the decline in use of concomitant sedating and/or anxiolytic medication during the study may be associated with the improvement of psychotic symptoms achieved with PP.

Improving personal and social functioning is another essential component of optimizing long-term outcomes for patients with schizophrenia. Control of symptoms is important to build a platform for patients to engage in psychosocial and rehabilitation therapies. However, even with effective symptom control, deficits in personal and social functioning can exist which may compromise the patient's capability to function in everyday life, form relationships and participate in useful activities, such as employment or school. While the patients' level of functioning was substantially lower in this acute patient population compared with non-acute patients switched from oral antipsychotics (Schreiner et al., 2014), improvements in patient functioning occurred early in the course of the study. There was a continuous improvement up to 6 months, suggesting that functional improvement is a gradual process that requires effective long-term treatment (Schreiner et al., 2014). In this study the behavioral components of social functioning, such as social contact and integration as well as patients' abilities and disabilities relevant for various aspects of functioning also showed significant improvement. These benefits may translate directly or indirectly into relevant functional outcomes such as employment (Kozma et al., 2011).

There were no new safety signals related to PP identified in this subset of patients and PP was generally well tolerated in line with earlier trials carried out in acutely exacerbated patients (Gopal et al., 2010; Nasrallah et al., 2010; Pandina et al., 2010). In randomized clinical trials of PP, prolactin levels were measured extensively at BL and at post-BL assessments; serum prolactin levels were considered elevated when they exceeded the upper limit of the testing laboratory's normal range (Einarson et al., 2010). In total, 2831/3173 (89.2%) patients in 10 clinical trials had prolactin levels recorded. Overall, at any time, elevated prolactin levels were found in 38.8% of patients and potentially prolactin-related AEs were reported in 107/3173 (3.4%) patients. As PALMFlexS was a pragmatic study designed to reflect routine clinical practice better, investigators could assess prolactin serum values at their own discretion at any time during the study. Potentially prolactin-related TEAEs were assessed by spontaneous reporting according to standards currently used in interventional studies. The 5.7% of patients reporting a potentially prolactin-related TEAE in this patient population was comparable to that reported in randomized clinical trials and therefore this approach seems appropriate for assessing the risk of potentially prolactin-related TEAEs for patients on PP in clinical practice.

While there has been much debate concerning the most appropriate means of assessing the relative benefits of LAT versus oral antipsychotics on outcomes in schizophrenia, including relapse prevention (Kishimoto et al., 2013; Leucht et al., 2011), the results reported here support the benefits of PP established from RCTs (Gopal et al., 2010; Nasrallah et al., 2010; Pandina et al., 2010) and provide supporting evidence for improved outcomes in patients with acute symptoms of schizophrenia unsuccessfully treated with oral antipsychotics upon direct switching to PP, in conditions closer to usual clinical practice. Limitations of the study should also be considered in interpreting the findings. As this is a non-comparative study, conclusions cannot be reached regarding the relative impact of previous oral antipsychotic treatment on patient outcome following switching to PP. The open-label nature of the study may also subject the results to the potential for bias. In addition, the absence of a control group may make it more difficult to put the incidence of side effects into perspective. However, using the same methodology of collecting TEAEs as in pivotal RCTs in this study allows for the comparison of reported side effects.

5. Conclusions

The design of this study provides useful data about the clinical experience of acute and longer-term treatment with PP in patients with schizophrenia more closely resembling patients encountered in routine clinical practice, drawing on the investigating physician's judgment of efficacy and tolerability to assess the most appropriate dose of PP.

Author contributions

All authors contributed towards the inception and development of the manuscript. Dr Bergmans performed statistical analysis of the results. All authors reviewed and approved each version of the manuscript.

Disclosures

Drs. Hargarter, Bergmans and Schreiner, and Ms. Keim are full-time employees of Janssen Cilag and shareholders of Johnson and Johnson. Dr. Cherubin is a full-time employee of Janssen Cilag. Dr. Rancans has received research grants from AstraZeneca, GlaxoSmithKline, Janssen Cilag and Lundbeck. In addition, Dr. Rancans received speaker honoraria from and is a member of advisory panels for AstraZeneca, GlaxoSmithKline, Janssen Cilag, Lundbeck, Sanofi Synthélabo and Servier. Dr. Bez has received research funds from Lundbeck, Sanofi-Aventis, AstraZeneca, Pfizer and Janssen Cilag. In addition, Dr. Bez has received speaker honoraria from Nobel, Bilim and Janssen Cilag, travel grants from Sanovel, Sanofi-Aventis, Janssen Cilag, Bilim and Janssen Cilag and is a member of advisory panels for Nobel and Janssen Cilag. Dr. Carpiniello has received research funds from AstraZeneca and Lundbeck. In addition, Dr. Carpiniello has received speaker honoraria from Lundbeck, Pfizer, Jannsen Cilag, AstraZeneca, Otsuka, ACRAF Angelini and Eli-Lilly, and is a member of advisory panels for Lundbeck and Otsuka. Dr. Parellada has received honoraria and/or research grants from the Fondo de Investigación Sanitaria (registered number PI080055) of the Spanish Ministry of Science and Innovation, Fundació la Marató de TV3 of Catalonia, Janssen Cilag and GlaxoSmithKline. Dr. Vidailhet has received speaker honoraria from Janssen, Otsuka, Lundbeck, Bristol Myers Squibb and Roche, travel grants from Janssen, Lundbeck and Otsuka, and is a member of advisory panels for Janssen, Roche and Otsuka.

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Appendix A. Supplementary data

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