

REGULAR RESEARCH ARTICLE

A Randomized, Double-Blind, Multicenter, Noninferiority Study Comparing Paliperidone Palmitate 6-Month Versus the 3-Month Long-Acting Injectable in Patients With Schizophrenia

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Abstract

Background: This double-blind (DB), randomized, parallel-group study was designed to evaluate efficacy and safety of paliperidone palmitate 6-month (PP6M) formulation relative to paliperidone palmitate 3-month (PP3M) formulation in patients with schizophrenia.

Methods: Following screening, patients entered an open-label (OL) maintenance phase and received 1 injection cycle of paliperidone palmitate 1-month (PP1M; 100 or 150 mg eq.) or PP3M (350 or 525 mg eq.). Clinically stable patients were randomized (2:1) to receive PP6M (700 or 1000 mg eq., gluteal injections) or PP3M (350 or 525 mg eq.) in a 12-month DB phase; 2 doses of PP6M (corresponding to doses of PP1M and PP3M) were chosen.

Results: Overall, 1036 patients were screened, 838 entered the OL phase, and 702 (mean age: 40.8 years) were randomized (PP6M: 478; PP3M: 224); 618 (88.0%) patients completed the DB phase (PP6M: 416 [87.0%]; PP3M: 202 [90.2%]). Relapse rates were PP6M, 7.5% (n=36) and PP3M, 4.9% (n=11). The Kaplan-Meier estimate of the difference (95% CI) between treatment groups (PP6M – PP3M) in the percentages of patients who remained relapse free was –2.9% (–6.8%, 1.1%), thus meeting noninferiority criteria (95% CI lower bound is larger than the pre-specified noninferiority margin of –10%). Secondary efficacy endpoints corroborated the primary analysis. Incidences of treatment-emergent adverse events were similar between PP6M (62.1%) and PP3M (58.5%). No new safety concerns emerged.

Conclusions: The efficacy of a twice-yearly dosing regimen of PP6M was noninferior to that of PP3M in preventing relapse in patients with schizophrenia adequately treated with PP1M or PP3M.

Trial Registration: Clinical Trials.gov identifier: NCT03345342

Keywords: Paliperidone palmitate 3-month, paliperidone palmitate 6-month, relapse-free, schizophrenia

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Significance Statement

Medications for schizophrenia in the form of injections that are long-lasting, known as long-acting injectable (LAI) antipsychotics, are more beneficial compared with oral pills in preventing the risk of relapse. Currently available LAIs can be received every 2 weeks up to once every 3 months, and there is a need for LAIs that are longer lasting, especially for patients with serious adherence issues and those living in isolated areas with healthcare access problems. Paliperidone palmitate 6-month (PP6M) is the first LAI that can be administered once every 6 months, enabling just 2 injections per year for patients who have been adequately treated on the 1-monthly or 3-monthly LAIs of paliperidone palmitate. In this phase 3 clinical study, the efficacy of PP6M was noninferior or comparable with the 3-monthly equivalent formulation (PP3M) for prevention of relapses, and there were no new safety concerns.

Introduction

Long-acting injectable (LAI) antipsychotics encourage better treatment outcomes in patients with schizophrenia by offering numerous advantages, including infrequent dosing, stable plasma medication levels, and adherence transparency and provide clinicians, patients, and caregivers the opportunity to intervene before further symptomatic worsening occurs (Brissos et al., 2014; Correll et al., 2016). LAI antipsychotics have shown superior efficacy to their oral equivalents in improving adherence, reducing hospitalizations and relapses in schizophrenia (Brissos et al., 2014; Marcus et al., 2015; Schreiner et al., 2015; Alphas et al., 2016; Correll et al., 2016; Greene et al., 2018).

There is extensive clinical trial evidence for the use of paliperidone palmitate 1-month (PP1M) and paliperidone palmitate 3-month (PP3M) formulations for maintaining treatment continuity and preventing relapses and risk of hospitalizations in patients with schizophrenia (Gopal et al., 2010, 2011; Hough et al., 2010; Berwaerts et al., 2015; Savitz et al., 2016; Di Lorenzo et al., 2018; Garcia-Portilla et al., 2020). The evidence is further strengthened by findings from real-world studies (Emsley et al., 2018; Emond et al., 2019; Patel et al., 2020). Both PP1M and PP3M have demonstrated efficacy in maintaining symptom and functional stability and acceptable safety and tolerability for long-term use in patients with schizophrenia (Attard et al., 2014; Bioque and Bernardo, 2018; Mathews et al., 2019). LAIs with longer dosing durations could be more patient-centric as they enable fewer injections per year with sustained medication delivery, particularly useful for patients living in isolated areas who may have transportation limitations or healthcare access problems (Mace et al., 2019; Pietrini et al., 2019; Blackwood et al., 2020; Moreno et al., 2020). To address this need, a paliperidone palmitate 6-month (PP6M) formulation was developed and is the first LAI with a substantially longer dosing interval of 6 months, enabling just 2 injections per year. The PP6M LAI is not intended for acutely symptomatic patients. Patients need to be stabilized on the shorter-acting equivalents (PP1M or PP3M) before transitioning to the longer-acting treatment with PP6M.

The present study was an active-controlled, non-inferiority study to evaluate the efficacy of PP6M relative to PP3M in preventing relapses and assess the safety and pharmacokinetics (PK) of PP6M in clinically stabilized patients with schizophrenia.

MATERIALS AND METHODS

Ethical Practices

The study protocol and amendments were approved by an independent ethics committee or institutional review board (See list of institutional review boards and independent ethics committees in the [online supplement](#)). The trial was conducted in compliance with the ethical principles of the Declaration of Helsinki, Good Clinical

Practices, and applicable regulatory requirements. All patients provided written informed consent before study participation.

Patients

Eligible patients were between 18 and 70 years of age, had a Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) diagnosis of schizophrenia for ≥ 6 months before screening, and had a Positive and Negative Syndrome Scale (PANSS) total score of < 70 points at screening. Patients were receiving treatment with paliperidone palmitate (PP1M [100 or 150 mg eq.] or PP3M [350 or 525 mg eq.], with dose timing that fits the current study schedule), injectable risperidone microspheres, or any oral antipsychotic (except clozapine), which in the opinion of the investigator could have been discontinued during screening (except for PP1M/PP3M).

Patients who met any of the following criteria were excluded from the study: active primary DSM-5 diagnosis other than schizophrenia; receiving any form of involuntary treatment (e.g., involuntary psychiatric hospitalization); attempted suicide within 12 months before screening and was at imminent risk of suicide or violent behavior, as clinically assessed by the investigator; DSM-5 diagnosis of moderate or severe substance use disorder (except for nicotine or caffeine) within 6 months of screening; history of neuroleptic malignant syndrome, tardive dyskinesia, or clinically significant and unstable medical illness; history of treatment-resistant schizophrenia (i.e., failure to respond to 2 adequate trials of different antipsychotic medications with adequate doses); or intolerability or severe reactions to moderate or higher doses of antipsychotic medications. Please see [supplementary Methods](#) for details on entry criteria.

Patients were recruited from various sites, and the recruitment method was dependent on the regulations of the respective independent ethics committee or institutional review board and meeting eligibility criteria. Acutely ill patients were excluded, and the recruitment was at the discretion of the investigators.

Study Design

This study (NCT03345342) was a double-blind (DB), randomized, active-controlled, parallel-group multicenter study conducted between November 2017 and May 2020 at 121 research sites in 20 countries.

The study had 3 phases: (1) a screening phase (up to 28 days), (2) an open-label (OL) maintenance phase (duration of 1 or 3 months depending on treatment received [1 injection cycle of PP1M/PP3M]), and (3) DB phase (12 months) ([Figure 1](#)). Patients who entered the study on an oral antipsychotic, injectable risperidone microspheres, or PP1M previously initiated but not stabilized at

study entry were eligible to participate in an OL transition phase just prior to the OL maintenance phase to initiate and/or continue treatment with PP1M for up to 4 months. Patients on PP1M or PP3M OL maintenance treatment could be randomized to DB treatment with equivalent doses of PP6M or PP3M.

Treatment

Patients could have entered the study screening phase on PP1M (100 or 150 mg eq.), PP3M (350 or 525 mg eq.), injectable risperidone microspheres (50 mg), or oral antipsychotics (at any dosage with a reason to change, such as problems with efficacy, safety or tolerability, or a preference for a LAI) as prior medications. Patients without documented tolerability to any oral or injectable risperidone or paliperidone formulations received paliperidone extended-release/prolonged-release 6-mg tablets or risperidone 3 mg/d for 4–6 consecutive days during screening. Patients previously treated with oral antipsychotics, injectable risperidone microspheres, or a moderate or higher dose of PP1M but without previous stabilization (defined as ≥ 3 monthly injections, with the last 2 doses being the same dose strength) received additional doses of PP1M during the conditional OL transition phase (Figure 1).

In the OL maintenance phase, all patients received only 1 dose of PP1M (100 or 150 mg eq.) or PP3M (350 or 525 mg eq.), which was either matched (PP1M to PP1M, or PP3M to PP3M) or

converted (PP1M to PP3M) to an equivalent of the dose last received in the OL transition phase or prior to enrollment (Figure 1). To ensure adequate numbers of PP1M- and PP3M-treated patients were switched to PP6M when randomized, some patients (after appropriate treatment with PP1M) were switched to PP3M on entry to the OL maintenance phase (until approximately one-half of the total maintenance phase sample was treated with PP3M) because low enrollment of patients previously treated with PP3M was anticipated. Injections of PP1M or PP3M during the OL phase were deltoid or gluteal in accordance with the prescribing information. In the DB phase, patients were randomized to PP6M or PP3M (2:1, respectively). Patients in the PP3M group who received OL PP1M doses (100 or 150 mg eq.) were assigned to DB PP3M doses (350 or 525 mg eq., respectively), and those on OL PP3M doses (350 or 525 mg eq.) continued at the same DB dose level (Figure 1). Patients in the PP6M group were transitioned to PP6M doses corresponding to the prescribed doses of PP1M (100 mg eq. or 150 mg eq.) and PP3M (350 mg eq. or 525 mg eq.) (supplementary Table 1). Patients who received “moderate” doses of OL PP1M (100 mg eq.) or PP3M (350 mg eq.) received the “moderate” dose of PP6M (700 mg eq.) in the DB phase, and those on the “high” doses of OL PP1M (150 mg eq.) or PP3M (525 mg eq.) received the “high” dose of PP6M (1000 mg eq.) in the DB phase. Injections (PP6M and PP3M) were administered dorsogluteally due to the larger volume of PP6M.

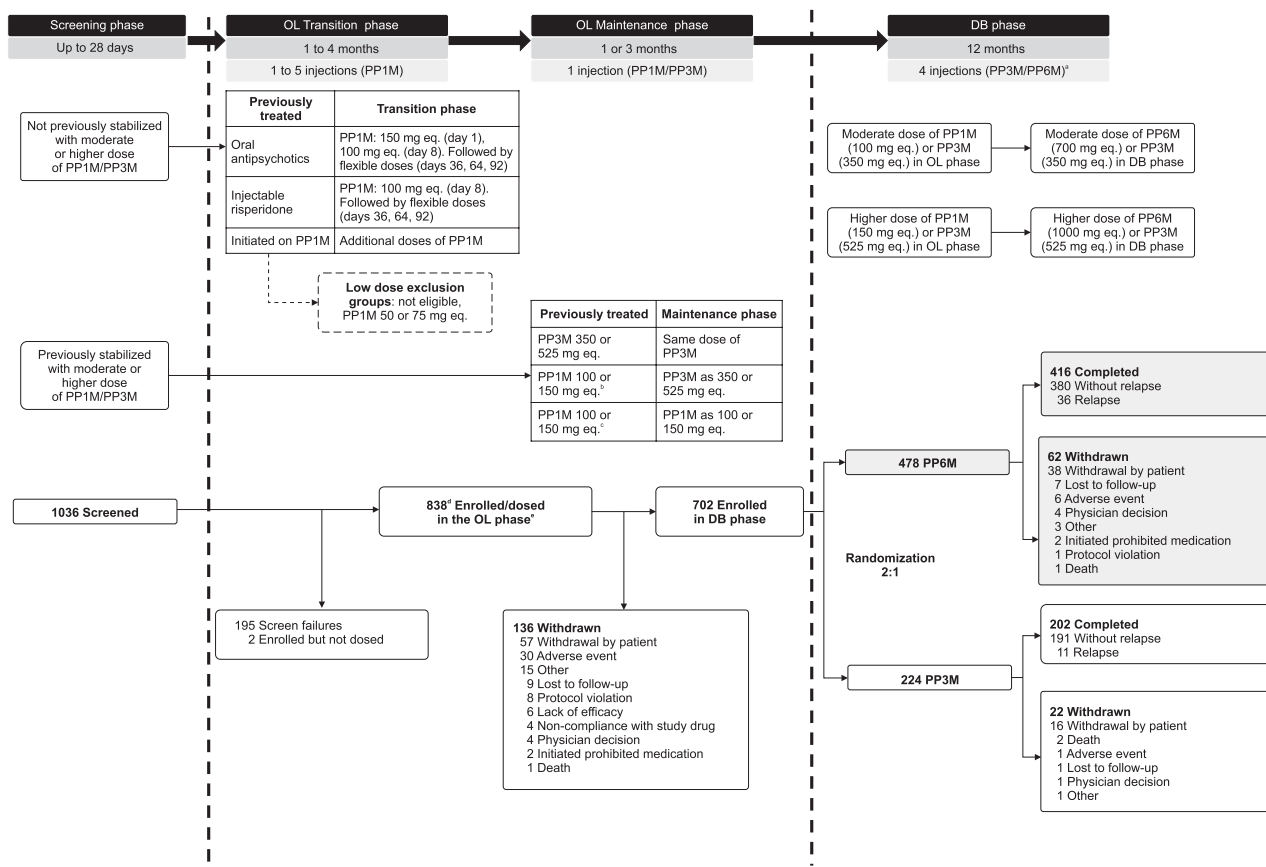


Figure 1. Study design and patient disposition. Abbreviations: DB, double-blind; OL, open label; PP1M, paliperidone palmitate once-monthly formulation; PP3M, paliperidone palmitate 3-month formulation; PP6M, paliperidone palmitate 6-month formulation. ^aPatients in PP6M group received 2 placebo injections. ^bBefore pre-randomization (approximately one-half of the total maintenance phase sample was treated with PP3M) criteria are met. ^cAfter pre-randomization criteria are met. ^dOne patient entered the OL transition phase, withdrew, then re-screened again and entered the DB phase. ^eAmong 838 patients who entered the OL phase, 71 withdrew during OL transition phase and 767 entered the OL maintenance phase.

Randomization and Blinding

Randomization was based on a computer-generated randomization schedule, balanced using randomly permuted blocks, and stratified by study site and moderate or high dose in the maintenance phase. To maintain the blinding, patients treated with PP6M received injections of placebo at the 3-month time points between their 6-month doses. The placebo was 20% Intralipid® (200 mg/mL) injectable emulsion and matched the appearance of the active treatment. Therefore, the 12-month DB phase included a total of 4 injections at 3-month intervals, irrespective of treatment group. Due to differences in syringe sizes for PP6M vs PP3M, the study drug administrator was unblinded and not allowed to perform any other study-related procedures or communicate patient-related information with study-site personnel to ensure integrity of the blind.

PK Assessments

See [supplementary Methods](#).

Efficacy Assessments

The primary endpoint was time to relapse during the DB phase. This noninferiority primary endpoint was based on the difference in the Kaplan-Meier 12-month estimate of survival (i.e., percentage of patients remaining relapse free) between PP6M and PP3M. The relapse criteria were identical to those used in previous clinical studies of PP3M and PP1M (Berwaerts et al., 2015; Savitz et al., 2016). Relapse was defined as ≥ 1 of the following: (1) psychiatric hospitalization due to exacerbation of schizophrenia symptoms (involuntary or voluntary admission); (2) 25% increase (for patients with PANSS scores >40 at randomization) or 10-point increase (for patients with PANSS scores ≤ 40 at randomization) in PANSS total score from randomization for 2 consecutive assessments between 3 to 7 days; (3) deliberate self-injury resulting in suicide or exhibited violent behavior resulting in clinically significant injury; (4) aggressive behavior, suicidal or homicidal ideation; (5) PANSS items scores ≥ 5 (if PANSS items was ≤ 3 at randomization); or ≥ 6 (PANSS items was 4 at randomization) after randomization for 2 consecutive assessments between 3 to 7 days on any of the following items: P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), P6 (suspiciousness/persecution), P7 (hostility), and G8 (uncooperativeness). The date of relapse was the date of the first assessment for symptoms of relapse (not the date of confirmation).

Secondary efficacy endpoints included changes from baseline during the 12 months of the DB phase in the following scales: PANSS total score and subscale scores (Kay et al., 1987), Clinical Global Impression-Severity (CGI-S) (Busner and Targum, 2007), and Personal and Social Performance (PSP) scale (Morosini et al., 2000). Additionally, the proportion of patients during the DB phase who met criteria for symptomatic remission (defined as having a score ≤ 3 on all of the following 8 PANSS items: P1, P2, P3, N1, N4, N6, G5, and G9 for the last 6 months of DB treatment, with 1 excursion allowed) was summarized (Andreasen et al., 2005).

Safety Assessments

Safety was assessed by treatment-emergent adverse events (TEAEs), 12-lead electrocardiograms, vital signs, clinical laboratory tests, and injection-site evaluations. Extrapyramidal symptoms (EPS) were assessed by the Simpson-Angus Scale, Barnes Akathisia Rating Scale, and Abnormal Involuntary Movement

Scale. Suicidal ideation and behavior were assessed using Columbia Suicide Severity Rating Scale.

Statistical Analysis

Sample Size Determination—Sample size calculation for the DB phase was based on the primary endpoint, which was also tested for noninferiority. The study was designed to have a minimum of 80% power to demonstrate an 85% survival rate (percentage of patients remaining relapse free at 12 months) in the PP3M group based on 1-sided significance level of 2.5%. A total 549 patients were expected to be randomized (2:1, PP6M:PP3M) to demonstrate with 80% power that PP6M is no worse than PP3M by a noninferiority margin of -10% for the percentage of patients remaining relapse free at 12 months assuming efficacy similar as observed in previous studies of PP3M (rationale for the 10% noninferiority margin is described previously; Savitz et al., 2016). The study design assumed discontinuation rates of 20% and 40% during the transition and maintenance for patients who entered the study with or without previous PP1M or PP3M stability, respectively, and a dropout rate of 10% during the DB phase. Given these assumptions for discontinuation, the study targeted approximately 840 patients to enter the transition or maintenance phase.

Statistical Analyses—Plasma concentrations of paliperidone and paliperidone palmitate and the derived PK parameters were summarized descriptively for the PK data analysis set. Efficacy and safety during the OL phase were summarized for the OL intent-to-treat (ITT-OL) set (all patients who received ≥ 1 dose of OL study drug, including transition and maintenance phases). The primary efficacy analysis included all randomized patients who received ≥ 1 dose of treatment (PP3M or PP6M) during the DB phase (ITT-DB analysis set). Analyses involving changes from the DB baseline were provided for both observed case and last observation carried forward data. The ITT-DB set was used for all secondary efficacy endpoints. An additional analysis with the per-protocol analysis set (all patients who were randomized in the DB-phase received ≥ 1 dose of DB treatment and did not have any major protocol violations) was performed to evaluate consistency of results for the primary endpoint. Safety analysis during the DB phase was conducted using the DB safety analysis set (DB safety; same as the ITT-DB).

The null hypotheses to be tested using a 1-sided $\alpha=0.025$ level were as follows: $H_0: p_6 - p_3 \leq -\delta$ vs $H_1: p_6 - p_3 > -\delta$; where p_3 referred to the percentage of patients who remained relapse free at 12 months for the PP3M groups and p_6 referred to the percentage of patients who remained relapse free at 12 months for the PP6M group. The Kaplan-Meier method was used to estimate the 12-month cumulative estimate of survival. Standard error (SE) estimates were based on Greenwood's formula. Noninferiority of PP6M to PP3M was to be concluded if the lower limit of the 2-sided 95% confidence interval (CI) of the difference in the relapse-free rates between PP6M and PP3M exceeded -10% . Hazard ratios (HR) along with 95% CI were estimated using the Cox proportional hazards model with treatment as the only factor to compare treatment effects on the time to relapse of schizophrenia symptoms. The change from baseline (DB) at each visit in PANSS total and subscale scores and CGI-S and PSP scores during the DB phase was analyzed using an ANCOVA model with factors for treatment and country and baseline score as a covariate. Estimates of treatment effects as least square mean difference (PP6M – PP3M) and the accompanying 95% CI were presented. The proportion of patients achieving symptomatic remission in the DB phase was calculated using the Cochran-Mantel-Haenszel test controlling for country.

RESULTS

Patient Disposition

Of the 838 patients enrolled and dosed in the OL phases, 702 (83.8%) completed the OL phases and were randomized (PP6M, $n=478$; PP3M, $n=224$) in the DB phase (Figure 1). All 702 patients were included in the ITT-DB set. Withdrawal by patient (57/838 [6.8%]) or adverse events (30/838 [3.6%]) were the common reasons for discontinuations in the OL phases. A total of 618 (88.0%) patients completed the DB phase, with similar percentages in both treatment groups (PP3M, $n=202$ [90.2%]; PP6M $n=416$ [87.0%]). Withdrawal by patient (54/702 [7.7%]) was the most common reason for discontinuation during the DB phase.

Demographics and Baseline Characteristics

The demographics and baseline (OL) psychiatric characteristics of patients in the PP6M and PP3M groups in the DB phase were generally similar (Table 1). Overall demographics and baseline characteristics of dropouts/not randomized were similar to those randomized in the DB phase. Patients ($n=702$) were a mean age of 40.8 (range, 18–69) years and were mostly men (68.4%), White (74.2%), non-Hispanic (84.6%), and ≤ 50 years of age (79.6%). The PP6M and PP3M treatment groups were matched in terms of baseline severity of illness as measured by the PANSS, CGI-S, and PSP scores and age at first diagnosis. Duration of psychiatric hospitalization was numerically longer in the PP6M group (mean [SD] duration of hospitalization: PP6M, 63.1 [70.25] days vs PP3M, 44.6 [53.09] days).

Prior and Concomitant Therapies

At DB phase entry, the proportion of patients on prior psychotropic medication was similar between the PP3M and PP6M group (supplementary Table 2). Before study entry, 701/702 (99.9%) patients received psychotropic medications. Atypical antipsychotics (61.0%) were most commonly used, 18.4% of patients received benzodiazepines, and 14.2% were on anti-EPS medications.

During the DB phase, the concomitant use of benzodiazepines (23.6% vs 21.0%), anti-EPS medications such as anticholinergic medications (15.5% vs 12.9%), antihistamines (6.1% vs 8.5%), and beta-blockers (propranolol: 2.1% vs 1.8%; metoprolol: 1.3% vs 1.8%) were similar between PP6M and PP3M groups (supplementary Table 3). A total of 415/702 (59.1%) patients received concomitant medications other than benzodiazepines during the DB phase (PP6M: 60.5% vs PP3M: 56.3%), the common ones being acetaminophen (9.7%), metformin (8.3%), and biperiden (7.7%).

Drug Exposure

A total of 106/838 (12.6%) patients underwent oral tolerability testing, and none reported tolerability concerns. Of the 568 patients treated in the OL transition phase, 272 (47.9%) received 5 injections of PP1M and 217 (38.2%) received 4 injections; 458 (80.6%) patients received PP1M for ≥ 91 days. Of the 767 patients treated in the OL maintenance phase, 362 patients received PP1M (100 mg eq., $n=175$; 150 mg eq., $n=187$) and 405 received PP3M (350 mg eq. $n=193$; 525 mg eq., $n=212$). In the DB phase, the mean (SD) duration of exposure was 329.8 (86.97) days in the PP6M group and 336.4 (80.89) days in the PP3M group. The mean (SD) dose of PP6M was 855.6 (150.05) mg eq. and the mean (SD) dose of PP3M was 442.2 (87.57) mg eq. Overall, 86.4% of patients

in the PP6M group received 2 and 84.8% in the PP3M group received 4 active injections.

Pharmacokinetics

In the DB phase for all treatments and administered dosages, mean C_{max} was achieved around 1 month after each dose (Figure 2). After achieving mean C_{max} , concentrations gradually declined for the remainder of the dosing cycle. Patients who received PP6M had approximately 20%–25% lower trough concentrations (dose normalized C_{trough}) compared with patients who received PP3M. In the DB phase, mean peak paliperidone concentrations (dose normalized C_{max}) after PP6M dosing was slightly higher (1.4- to 1.5-fold) than after PP3M dosing, and mean total paliperidone exposure (dose normalized AUC_{6month}) was comparable after PP3M and PP6M dosing (see supplementary Results for more details).

Efficacy

Thirty-six (7.5%) patients in the PP6M group and 11 (4.9%) in the PP3M group experienced a relapse event during the DB phase (ITT-DB). The Kaplan-Meier estimate of the difference (95% CI) between the treatment groups (PP6M – PP3M) in the percentages of patients who remained relapse free was -2.9% (-6.8% , 1.1%). Thus, PP6M was noninferior to PP3M based on the lower bound of the 95% CI being larger than the pre-specified noninferiority margin of -10% (Figure 3). Analysis using the per-protocol set corroborated the ITT-DB analysis, with the lower bound of 95% CI of Kaplan-Meier estimate of treatment difference being larger than the pre-specified noninferiority margin of -10% (supplementary Figure 1). Thus, PP6M was declared noninferior to PP3M for the primary efficacy endpoint. The median time to relapse (the time at which the cumulative survival function equals 0.5 [or 50%]) was not estimable for either the PP6M or PP3M groups due to the low number of relapses during the DB phase (Table 2; Figure 3). The most common reasons for relapses were an increase of $\geq 25\%$ in PANSS total score (PP6M: 16 [3.3%]; PP3M: 5 [2.2%]), PANSS item (P1, P2, P3, P6, P7, G8) score of ≥ 5 after randomization (PP6M: 13 [2.7%]; PP3M: 5 [2.2%]), and psychiatric hospitalizations (PP6M: 11 [2.3%]; PP3M: 6 [2.7%]). The ratio (95% CI) of the instantaneous risk of relapse for a patient who received PP6M treatment vs the risk for a patient who received PP3M in the DB phase was 1.57 (0.80, 3.08).

Results for the secondary endpoints corroborated the primary efficacy analysis, indicating comparable improvements in PANSS total, subscale and Marder factor scores, and CGI-S and PSP scores between PP6M and PP3M groups from DB baseline to DB endpoint (Table 3; supplementary Figures 2 and 3). Changes in CGI-S and PSP scores indicated persistence of clinical stability over the 12-month DB period. The percentage of patients with $\geq 20\%$ improvement from DB baseline to DB endpoint in PANSS total scores was numerically higher in the PP6M (38.9%) compared with PP3M (32.1%); similar percentage of patients in the PP6M and PP3M treatment groups showed an improvement of $\geq 30\%$ and $\geq 40\%$ in PANSS total score (Table 3). More than 60% of patients in both treatment groups (PP6M: 66.3%; PP3M: 70.1%) achieved symptomatic remission during the DB phase.

Safety

A total of 341 of 838 patients (40.7%) had ≥ 1 TEAE in the OL phase; 23 (2.7%) patients had ≥ 1 serious TEAE, 31 (3.7%) had TEAEs leading to withdrawal of the study drug, and 1 (0.1%) death (due to completed suicide) was reported in the OL phase (Table 4).

Table 1. Demographic, Baseline Characteristics, and Psychiatric History (ITT-OL and ITT-DB Analysis Sets)

	DB phase (ITT-DB)		
	PP6M (n=478)	PP3M (n=224)	Total (n=702)
Age, ^a mean (SD), y	41.2 (11.77)	40.0 (10.98)	40.8 (11.53)
Sex, n (%)			
Men	326 (68.2)	154 (68.8)	480 (68.4)
Race, n (%)			
American Indian or Alaska Native	0	0	0
Asian ^b	66 (13.8)	30 (13.4)	96 (13.7)
Black or African American	49 (10.3)	23 (10.3)	72 (10.3)
Native Hawaiian or Other Pacific Islander	3 (0.6)	0	3 (0.4)
White	353 (73.8)	168 (75.0)	521 (74.2)
Other	0	0	0
Multiple	3 (0.6)	2 (0.9)	5 (0.7)
Not reported	4 (0.8)	1 (0.4)	5 (0.7)
Ethnicity, n (%)			
Hispanic or Latino	75 (15.7)	25 (11.2)	100 (14.2)
Not Hispanic or Latino	397 (83.1)	197 (87.9)	594 (84.6)
Not reported	6 (1.3)	2 (0.9)	8 (1.1)
Weight-baseline (OL), mean (SD), kg	81.9 (16.86)	80.8 (17.01)	81.5 (16.90)
BMI-baseline (OL), mean (SD), kg/m ²	27.9 (4.96)	27.5 (4.96)	27.7 (4.96)
Age at schizophrenia diagnosis, mean (SD), y	27.7 (9.01)	27.5 (9.05)	27.6 (9.02)
Prior hospitalization, ^c n (%)			
N	356	168	524
None	205 (57.6)	98 (58.3)	303 (57.8)
Once	97 (27.2)	47 (28.0)	144 (27.5)
Twice	37 (10.4)	18 (10.7)	55 (10.5)
Three times	11 (3.1)	4 (2.4)	15 (2.9)
Four times or more	6 (1.7)	1 (0.6)	7 (1.3)
PANSS total, n			
Baseline (MA), mean (SD)	53.1 (9.19)	52.9 (9.62)	53.0 (9.33)
Baseline (DB), mean (SD)	51.9 (9.60)	51.4 (9.77)	51.7 (9.65)
PSP			
Baseline (MA), mean (SD)	65.6 (12.37)	65.2 (11.78)	65.5 (12.18)
Baseline (DB), mean (SD)	66.3 (12.50)	66.5 (11.82)	66.4 (12.28)
CGI-S			
Baseline (MA), mean (SD)	3.1 (0.78)	3.1 (0.76)	3.1 (0.78)
Baseline (DB), mean (SD)	3.0 (0.78)	3.0 (0.77)	3.0 (0.78)

Abbreviations: BMI, body mass index; CGI-S, Clinical Global Impression-Severity; DB, double-blind; ITT, intent-to-treat; MA, maintenance phase; OL, open label; PANSS, Positive and Negative Symptom Scale; PP3M, paliperidone palmitate 3-month formulation; PP6M, paliperidone palmitate 6-month formulation PSP, Personal and Social Performance; SD, standard deviation.

^aAge at screening.

^bAsian subcategories include Chinese, Korean, Japanese, Filipino, Asian Indian, Thai, Malaysian, and Asian (other).

^cNumber of hospitalizations for psychosis within 24 months prior to study start.

In the DB phase, TEAEs were reported in a comparable percentage of patients in the PP6M (297/478 [62.1%]) and PP3M (131/224 [58.5%]) groups. The most common TEAEs ($\geq 5\%$ in either group) were increased weight, injection-site pain, headache, upper respiratory tract infections, and nasopharyngitis. Most TEAEs were mild or moderate in severity. In total, 24/478 (5.0%) patients in the PP6M group and 15/224 (6.7%) in the PP3M group experienced serious TEAEs that were mostly related to worsening of psychiatric symptoms; schizophrenia was the most frequent (PP6M: 1.7%; PP3M: 0.4%). Overall, 16/478 (3.3%) patients in the PP6M group and 6/224 (2.7%) in the PP3M group discontinued the DB phase due to TEAEs that were mostly psychiatric in nature, with schizophrenia (PP6M: 8 [1.7%]; PP3M: 1 [0.4%]) being the most common. Three deaths (PP6M: n=1 [cause not specified]; PP3M: n=2 [pulmonary embolism and sudden death, unknown cause, n=1 each]) were reported in the DB phase; investigators considered these deaths as not related to study medication.

The occurrences of TEAEs of special interest related to EPS (46 [9.6%] vs 19 [8.5%]), suicidality (5 [1.0%] vs 6 [2.7%]), agitation and aggression (3 [0.6%] vs none), somnolence (9 [1.9%] vs 3 [1.3%]), tachycardia (7 [1.5%] vs 1 [0.4%]), orthostatic hypotension (2 [0.4%] vs 2 [0.9%]) and QT prolongation (2 [0.4%] vs 2 [0.9%]), and diabetes mellitus and hyperglycemia (15 [3.1%] vs 6 [2.7%]) were generally similar between the treatment groups (PP6M vs PP3M). There were no reported TEAEs for neuroleptic malignant syndrome or post-injection delirium/sedation syndrome during the study.

Prolactin-related TEAEs also occurred in a similar percentage of patients (PP6M: 18/478 [3.8%]; PP3M: 7/224 [3.1%]). The magnitude of change in mean (SD) levels of serum prolactin from OL or DB baseline to DB endpoint was greater in patients from the PP3M vs the PP6M group (Table 5). Median prolactin levels in men remained relatively stable throughout the OL and DB phases, whereas women showed an increase from OL baseline to DB baseline (continued to week 3 in the DB phase and remained

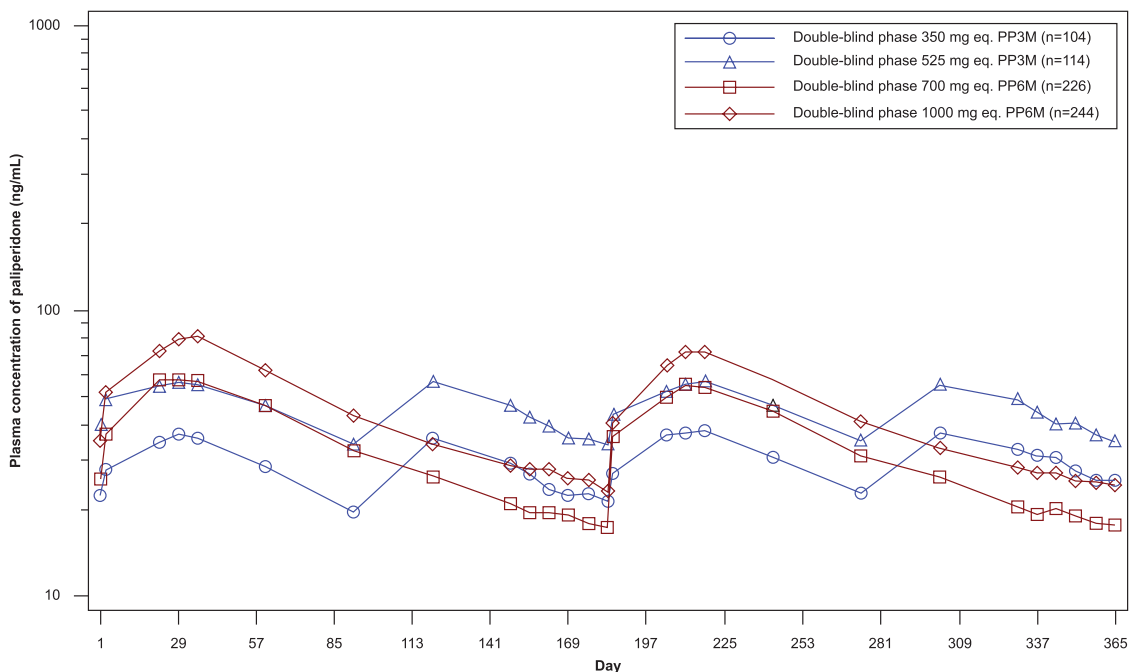
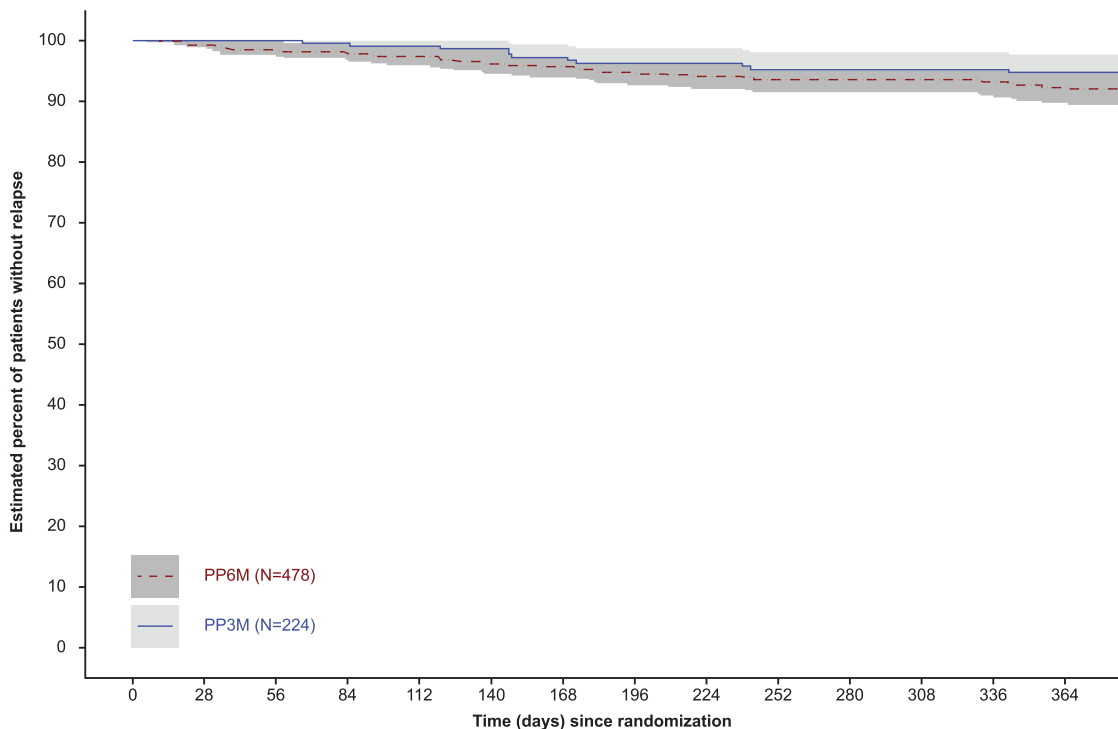


Figure 2. Semi-logarithmic mean (SD) plasma concentration time profiles of paliperidone after administration of PP3M at 350 or 525 mg eq. and PP6M at 700 or 1000 mg eq. (PK data analysis set) in the DB phase. The x-axis displays the day relative to the day of dosing (day 1) in the DB phase. Abbreviations: DB, double-blind; PK, pharmacokinetics; PP3M, paliperidone palmitate 3-month formulation; PP6M, paliperidone palmitate 6-month formulation.



		Number of patients remaining													
		0	28	56	84	112	140	168	196	224	252	280	308	336	364
PP3M		224	223	221	219	215	211	205	200	196	193	193	193	193	160
PP6M		478	471	465	457	447	440	436	417	408	404	403	399	393	328
		Cumulative number of patients with relapse													
PP3M		0	0	0	1	2	3	6	8	8	10	10	10	10	11
PP6M		0	3	8	11	13	18	20	25	27	29	29	29	32	35

Figure 3. Kaplan-Meier plot and 95% pointwise confidence-based percentage of patients without relapse during the DB phase (ITT-DB analysis set). Abbreviations: DB, double-blind; ITT, intent-to-treat; PP3M, paliperidone palmitate 3-month formulation; PP6M, paliperidone palmitate 6-month formulation.

Table 2. Time to Relapse During DB Phase and Number of Patients Who Remained Relapse Free at End of DB Phase (ITT-DB Analysis Set)

	PP6M (n=478)	PP3M (n=224)	Total (n=702)
No. assessed	478	224	702
No. censored (%) ^a	442 (92.5)	213 (95.1)	655 (93.3)
No. of relapse (%)	36 (7.5)	11 (4.9)	47 (6.7)
Time to relapse (days) ^b			
25% Quantile (95% CI)	NE	NE	NE
Median (95% CI)	NE	NE	NE
75% Quantile (95% CI)	NE	NE	NE
Relapse free ^b			
End of 12 mo (d 365 [DB])			
Percentage relapse free	91.9	94.8	
Difference (PP6M – PP3M)	–2.9		
95% CI	(–6.8; 1.1)		

Abbreviations: CI, confidence interval; DB, double-blind; ITT, intent-to-treat; NE, not estimable; PP3M, paliperidone palmitate 3-month formulation; PP6M, paliperidone palmitate 6-month formulation.

^aCensored include patients who completed the DB phase without relapses and patients who withdrew early during the DB phase.

^bBased on Kaplan-Meier product limit estimates.

relatively stable through month 6) (Figure 4). Incidences of TEAEs of weight gain in the DB phase were also similar between the groups: PP6M, 44/478 (9.2%) vs PP3M, 18/224 (8.0%). Injection site-related TEAEs were reported in 59/478 (12.3%) patients in the PP6M group and 11/224 (4.9%) in the PP3M group. Injection site pain was the most frequently reported TEAE in the PP6M (37 [7.7%]) and PP3M (9 [4.0%]) groups, and all other TEAEs including induration, redness, and swelling occurred in <2% of patients in both groups. Induration, redness, and swelling at the injection site, as noted by investigator evaluation, were observed in ≤6% of patients in both treatment groups and were mostly mild in severity. Reduction in mean (SD) value of injection site pain was observed in local tolerability assessments by patients using a visual analog scale from DB baseline to endpoint (Table 5).

Discussion

This multicenter, randomized, DB relapse prevention study demonstrated the noninferiority of PP6M at 700 and 1000 mg eq. doses in patients with schizophrenia, suggesting comparable efficacy with its 3-monthly equivalent formulation (PP3M) for patients who remained relapse free at the end of the 12-month DB phase. There were no appreciable differences in efficacy or safety when transitioning directly from PP1M or PP3M to PP6M. The safety profiles of PP6M and PP3M were largely similar aside from higher injection site pain with PP6M, which could be attributable to the larger injection volume.

The rate of relapse during the DB phase was low in both PP6M (7.5%) and PP3M (4.9%) groups, and a high proportion of patients remained relapse free and completed the 12-month DB phase (PP6M: 79.5%; PP3M: 85.3%). Results for the secondary efficacy analysis were supportive of the primary analysis. Overall, the type and incidence of TEAEs were comparable between PP6M and PP3M groups in the DB phase and consistent with the known profile of paliperidone palmitate (Hough et al., 2010; Kramer et al., 2010; Gopal et al., 2011; Berwaerts et al., 2015; Savitz et al., 2016). None of the TEAEs related to injection site, potentially prolactin-related, weight gain or diabetes mellitus and hyperglycemia—were reported as serious or resulted in treatment discontinuation during the OL or DB phase. Investigator evaluations of swelling, redness, and induration were similar across treatment groups, and patient assessment of injection site pain showed reduction from DB baseline to endpoint for

both treatments, suggesting good tolerability and acceptance of the dorsogluteal injections.

Two doses of PP6M (moderate: 700 mg eq.; high: 1000 mg eq.) that resulted in a range of paliperidone plasma exposures similar to simulated exposures obtained with the most commonly prescribed monthly doses of PP1M (100 and 150 mg eq.), 3-monthly doses of PP3M (350 and 525 mg eq.), and corresponding doses of once-daily paliperidone ER (8 [dose used for comparing moderate-dose level] and 12 mg) were selected for assessment (data on file). Dose-normalized total exposure over a 6-month period (2 PP3M administrations vs 1 PP6M administration) were comparable between dose levels for both products. Overall, administration of PP6M once every 6 months, at doses of 700 and 1000 mg. eq., resulted in a range of paliperidone exposures that overlapped with the range of exposures obtained with corresponding doses of PP3M. Relapses were observed throughout dosing cycle and did not appear to be clustered near the end of dosing cycle for both treatments, implying that the comparably lower PP6M C_{trough} is likely not the key determinant of relapse.

To date, the PP6M LAI has the longest available dosing interval of 6 months and is intended for use in stable patients with schizophrenia who have been adequately treated with PP1M and PP3M. Its widespread use will require a paradigm shift in how clinicians and patients place oral antipsychotics and LAIs in the management of schizophrenia. Longer-term treatment planning will be required. Evidence supporting patient-centric care also indicates that long-term treatment continuation in schizophrenia improves when treatment injections are less frequent or have longer dosing intervals (Citrome, 2017; Pietrini et al., 2019). Fewer injections are associated with less social stigma, which is a barrier in patients with severe mental illness (da Silva et al., 2020). The twice-yearly dosing regimen of PP6M represents a significant advancement over existing treatments for the management of a chronic illness such as schizophrenia. The use of PP6M would allow patients with limited access to healthcare (due to geographic or economic constraints) to have more consistent medication coverage. Real-world data from specific groups of clinical interest such as homeless patients who often have infrequent contact with outreach workers, patients with recent-onset schizophrenia who have high relapse rates within 5 years after initial recovery, or patients with a history of incarceration or self-harm could provide useful insights on

Table 3. Summary of Change From DB Baseline in Secondary Efficacy Measures During the DB Phase (ITT-DB Analysis Set)

	PP6M (n=478)	PP3M (n=224)	Between-group difference LS means (SE), (95% CI)
PANSS total score^a			
Baseline, mean (SD)	51.9 (9.60)	51.4 (9.77)	-0.1 (0.67)
Change from baseline, mean (SD)	-1.8 (8.92)	-1.6 (7.40)	(-1.44; 1.19)
PANSS subscale scores,^a mean (SD)			
Positive subscale			
Baseline	11.0 (3.21)	10.8 (2.98)	0.0 (0.25)
Change from baseline	-0.1 (3.30)	-0.1 (2.82)	-0.46; 0.51
Negative subscale			
Baseline	16.0 (4.20)	15.9 (4.18)	-0.1 (0.21)
Change from baseline	-0.7 (2.70)	-0.6 (2.61)	-0.48; 0.35
General psychopathology subscale			
Baseline	24.9 (4.78)	24.7 (5.05)	-0.0 (0.36)
Change from baseline	-1.0 (4.86)	-0.9 (4.18)	-0.76; 0.66
PANSS Marder standardized factor scores,^a mean (SD)			
Positive symptoms			
Baseline	13.9 (4.10)	13.7 (3.73)	0.0 (0.27)
Change from baseline	-0.4 (3.65)	-0.4 (3.19)	-0.50; 0.56
Negative symptoms			
Baseline	14.9 (4.07)	14.8 (4.12)	-0.0 (0.21)
Change from baseline	-0.8 (2.82)	-0.7 (2.61)	-0.45; 0.38
Disorganized thoughts			
Baseline	12.6 (3.39)	12.5 (3.47)	-0.2 (0.19)
Change from baseline	-0.4 (2.35)	-0.2 (2.56)	-0.59; 0.16
Uncontrolled hostility/excitement			
Baseline	4.8 (1.38)	4.7 (1.15)	0.1 (0.12)
Change from baseline	0.1 (1.71)	0.0 (1.31)	-0.14; 0.32
Anxiety/depression			
Baseline	5.7 (1.94)	5.7 (2.05)	0.0 (0.16)
Change from baseline	-0.3 (2.24)	-0.3 (2.17)	-0.28; 0.34
CGI-S score,^a n			
	477	224	
Baseline, mean (SD)	3.0 (0.78)	3.0 (0.77)	-0.0 (0.05)
Change from baseline, mean (SD)	0.0 (0.70)	0.0 (0.63)	-0.11; 0.09
PSP score,^a n			
	478	224	
Baseline, mean (SD)	66.3 (12.50)	66.5 (11.82)	-0.2 (0.57)
Change from baseline, mean (SD)	1.0 (7.12)	1.1 (8.11)	-1.27; 0.97
Improvement in PANSS total, n (%)			
≥20%	183 (38.9)	70 (32.1)	Relative risk (95% CI) ^b 1.12 (1.00; 1.25)
<20%	287 (61.1)	148 (67.9)	
≥30%	119 (25.3)	52 (23.9)	1.02 (0.93; 1.12)
<30%	351 (74.7)	166 (76.1)	
≥40%	77 (16.4)	33 (15.1)	1.01 (0.94; 1.08)
<40%	393 (83.6)	185 (84.9)	
DB 6-month remission status,^c n (%)			
	478	224	
Achieved	317 (66.3)	157 (70.1)	0.89 (0.71; 1.13)

Abbreviations: CGI-S, Clinical Global Impression-Severity; CI, confidence interval; DB, double-blind; ITT, intent-to-treat; LS, least squares; PANSS, Positive and Negative Symptom Scale; PP3M, paliperidone palmitate 3-month formulation; PP6M, paliperidone palmitate 6-month formulation; PSP, Personal and Social Performance; SD, standard deviation; SE, standard error;

^aBased on ANCOVA model with treatment (PP6M vs PP3M) and country as factors, and baseline value as a covariate.

^bPoint estimate (95% CI) of relative risk is based on Cochran-Mantel-Haenszel test controlling for country.

^cRemission is defined as having a score of ≤3 on all of the following 8 PANSS items: P1, P2, P3, N1, N4, N6, G5, and G9 for the last 6 months of DB treatment, with 1 excursion allowed.

the potential benefits of treatment with PP6M in these patients (Robinson et al., 1999; Morken et al., 2008; Sajatovic et al., 2013). Studies investigating LAIs in adults with first-episode schizophrenia have shown favorable neuropathological changes along with early symptom improvement and reduced risk of relapse (Taylor and Ng, 2013; Stevens et al., 2016). A recent guideline also recommended LAI use in stabilized adult patients after first episode and in early-phase patients to maintain treatment continuity (floridabhcenter.org, 2020). In accordance with a recent clinical guideline issued by Serious Mental Illness (SMI) Adviser

(an initiative from the American Psychiatric Association and the Substance Abuse and Mental Health Services Administration), the use of LAIs such as PP6M can be of great value to ensure medication continuation while minimizing interpersonal contact and hospital visits (Moreno et al., 2020; SMI-Adviser, 2020). However, the 6-month dosing interval of PP6M does not dictate the frequency of clinical visits, which can be decided mutually by the patient and clinician.

The present study was adequately powered to assess efficacy using a noninferiority approach. The noninferiority margin of

Table 4. Summary of Treatment-Emergent Adverse Events During the OL and DB Phases (DB Safety Analysis Set)

	ITT-DB safety analysis sets		
	ITT-OL	No. of patients (%)	
	PP1M/PP3M (n=838)	PP6M (n=478)	PP3M (n=224)
Patients with ≥1 TEAEs	341 (40.7)	297 (62.1)	131 (58.5)
Patients with ≥1 serious TEAEs	23 (2.7)	24 (5.0)	15 (6.7)
Most common (>5 patients) serious TEAE			
Schizophrenia	6 (0.7)	8 (1.7)	1 (0.4)
TEAEs leading to drug withdrawal ^a	31 (3.7)	16 (3.3)	6 (2.7)
Most common (>5 patients) TEAEs leading to drug withdrawal ^a			
Schizophrenia	6 (0.7)	8 (1.7%)	1 (0.4)
TEAEs leading to death	1 (0.1)	1 (0.2)	2 (0.9)
Most common (≥2% of patients) TEAEs			
Weight increase	8 (1.0)	40 (8.4)	17 (7.6)
Injection site pain	72 (8.6)	37 (7.7)	9 (4.0)
Headache	16 (1.9)	32 (6.7)	12 (5.4)
Upper respiratory tract infection	19 (2.3)	24 (5.0)	9 (4.0)
Nasopharyngitis	22 (2.6)	22 (4.6)	13 (5.8)
Akathisia	21 (2.5)	17 (3.6)	8 (3.6)
Insomnia	27 (3.2)	15 (3.1)	5 (2.2)
Anxiety	25 (3.0)	15 (3.1)	1 (0.4)
Influenza	11 (1.3)	13 (2.7)	4 (1.8)
Urinary tract infection	4 (0.5)	13 (2.7)	2 (0.9)
Schizophrenia	9 (1.1)	11 (2.3)	3 (1.3)
Weight decrease	4 (0.5)	8 (1.7)	7 (3.1)
Suicidal ideation	9 (1.1)	4 (0.8)	6 (2.7)
Patients with ≥1 EPS-related TEAEs	53 (6.3)	46 (9.6)	19 (8.5)
Most common (>5 patients) EPS-related TEAEs			
Parkinsonian rest tremor	11 (1.3)	9 (1.9)	2 (0.9)
Muscle rigidity	7 (0.8)	2 (0.4)	0 (0.0)
Parkinsonism	7 (0.8)	6 (1.3)	2 (0.9)
Akathisia	21 (2.5)	17 (3.6)	8 (3.6)
Dyskinesia	11 (1.3)	6 (1.3)	2 (0.9)
Dystonia	3 (0.4)	1 (0.2)	0
Tremor	1 (0.1)	1 (0.2)	0 (0.0)
Patients with ≥1 injection site-related TEAEs	89 (10.6)	59 (12.3)	11 (4.9)
Injection site pain	72 (8.6)	37 (7.7)	9 (4.0)
Injection site swelling	8 (1.0)	8 (1.7)	1 (0.4)
Injection site induration	8 (1.0)	7 (1.5)	2 (0.9)
Pain in extremity	6 (0.7)	7 (1.5)	3 (1.3)
Injection site discomfort	2 (0.2)	3 (0.6)	1 (0.4)
Injection site erythema	2 (0.2)	3 (0.6)	1 (0.4)
Musculoskeletal pain	2 (0.2)	3 (0.6)	0 (0.0)
Injection site haemorrhage	0	1 (0.2)	0 (0.0)
Injection site nodule	0	1 (0.2)	0 (0.0)
Injection site oedema	3 (0.4)	1 (0.2)	0 (0.0)

Abbreviations: DB, double-blind; EPS, extrapyramidal syndrome; ITT, intent-to-treat; OL, open label; PP1M, paliperidone palmitate 1-month formulation; PP3M, paliperidone palmitate 3-month formulation; PP6M, paliperidone palmitate 6-month formulation; TEAE, treatment-emergent adverse event.

^aAn adverse event that started in the open-label phase and resulted in study drug being discontinued in the double-blind phase is counted as treatment-emergent in the open-label phase.

–10% (different from the PP3M study: –15%) was selected based on the efficacy results of a phase 3 non-inferiority study comparing PP3M to PP1M (Berwaerts et al., 2015; Savitz et al., 2016) and on advice from experts and health authorities and endorsed by the Committee for Medicinal Products for Human Use. The eligibility criteria for the present study were similar to the PP3M studies and designed to give a representative patient population likely to be treated with PP6M in clinical practice (Berwaerts et al., 2015; Savitz et al., 2016). Notably, at study entry (OL baseline), the criterion for PANSS total score (<70 indicating clinical stability) was different from the previous PP3M studies (between

70 and 120, not indicating clinical stability, although a PANSS <70 score was the criteria for DB entry).

Several study limitations should be noted. The noninferiority design was based on the principle of enrichment, that is, criteria of clinical stability were applied prior to entry into the DB phase; thus, the results may not reflect true efficacy for prevention of relapses in the overall population. However, the criterion of clinical stability was fundamental to the study design, and PP6M is not intended for use in acutely ill patients with schizophrenia. Furthermore, an OL long-term study (NCT04072575) with more real-world features is currently ongoing and will provide

Table 5. Summary of Changes From Baseline in Serum Prolactin Levels, ECG, EPS Scales, and Injection Site Evaluations During the DB Phase (DB Safety Analysis Set)

	PP6M (n=478)	PP3M (n=224)
Prolactin, µg/L	n=477	n=221
Mean (SD) change from baseline	-3.03 (22.37)	3.89 (27.93)
QTcF, n (%), msec	n=474	n=220
≤30	422 (89.0)	194 (88.2)
>30-60	50 (10.5)	26 (11.8)
>60	2 (0.4)	0
AIMS total score, median (range)	n=477	n=221
Changes from baseline	0.0 (-7, 14)	0.0 (-3, 2)
BARS global clinical rating of akathisia, DB baseline, n (%)	n=478	n=224
Absent	453 (94.8)	218 (97.3)
Questionable	16 (3.3)	6 (2.7)
Mild akathisia	9 (1.9)	0 (0.0)
Moderate akathisia	0 (0.0)	0 (0.0)
Marked akathisia	0 (0.0)	0 (0.0)
Severe akathisia	0 (0.0)	0 (0.0)
BARS global clinical rating of akathisia, DB end point, n (%)	n=477	n=221
Absent	451 (94.5)	212 (95.9)
Questionable	19 (4.0)	7 (3.2)
Mild akathisia	6 (1.3)	2 (0.9)
Moderate akathisia	1 (0.2)	0 (0.0)
Marked akathisia	0 (0.0)	0 (0.0)
Severe akathisia	0 (0.0)	0 (0.0)
SAS global score, median (range)	n=477	n=220
Change from baseline	0.0 (-1;2)	0.0 (-1;2)
Injection site evaluation ^a		
Redness, DB baseline	n=478	n=224
Absent	473 (99.0)	222 (99.1)
Mild	5 (1.0)	2 (0.9)
DB endpoint	n=477	n=223
Absent	476 (99.8)	222 (99.6)
Mild	1 (0.2)	1 (0.4)
Induration/swelling, DB baseline	n=478	n=224
Absent	469 (98.1)	220 (98.2)
Mild	9 (1.9)	4 (1.8)
DB endpoint	n=477	n=223
Absent	475 (99.6)	222 (99.6)
Mild	2 (0.4)	1 (0.4)
Tenderness, DB baseline	n=478	n=224
Absent	425 (88.9)	207 (92.4)
Mild	48 (10.0)	16 (7.1)
Moderate	5 (1.0)	1 (0.4)
DB endpoint	n=477	n=223
Absent	474 (99.4)	221 (99.1)
Mild	3 (0.6)	2 (0.9)
Injection site pain (mm) ^b		
DB baseline, n	478	224
Mean (SD)	17.2 (20.86)	15.0 (18.98)
DB endpoint, n	477	223
Mean (SD)	5.4 (10.78)	4.54 (8.93)

Abbreviations: AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; DB, double-blind; ECG, electrocardiogram; EPS, extrapyramidal symptoms; ITT, intent-to-treat; PP3M, paliperidone palmitate 3-month formulation; PP6M, paliperidone palmitate 6-month formulation; QTcF, QT interval, corrected according to Fridericia's formula; SAS, Simpson-Angus Scale.

^aInvestigator assessment.

^bAssessment of local tolerability by the patient using a visual analog scale (VAS) (within 30 mins of injection) presented as a 100-mm horizontal line on which the patient's pain intensity is represented by a point between the "no pain at all" (0) and "unbearably painful" (100).

additional insight on the relapse prevention efficacy of PP6M. Also, the absence of a placebo group further limits interpretation of findings, and it is unknown how these findings compare with oral antipsychotics. The fixed doses evaluated during the DB phase were not directly informative of any changes in the dose of PP6M that could occur during long-term treatment in

clinical practice or directly inform the dose response of PP6M for use as maintenance therapy, as patients were not randomly assigned to distinct dose levels of PP6M. Notably, patients in the PP6M group received injections every 3 months to maintain the blinding (2 active, 2 placebo injections), thus limiting the interpretation on injection site ratings, patient preference, caregiver

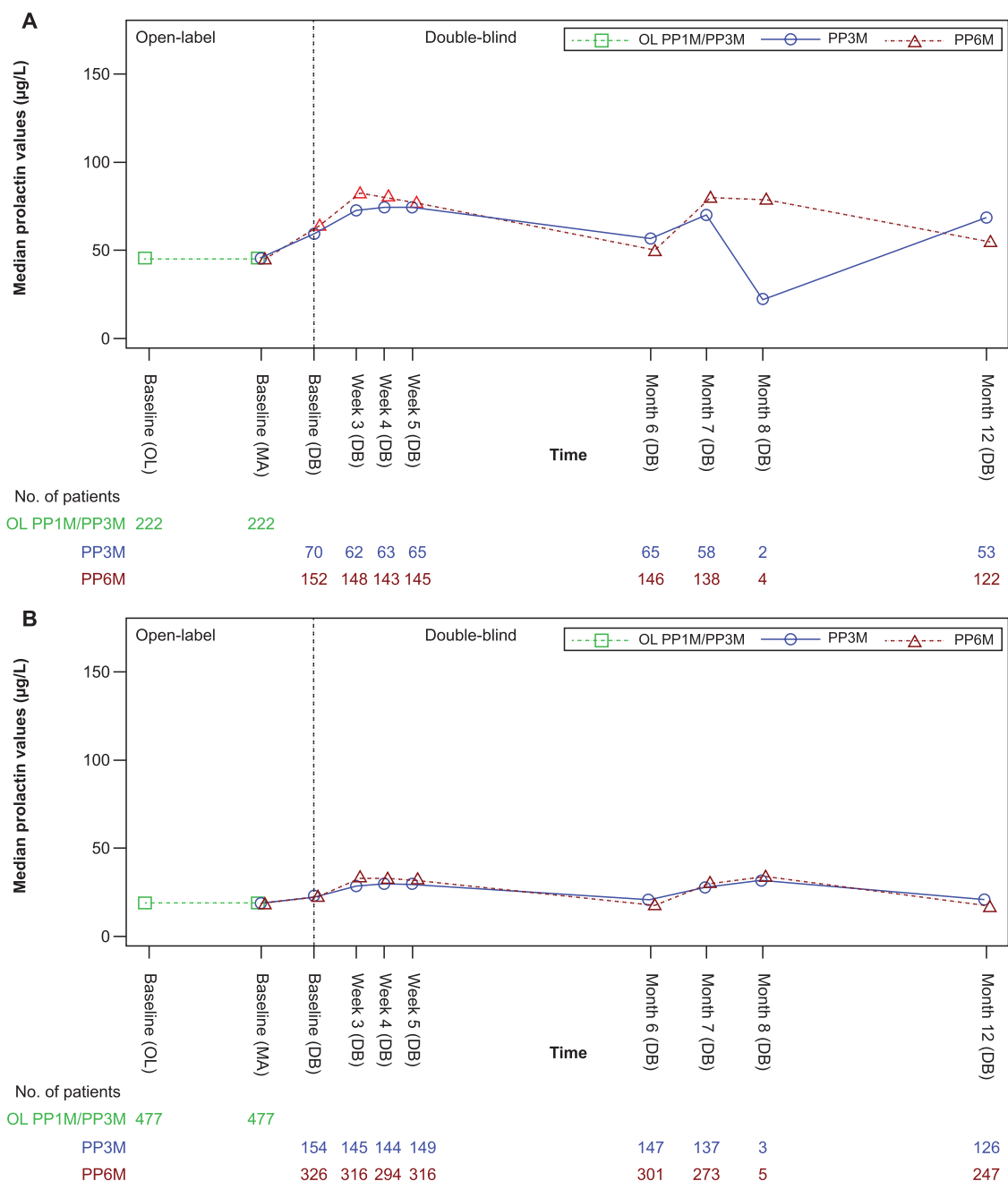


Figure 4. Median prolactin level over time (safety analysis set). (A) Women (B) Men. Abbreviations: DB, double-blind; OL, open label; PP1M, paliperidone palmitate once-monthly formulation; PP3M, paliperidone palmitate 3-monthly formulation; PP6M, paliperidone palmitate 6-monthly formulation.

burden, etc., that are directly related to different dosing intervals between the 2 formulations. The use of placebo injections could also introduce a potential placebo effect in the PP6M group, which is an inherent limitation of most randomized controlled trials.

Conclusions

The primary efficacy analysis of this clinical trial confirmed that the efficacy (measured by percentage of patients who remained relapse free) of PP6M (700 or 1000 mg eq.) was noninferior to PP3M (350 or 525 mg eq.) in clinically stable patients with schizophrenia adequately treated with PP1M for ≥ 4 months or PP3M for ≥ 1 injection cycle. Safety findings for PP6M were consistent

with the known profile of paliperidone palmitate, and no new signals specific for PP6M emerged. There were no appreciable differences in efficacy or safety when transitioning directly from PP1M or PP3M to PP6M. Thus, PP6M offers the longest LAI dosing interval available to date and, along with PP1M and PP3M, provides flexible dosing regimens for a patient-centric approach in the management of schizophrenia. An OL extension study is currently underway to assess the long-term safety and tolerability of PP6M.

Supplementary Materials

Supplementary data are available at *International Journal of Neuropsychopharmacology (IJNPPY)* online.

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Interest Statement

D.N. is an employee of Janssen Scientific affairs, LLC and may hold company stocks or stock options. P.S., S.W., P.L., A.S., M.J.R., K.C., R.M., R.V., H.T., and S.G. are employees of Janssen Research & Development (a Johnson & Johnson company) and may hold company stocks or stock options. Alain Schotte was an employee of Janssen Research & Development, Beerse, Belgium, during the study and has now retired. Dr Walling reports grants

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