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Pharmacokinetics, Safety, and Tolerability of Paliperidone Palmitate 3-Month Formulation in Patients With Schizophrenia: A Phase-1, Single-Dose, Randomized, Open-Label Study

Paulien Ravenstijn, PhD[1], Bart Remmerie, Chem Eng[1], Adam Savitz, MD, PhD[2], Mahesh N. Samtani, PhD[3], Isaac Nuamah, PhD[2], Cheng-Tao Chang, PhD[3], Marc De Meulder, MSc[1], David Hough, MD[2], and Srihari Gopal, MD, MHS[2]

Abstract

This multicenter, randomized, open-label, parallel-group, phase-1 study assessed the pharmacokinetics (PK), safety, and tolerability of the investigational intramuscular paliperidone palmitate 3-month (PP3M) formulation in patients with schizophrenia or schizoaffective disorder. A total of 328 patients (men or women, aged 18–65 years) were enrolled in 1 of 4 separately conducted panels (A to D). Each panel had 2 single-dose treatment periods (period 1, 1 mg intramuscular paliperidone immediate release [IR]; period 2, intramuscular PP3M 75−525 mg eq) separated by a washout of 7–21 days. Overall, 245 of 308 (79.5%) PP3M-dosed patients completed the study. Because the PK studies of panels A and C were compromised by incomplete injection in some patients, PK data from only panels B and D are presented. Safety data from all panels are presented. Peak paliperidone plasma concentration was achieved between 23 and 34 days, and apparent half-life was ∼2–4 months. Mean plasma AUC_{∞} and C_{max} of paliperidone appeared to be dose-proportional. Relative bioavailability in comparison with paliperidone was ∼100% independent of the dose and injection site. Headache and nasopharyngitis were the most common (>7%) treatment-emergent adverse events. Overall, safety and tolerability were similar to those of the 1-month formulation. Results support a once-every-3-months dosing interval in patients with schizophrenia or schizoaffective disorder.

Keywords

long-acting injectable, paliperidone palmitate 3-month (PP3M), pharmacokinetics, safety, schizophrenia

In the clinical management of patients with schizophrenia, poor adherence to antipsychotic treatment is a major challenge because it results in an increased risk of relapse and rehospitalization.[1–4] Several factors may contribute to poor adherence, including disorganization and cognitive impairments that are associated with schizophrenia, dosing frequency, adverse events, and complexity of the treatment regimen.[3] In addition, patients and their caregivers may prefer to receive injectable medications so that medications do not need to be remembered on a daily basis. Currently available long-acting injectable (LAI) formulations of antipsychotic medications provide sustained therapeutic plasma concentrations for several weeks, minimizing the risk of nonadherence and providing long-term clinical benefits.[1,2,5] Paliperidone palmitate (PP [Invega®; Sustenna®; Xeplion®]), a once-monthly (PP1M) atypical LAI antipsychotic, is approved for the treatment of schizophrenia and schizoaffective disorder.[6]

Following a single intramuscular dose of PP1M, paliperidone gradually reaches maximum plasma concentrations (C_{max}) at ∼13 days (t_{max}).[6] A number of factors including injection site, injection volume, and particle size affect the pharmacokinetic (PK) profile of PP.[7–10]

Multiple studies have demonstrated the safety and efficacy of PP1M (25, 50, 75, 100, or 150 mg eq; deltoid or gluteal injections) in patients with schizophrenia.[1,2,11–19] A recently developed 3-month formulation (PP3M) utilizes a similar NanoCrystal® technology as PP1M but with increased particle size, which provides an extended sustained release of paliperidone and permits a significantly extended dosing interval (4 doses per year). This may further help patients and physicians to successfully manage the symptoms of schizophrenia nonadherence and

[1]Janssen Research & Development, a Division of Janssen Pharmaceutica NV, Beerse, Belgium
[2]Janssen Research & Development, Titusville, NJ, USA
[3]Janssen Research & Development, Raritan, NJ, USA

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Corresponding Author:
Paulien Ravenstijn, PhD, Clinical Pharmacology, Janssen Research & Development, a Division of Janssen Pharmaceutica NV, Turnhoutseweg 30, B-2340 Beerse, Belgium
Email: pravenst@its.jnj.com
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potentially reduce the risk of relapse, as recently demonstrated in a safety and efficacy study of PP3M.[20]

This study was designed to evaluate the PK, safety, and tolerability of PP3M after a single-dose (range: 75–525 mg eq, deltoid or gluteal) in patients with schizophrenia. Secondary objectives were to evaluate the relative bioavailability (F_{rel}) of PP3M after a deltoid or gluteal injection compared with an intramuscular injection of 1 mg paliperidone as an immediate-release (IR) formulation (solution) and to explore the dose-proportionality of PP3M after deltoid and gluteal injections.

Methods

Study Participants

The Independent Ethics Committee or Institutional Review Board at each study site reviewed and approved the protocol, and the study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Conference on Harmonization for Good Clinical Practices guidelines and applicable local and regulatory requirements. Written informed consent was obtained from each patient before enrollment.

Men and women aged 18–65 years, with body mass index (BMI) 17–35 kg/m^2, body weight $\geq$47 kg, a diagnosis of schizophrenia or schizoaffective disorder consistent with the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria at least 1 year before screening, and Positive and Negative Syndrome Scale (PANSS) total score $\leq$70 at both screening and day –1 (period 1) were enrolled in this study. Exclusion criteria included a DSM-IV diagnosis of alcohol or substance dependence (within 12 months before screening) or a DSM-IV diagnosis of substance abuse (within 3 months before screening), history of suicide attempt (within 12 months), and history of neuroleptic malignant syndrome or tardive dyskinesia at screening. Patients taking risperidone or paliperidone (oral or LAI versions, any panel) or with plasma levels of these medications exceeding a predefined threshold (0.1 ng/mL) were not eligible to participate in panel D.

Study Design

This phase-1, open-label, randomized, parallel-group, single-dose study was conducted between February 2008 and May 2014 at 72 sites across 11 countries (Belgium, Bulgaria, Croatia, Israel, Malaysia, Republic of Korea, Slovakia, South Africa, Spain, Taiwan, and the United States). Not all sites and countries participated in all 4 panels.

The study consisted of 4 panels (A, B, C, and D). Each panel included a screening phase of up to 21 days, an open-label treatment phase comprising 2 sequential single-dose treatment periods (period 1 and period 2) with a washout period of 7–21 days between them. Panels B and D also included an extension period, which was optional for panel B (Figure 1). Eligible patients were randomized (except panel C) to one of the treatment groups based on a computer-generated randomization schedule using permuted blocks and stratified by BMI category (<25, 25–30, >30 kg/m^2) and sex. During period 1 of the open-label phase, patients received a single-dose intramuscular injection of 1 mg paliperidone IR solution (panels A and C, gluteal muscle; panels B and D, deltoid or gluteal muscle). During period 2, patients received a single-dose intramuscular injection of long-acting PP3M formulation in the same muscle (deltoid or gluteal) as in period 1, but in the opposite side (left or right). Patients were followed for 96 hours during period 1 and for up to 364 days during period 2 (544 days in panel D and optional follow-up up to 544 days for panel B). The total duration of the study was 53–58 weeks for panels A and C and longer (+26 weeks) for panels B and D.

The proposed doses of PP3M for clinical use were 3.5-fold higher than PP1M (supplementary Table S1). The dose strengths of PP can be expressed in both milligram equivalents (mg eq) of the active moiety, paliperidone, and in milligrams of PP. In this article, the dosages are expressed as milligram equivalents; eg, PP 819 mg is equivalent to paliperidone 525 mg eq. The doses administered during period 2 were as follows: in panel A, 300 mg eq (gluteal); in panel B, 75, 150, or 450 mg eq (gluteal), or 300 or 450 mg eq (deltoid); in panel C, 150 mg eq (gluteal); in panel D, 175 mg eq (deltoid), 350 mg eq (gluteal), 525 mg eq (gluteal), or 525 mg eq (deltoid). The enrollment in panel C was started only after enrollment in panel A had been completed. However, enrollment in panel B was started after enrollment was complete and the safety tolerability was confirmed in panel A (after 63 patients completed their day-196 assessments in period 2). Similarly, enrollment in panel D was initiated after the safety tolerability had been confirmed in panel B (after at least 15 patients per treatment group completed their day-196 assessments in period 2).

No modifications in patients' current antipsychotic medications were required in order to enroll in this study. All allowed medications, including antipsychotics that had been started before screening, were continued during the course of the study. Medications that could potentially affect or interfere with the measurement of the PK of paliperidone were prohibited. Antipsychotics not allowed during the open-label phase were risperidone, paliperidone, clozapine, ziprasidone, thioridazine, and all LAI antipsychotics. Hepatic enzyme inducers (eg, rifampicin, carbamazepine, oxcarbazepine, barbiturates, phenytoin, troglitazone), certain anticonvulsant medications (eg, carbamazepine, oxcarbazepine, felbamate), and drugs that prolong the QTc interval (including Class 1A [eg,

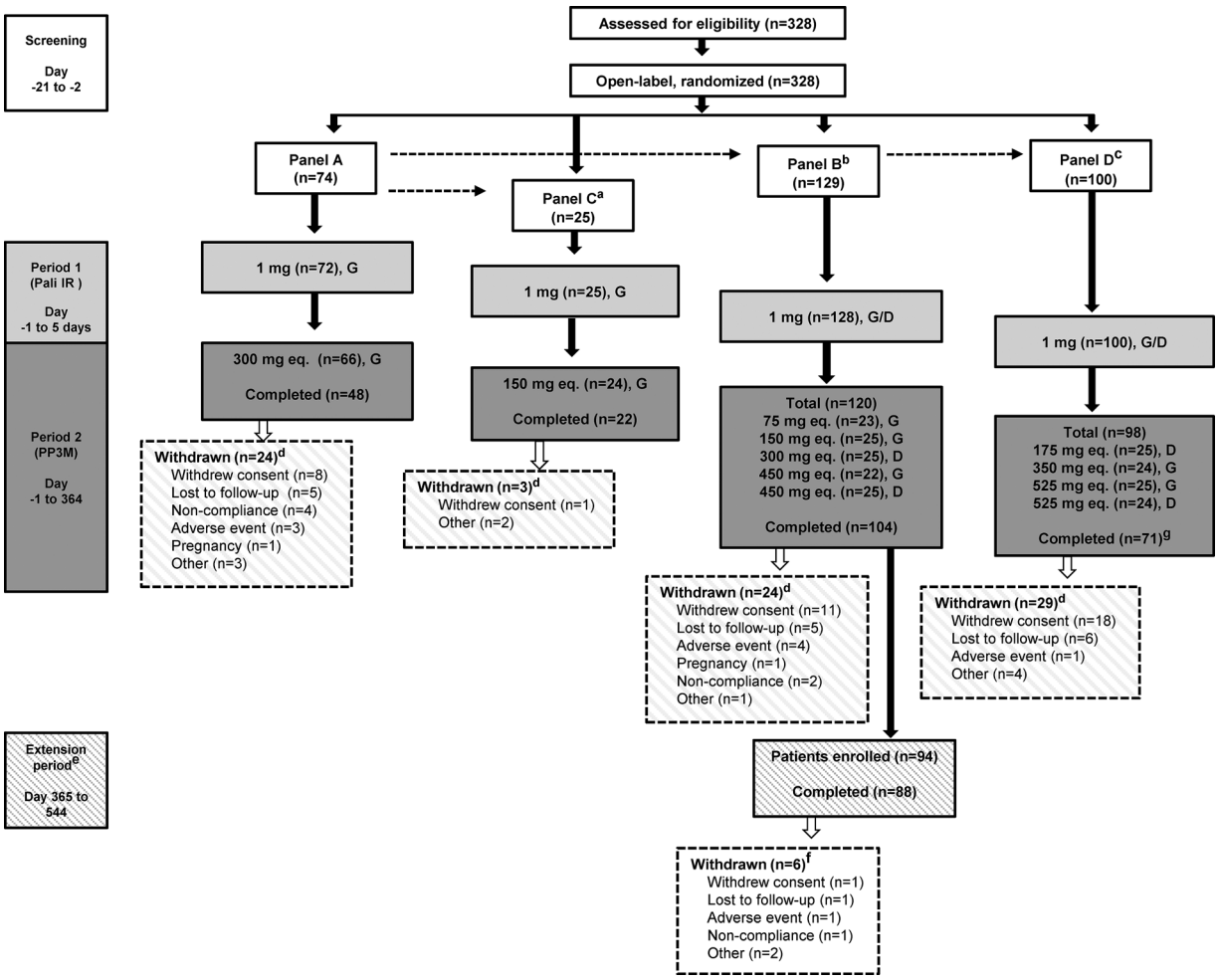

Figure 1. Study design and patient flow. D, deltoid; G, gluteal; Pali IR, paliperidone immediate-release formulation; PP3M, paliperidone palmitate 3-monthly formulation. Two patients from panel A and 1 patient from panel B were randomized but did not receive study medication. [a]Dashed arrow indicates that enrollment into panel C started after the enrollment in panel A had been completed. [b]Dashed arrow indicates that enrollment in panel B started after the safety and tolerability had been confirmed in panel A. [c]Dashed arrow indicates that enrollment in panel D was initiated after safety and tolerability had been confirmed in panel B. [d]Withdrawn patients include those withdrawn from both periods 1 and 2. [e]Optional for panel B. [f]Patients withdrawn from extension phase. [g]Extension period in panel D was integrated into the study; hence, completion rates are for the entire 18-month study.

quinidine, procainamide] or Class III [eg, amiodarone, sotalol] antiarrhythmic medications) were also not allowed. Psychotropic medications, including antipsychotics, could be changed during the follow-up phase of period 2 except for those medications mentioned above.

The aim of panel A was to assess the local tolerability and safety of PP3M formulation after gluteal injection of 300 mg eq, and to confirm the release profile. However, panels B and D assessed PK, safety, and tolerability of a single-dose of PP3M over the entire expected therapeutic dose range after gluteal and deltoid administration. The extension period in panel D (optional for panel B) was planned to obtain additional assessments enabling better characterization of the PK profile. Panel C, which occurred before panel B, was designed to address formulation factors that could influence the pharmacokinetics of the suspension.

Inadequate Shaking of Study Medication

After the bioavailability results of panels A and C became available, it was evident that some patients had received incomplete injections of study medication, likely as a result of improper shaking of the syringe before injection. After this, a formal training procedure (vigorous shaking for 15 seconds) was implemented for all sites worldwide before initiation of panels B and D.

Pharmacokinetic Assessments

For the PK assessment of paliperidone, blood samples (4 mL each) were collected predose and at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, and 96 hours postdose during period 1; predose and on day 1 (1 and 6 hours), 2 (24 hours), 4, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 56, 84, 112, 140, 168, 196, 224, 252, 280, 308, 336, and 364 (additional samples on day 454 and 544 for extension period) during period 2. The

PK of the prodrug, paliperidone palmitate (PP), was assessed from blood samples collected during period 2, at predose, and on days 1 (1 and 6 hours), 2 (24 hours), 4, and 6. The paliperidone enantiomers (R078543[+], R078544[–]) were also quantified in samples obtained from 12 patients each from 175 mg eq (deltoid) and 525 mg eq (gluteal) groups who completed 12 months in period 2. Samples were collected in heparin-containing tubes, centrifuged within 1 hour of collection for 10 minutes, and stored at −20°C or lower in a frost-free freezer until their transfer to the central laboratory.

The PK parameters, including C_{max}, t_{max}, area under the plasma concentration-time curve from time 0 to infinite time (AUC_∞), half-life ($t_{1/2}$), and F_{rel} of PP, were calculated. Plasma samples were analyzed using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) detection method.[21] The lower limit of quantification (LLOQ) for plasma paliperidone was 0.100 ng/mL.

Safety Assessments

Safety assessments included monitoring of treatment-emergent adverse events (TEAEs), physical examination, electrocardiograms, vital signs measurement, clinical laboratory examination, and local tolerability evaluations. Injection-site pain was assessed using a visual analogue scale (VAS). Additionally, extrapyramidal symptoms (EPS) were monitored using the Abnormal Involuntary Movement Scale (AIMS),[22] the Barnes Akathisia Rating Scale (BARS),[23] the Simpson and Angus Rating Scale (SAS),[24] and the Columbia Suicide Severity Rating Scale (C-SSRS,[25] panels B and D).

Statistical Analysis

Sample size calculations were based on prior studies of PP1M. Sample size for each panel was calculated considering the key parameters: $t_{1/2}$ (panels A and C) and AUC and C_{max} (panels B and D). Assuming a dropout rate of 45%, 74 patients in panel A, 125 patients in panel B (25 per treatment group), 25 patients in panel C, and 100 patients in panel D (25 patients per treatment group) were planned to be enrolled to ensure that at least 40 patients in panel A, 70 patients (14 per treatment group) in panel B, 14 patients in panel C, and 56 patients (14 per treatment group) in panel D would complete all assigned treatments and assessments on day 364 (day 544 for panel D).

Descriptive statistics were used to summarize PK and safety parameters. The PK analysis data set included all available samples. For the calculation of F_{rel}, patients had to complete both periods. Safety analysis included all patients who received at least 1 dose of the study medication. To evaluate the F_{rel} of PP3M vs 1 mg paliperidone IR, the AUCs (AUC_{last}, AUC_∞) from period 1 and period 2 were log-transformed.

For each injection site, the slopes of AUC_∞ and C_{max} were estimated using a linear regression model with log-transformed dose-normalized (to 350 mg eq) PK parameters vs log-transformed dose to assess dose-proportionality. The noncompartmental PK and statistical analysis were conducted using WinNonlin Professional™ version 4.1 (Pharsight, Mountainview, California) and Phoenix™ WinNonlin® version 6.2.1 (Copyright©1998–2011, Tripos LP). Dose-proportionality and pairwise comparisons were performed using SAS® (version 9.3, SAS Institute Inc., Cary, NC).

Results

Study Participants

A total of 328 patients were enrolled in the four panels (panel A, 74; panel B, 129; panel C, 25; and panel D, 100); 245 patients (74.7%) completed the study. Overall, 325 out of 328 patients received 1 mg intramuscular paliperidone during period 1, and 308 patients received intramuscular PP3M (75 mg eq to 525 mg eq, deltoid/gluteal) (Figure 1). Overall, the demographic characteristics were similar across panels. The majority of patients were men (216/325, 66.5%) and white (184/325, 56.6%). The mean patient age across all 4 panels ranged from 41.4 to 42.6 years (Table 1).

Pharmacokinetics

The PK results of panels A and C were compromised by incomplete injections of PP3M as a result of inadequate shaking before injection in some patients (the estimated F_{rel} in panels A and C ranged between 59% and 90%). Hence, only the PK results from panels B and D are presented.

Depending on the dose and the injection site, the $t_{1/2}$ of IR paliperidone was 22–25 hours. The median C_{max} of paliperidone appeared to be dose-proportional and ranged from 21.2 to 57.9 ng/mL when given in deltoid muscle (175−525 mg eq) and 8.3–56.3 ng/mL when given in gluteal muscle (75−525 mg eq); whereas the median t_{max} was comparable for all dose groups, ranging from 24 to 34 days (deltoid) and 23 to 31 days (gluteal) (Figure 2; Table 2). The median AUC_∞ for paliperidone increased dose-proportionally and ranged from 46,480 to 131,651 ng · h/mL for deltoid (175–525 mg eq) and 22,214 to 142,201 ng · h/mL for gluteal (75–525 mg eq) (Table 2).

For panels B and D, the F_{rel} was approximately 100%, independent of the dose, injection site (Table 3), BMI, race, or sex (data not shown). The paliperidone AUC_∞ was also not influenced by BMI, race, or sex. Women and overweight or obese patients tended to have lower paliperidone C_{max} than men and patients with normal BMI, respectively.

Overall (panels B and D), the PP plasma concentrations were quantifiable in only 3% of patients (1.4% of samples; n = 7), of which all were from panel D (525 mg eq: deltoid, n = 2; gluteal, n = 5). These concentrations ranged from

Table 1. Demographics and Baseline Characteristics

	Panel A n = 72	Panel B n = 128	Panel C n = 25	Panel D n = 100
Age (years), mean (SD)	41.4 (8.8)	42.1 (9.4)	42.6 (9.0)	41.9 (10.5)
Men, n (%)	52 (72.2)	75 (58.6)	18 (72.0)	71 (71.0)
Race, n (%)				
White	32 (44.4)	81 (63.3)	8 (32.0)	63 (63.0)
Black	33 (45.8)	17 (13.3)	1 (4.0)	10 (10.0)
Asian	7 (9.7)	29 (22.7)	15 (60.0)	17 (17.0)
Other	–	1 (0.8)	1 (4.0)	10 (10.0)
Weight (kg), mean (SD)	77.6 (16.0)	78.6 (14.0)	67.1 (12.2)	77.7 (15.4)
Height (cm), mean (SD)	171.5 (9.2)	168.2 (8.6)	166.4 (7.0)	170.6 (9.1)
BMI (kg/m^2), mean (SD)	26.3 (4.5)	27.7 (4.1)	24.2 (3.5)	26.6 (4.3)

BMI, body mass index; SD, standard deviation. Panel A, 300 mg eq (gluteal); panel B, 75, 150, or 450 mg eq (gluteal), or 300 or 450 mg eq (deltoid); panel C, 150 mg eq (gluteal); panel D, 175 mg eq (deltoid), 350 mg eq (gluteal), 525 mg eq (gluteal), or 525 mg eq (deltoid).

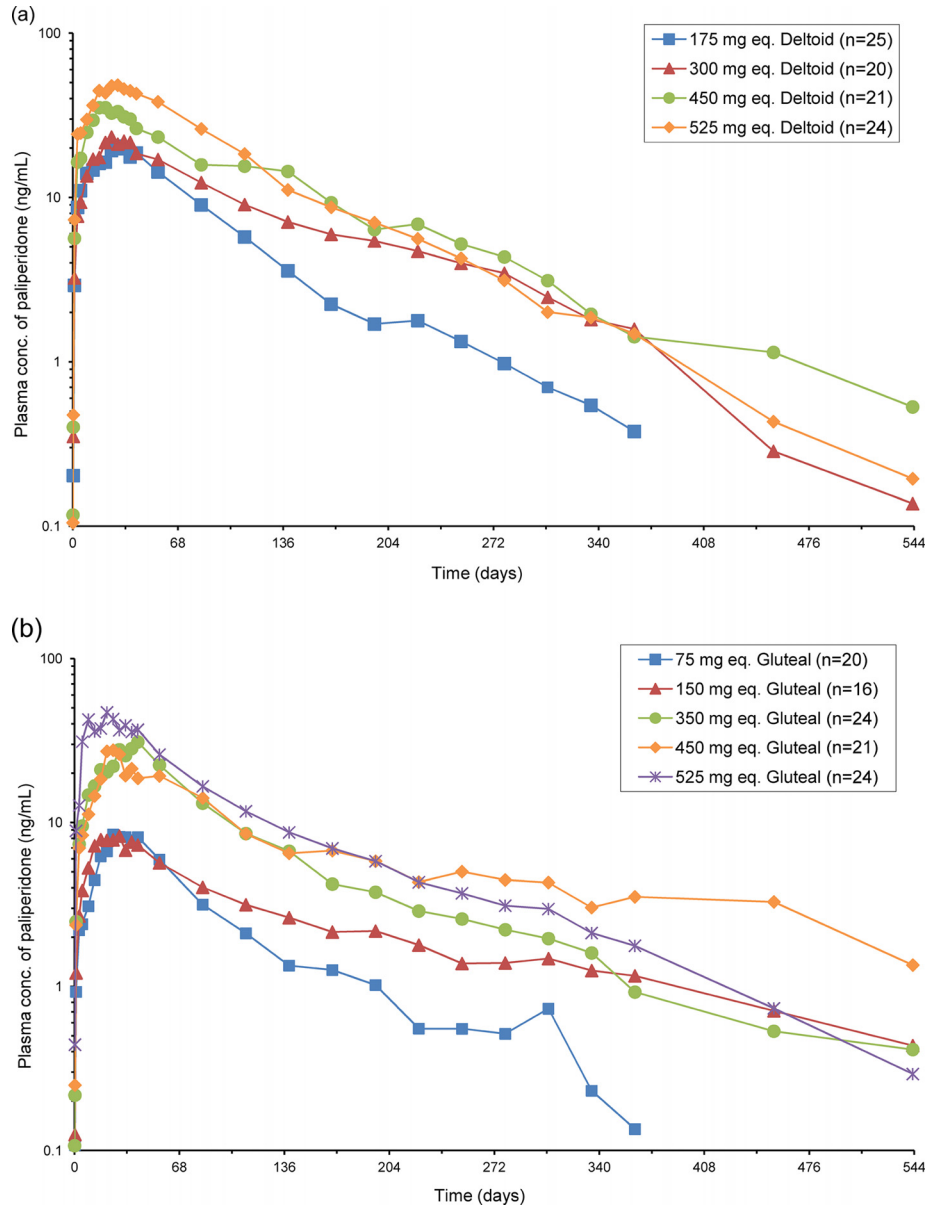

Figure 2. Median plasma concentration-time profiles of (a) deltoid and (b) gluteal injections.

Table 2. Pharmacokinetic Parameters of Paliperidone (Panels B and D, Period 2)

		Pharmacokinetic Parameter							
		C_{max}, ng/mL		t_{max}, Days		AUC_{∞}, ng·h/mL		$t_{1/2}$, Days	
Dose, mg eq.	Panel	n	Median (Range)	n	Median (Range)	n	Median (Range)	n	Median (Range)
Gluteal									
75	B	20	10.1 (1.4–23.3)	20	29.0 (17.0–114.0)	16	22,214 (10,671–34,683)	18	44.9 (26.9–341.5)
150	B	18	8.3 (3.9–57.4)	18	27.5 (8.1–41.0)	10	42,963 (26,283–49,399)	10	79.6 (27.7–198.9)
350	D	24	36.7 (1.4–187)	24	31.0 (5.0–84.1)	16	102,894 (47,481–157,706)	19	77.4 (22.8–274.1)
450	B	21	35.0 (7.3–80.7)	21	28.0 (13.0–55.0)	13	123,273 (35,579–159,235)	15	81.5 (21.2–349.5)
525	D	24	56.3 (11.1–143)	24	23.0 (2.0–41.0)	18	142,201 (77,446–285,761)	20	68.5 (29.0–254.4)
Deltoid									
175	D	25	21.2 (9.9–67.3)	25	24.0 (5.0–56.1)	22	46,480 (26,773–100,550)	22	51.7 (19.7–143.1)
300	B	20	28.0 (11.7–69.4)	20	34.0 (13.0–83.1)	17	77,925 (50,607–112,132)	17	73.5 (28.3–177.8)
450	B	22	40.1 (6.5–113)	22	24.0 (13.0–51.1)	17	131,651 (64,417–216,177)	18	71.8 (24.5–226.5)
525	D	24	57.9 (27.6–416)	24	24.5 (1.0–55.0)	22	128,969 (85,887–257,003)	22	56.9 (21.3–115.2)

AUC_{∞}, area under the plasma concentration-time curve from time 0 to infinite time; C_{max}, maximum plasma concentration; t_{max}, time to reach the C_{max}; $t_{1/2}$, elimination half-life.

0.27 to 19.20 ng/mL in deltoid and from 0.23 to 4.13 ng/mL in gluteal and had no impact on safety. In panel B, none of the samples had a quantifiable PP plasma concentration (LLOQ was 0.20 ng/mL) (data not shown). The plasma concentrations of the R078543(+) enantiomer were consistently higher than those of the R078544(−) enantiomer. The R078543(+)/R078544(−) PK parameter ratios after intramuscular injections of PP3M were approximately 1.8 for AUC and 1.9 for C_{max} (data not shown).

Dose-Proportionality Assessment

Log-transformed dose-normalized (to 350 mg eq) paliperidone C_{max} and AUC_{∞} appeared to be dose-proportional. The slopes for AUC_{∞} were not significantly different from zero for both the deltoid (slope −0.004, $P = 1.0$) and gluteal (slope −0.033, $P = 0.5$) injection sites (Figure 3a). Similarly for C_{max}, the slopes were also not significantly different from zero for either the deltoid (slope −0.177, $P = 0.2$) or gluteal (slope −0.081, $P = 0.5$) injection site (Figure 3b).

Across all doses, the least-squares (LS) means of C_{max} were higher (27%) following injections in deltoid (38.5 ng/mL) compared with gluteal muscle (30.3 ng/mL), whereas there was no difference in AUC_{∞} between those injection sites (2.2% difference; gluteal [92,465 ng · h/mL] vs deltoid [94,504 ng · h/mL]) (Table 4).

Safety

Overall, 26.8% (87/325) of patients during period 1 and 73.7% (227/308) of patients during period 2 experienced

Table 3. Relative Bioavailability of Paliperidone After Administration of Paliperidone Palmitate Treatment Groups (Test) Compared to 1 mg Paliperidone IR (Reference) (Panels B and D)

				LS mean		
PK Parameter[a], ng · h/mL	Injection Site	Test Treatment	n	1 mg Paliperidone IR (Reference)	Test Treatment	LS Mean Ratio, % (90%CI)
AUC_{∞}	Gluteal	75 mg eq.[b]	13	254	285	112.26 (102.41–123.07)
		150 mg eq.[b]	10	257	256	99.64 (81.27–122.16)
		350 mg eq.[c]	16	236	274	116.44 (106.08–127.82)
		450 mg eq.[b]	11	243	262	107.84 (97.86–118.84)
		525 mg eq.[c]	18	251	263	104.81 (94.58–116.14)
	Deltoid	175 mg eq.[c]	22	257	276	107.25 (100.65–114.29)
		300 mg eq.[b]	15	249	261	105.04 (96.84–113.93)
		450 mg eq.[b]	14	253	269	106.43 (96.90–116.90)
		525 mg eq.[c]	20	233	260	111.32 (104.56–118.53)

[a]Dose-normalized PK parameters. [b]Panel B. [c]Panel D

AUC, area under the plasma concentration-time curve; CI, confidence interval; IR, immediate-release; LS, least square; PK, pharmacokinetic.

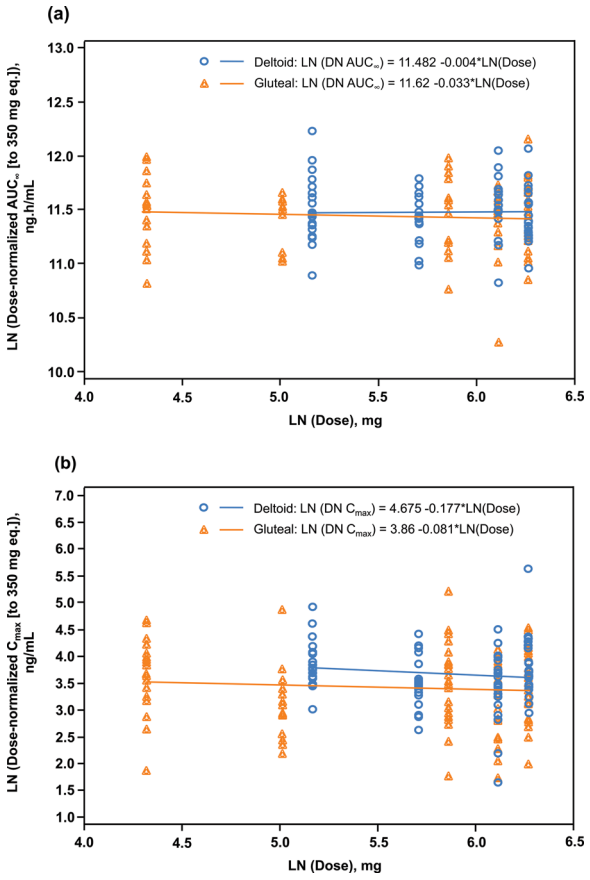

Figure 3. Linear regression model of paliperidone individual dose-normalized (to 350 mg eq) AUC_{∞} (a) and C_{max} (b) (panels B and D). AUC_{∞}, area under the plasma concentration-time curve from time 0 to infinite time; C_{max}, maximum plasma concentration; DN, dose-normalized; LN, linear regression. Panel B, 75, 150, or 450 mg eq (gluteal) or 300 or 450 mg eq (deltoid); panel D, 175 mg eq (deltoid), 350 mg eq (gluteal), 525 mg eq (gluteal), or 525 mg eq (deltoid).

at least 1 TEAE. Most of these TEAEs were rated as mild to moderate in severity. Among all panels, the most common TEAEs during period 2 were nasopharyngitis and headache (n = 34, each), followed by weight increase, back pain (n = 16, each), and anxiety (n = 14); whereas during period 1, headache (n = 14) was the most common TEAE (Table 5).

No deaths occurred in panels A, C, and D. One death was reported in panel B, which was due to serious TEAE (metastatic melanoma), not considered to be related to the study medication. Overall, 35 patients (panels A, n = 9; B, n = 14; C, n = 1; D, n = 11) reported ≥1 serious TEAEs. The most common serious TEAEs were psychiatrically related. Panel A included suicidal ideation (n = 3), agitation, depression, and psychotic disorder (n = 2, each); panel B included psychotic disorder and schizophrenia (n = 4, each); and panel D showed psychotic disorder and schizophrenia (n = 2, each). Overall, 7 patients discontinued the study because of TEAEs: 3 in panel A (anxiety, suicidal ideation, hypertension), 3 in panel B (myocardial ischemia, psychotic disorder, metastatic malignant melanoma, muscle spasticity, and dysphemia), and 1 in panel D (psychotic disorder). No clinically meaningful changes were noted in the EPS scales across the 4 panels.

Overall, 25 patients (gluteal, n = 7; deltoid, n = 18) reported injection-site-related TEAEs (5 in panel A, 8 in panel B, 2 in panel C, and 10 in panel D) during period 2. None of these were severe in intensity except for severe pain in 1 patient from panel D receiving 175 mg eq PP (deltoid region). The mean VAS scores for injection-site pain were low across all panels and decreased within 2 to 4 days (supplementary Figure S1).

One patient from panel B (300 mg eq, deltoid) reported QTcF >500 milliseconds (day 140), and 1 patient from panel D (525 mg eq, gluteal) reported QTcF >480 milliseconds (day 224); none of the mean changes in electrocardiograms were clinically relevant (for all panels). Also, no clinically relevant changes were observed in hematology, chemistry, urinalysis, or vital parameters in any of the 4 panels.

Discussion

This phase-1 study was designed to characterize the PK, safety, and tolerability of a PP3M formulation in patients

Table 4. Relative Bioavailability of Paliperidone Following Deltoid and Gluteal Administration of Paliperidone Palmitate 3-Month Formulation (PP3M) (Panels B and D)

	LS Mean[a]		
Parameter	PP3M Gluteal Injection (Reference)	PP3M Deltoid Injection (Test)	LS Mean Ratio (90%CI), %
C_{max}, DN, ng/mL[a]	30.3	38.5	127.1 (107.9–149.6)
AUC_{∞}, DN, ng·h/mL[b]	92,465	94,504	102.2 (94.3–110.8)
F_{rel} AUC_{∞}, %[c]	108.6	107.9	99.3 (93.7–105.2)

AUC_{∞}, area under the plasma concentration-time curve from time 0 to infinite time; CI, confidence interval; C_{max}, maximum plasma concentration; DN, dose-normalized; F_{rel} AUC_{∞}, relative bioavailability of paliperidone palmitate is estimated as the AUC_{∞} ratios (%) of Treatment Period 2/Treatment Period 1; LS, least squares.

[a]N = 107 for reference and N = 91 for test; [b]N = 73 for reference and N = 78 for test; [c]N = 68 for reference and N = 71 for test. Panel B, 75, 150, or 450 mg eq (gluteal), or 300 or 450 mg eq (deltoid); panel D,175 mg eq (deltoid), 350 mg eq (gluteal), 525 mg eq (gluteal), or 525 mg eq (deltoid).

Table 5. Treatment-Emergent Adverse Events ≥5% in Any Treatment Group

	Panel A		Panel B		Panel C		Panel D	
	Period 1 n = 72	Period 2 n = 66	Period 1 n = 128	Period 2 n = 120	Period 1 n = 25	Period 2 n = 24	Period 1 n = 100	Period 2 n = 98
Patients with ≥1 TEAEs	27 (37.5)	49 (74.2)	40 (31.3)	99 (82.5)	5 (20.0)	18 (75.0)	15 (15.0)	61 (62.2)
Nasopharyngitis	1 (1.4)	9 (13.6)	–	15 (12.5)	–	–	–	10 (10.2)
Headache	4 (5.6)	9 (13.6)	6 (4.7)	14 (11.7)	2 (8.0)	4 (16.7)	2 (2.0)	7 (7.1)
Weight increased	1 (1.4)	2 (3.0)	2 (1.6)	9 (7.5)	–	–	2 (2.0)	5 (5.1)
Back pain	–	–	–	8 (6.7)	–	2 (8.3)	1 (1.0)	6 (6.1)
Anxiety	2 (2.8)	2 (3.0)	4 (3.1)	12 (10.0)	–	–	–	–
Toothache	1 (1.4)	4 (6.1)	1 (0.8)	9 (7.5)	–	–	–	–
Psychotic disorder	–	3 (4.5)	–	6 (5.0)	–	–	–	4 (4.1)
Diarrhea	1 (1.4)	3 (4.5)	2 (1.6)	9 (7.5)	–	–	–	–
Insomnia	4 (5.6)	3 (4.5)	1 (0.8)	9 (7.5)	–	–	–	–
Depression	–	3 (4.5)	–	6 (5.0)			–	2 (2.0)
Tachycardia	1 (1.4)	2 (3.0)	–	7 (5.8)	–	–	–	2 (2.0)
Abdominal pain	–	2 (3.0)	1 (0.8)	8 (6.7)	–	–	–	–
Weight loss	–	–	–	7 (5.8)	–	–	–	3 (3.1)
Upper respiratory tract infection	–	–	–	3 (2.5)	–	6 (25.0)	–	–
Schizophrenia	–	–	1 (0.8)	6 (5.0)	–	–	–	–
Vomiting	–	–	–	–	–	2 (8.3)	–	–
Warmness at injection site	–	–	–	–	–	2 (8.3)	–	–
Diabetes mellitus	–	–	–	–	–	2 (8.3)	–	–

Data shown as n (%). TEAE, treatment-emergent adverse events.
Panel A, 300 mg eq (gluteal); panel B, 75, 150, or 450 mg eq (gluteal) or 300 or 450 mg eq (deltoid); panel C, 150 mg eq (gluteal); panel D, 175 mg eq (deltoid), 350 mg eq (gluteal), 525 mg eq (gluteal), or 525 mg eq (deltoid).

with schizophrenia. The present study confirms that the new formulation of paliperidone palmitate (PP3M) resulted in a longer $t_{1/2}$ (~2–3 months) and t_{max} (23–34 days) than the existing PP1M formulation; the extended $t_{1/2}$ substantiates the longer dosing interval of 3 months in patients with schizophrenia. Overall, C_{max} of single-dose PP3M, when administered in either the deltoid (175–525 mg eq) or gluteal (75–525 mg eq) muscle, appeared to be dose-proportional. The median $t_{1/2}$ of paliperidone after a single dose of PP3M (75–525 mg eq) in deltoid (range: 51.7–73.5 days) and gluteal muscles (range: 44.9–81.5 days) was higher than that for PP1M (range: 24.9–43.7 days, deltoid; 25.1–49.1 days, gluteal; 25–150 mg eq). [7] The median $t_{1/2}$ may be biased due to exclusion of profiles exhibiting a long $t_{1/2}$ (not estimable). More accurate estimates will be assessed in a population PK analysis and presented in another article. The PP3M formulation as an aqueous suspension has different formulation factors than PP1M to provide slower dissolution and extended release of paliperidone over several months.

The PK parameters presented here may therefore differ slightly from those presented in the United States product insert (USPI), which instead are based on findings of the pooled population PK analysis of phase-1 and -3 data (manuscript under preparation), and which is also the basis of the product inserts worldwide.

The complete F_{rel} observed in panels B and D confirmed that incomplete shaking of suspension before injection had compromised the PK results in panels A and C at a few investigational sites. Therefore, the PK results for panels A and C were not considered reliable or interpretable and are not presented. Before the subsequent panels (B and D), additional training was provided to the respective personnel specifying vigorous shaking of the suspension before injection and examination of used syringes for residual solute. Additional training on the need for vigorous shaking was also implemented before initiation of the phase-3 study.[20]

Injection site (deltoid vs gluteal) is an important factor in the PK of intramuscular injections of PP. When administered in deltoid muscle, PP1M resulted in 28% higher C_{max} than when administered in gluteal muscle.[6] Our results also further corroborate that C_{max} of paliperidone after administration of PP3M was higher (27%) in patients receiving deltoid injection compared to gluteal injection, with no difference for AUC_{∞} between the injection sites. The difference in the absorption rate is likely due to the increased adipose tissue overlying the gluteal muscle, resulting in a slower uptake of paliperidone than would be normally found in the deltoid region, as also observed with PP1M.[10] However, given that PP3M will be administered only after 4 or more injections of PP1M have been administered, and plasma levels will

be at near steady-state concentrations, this difference between the injection sites will likely not be clinically significant.

In this study, the quantifiable prodrug concentrations were observed in very few patients (3% of patients; 1.4% of samples; overall in panels B and D), which was lower than that observed for PP1M (18% of patients; 2.3% of samples) (data on file). This indicates that, following intramuscular injection of PP3M, almost none of the injected product (PP) reaches systemic circulation, and paliperidone only after cleavage is available.

Interpretation of safety and tolerability results (other than injection site ratings and TEAEs) may be confounded because patients received only a single-dose of PP3M and were maintained on oral concomitant antipsychotic medications throughout the course of the study, and these could be changed during the extended (12- to 18-month) follow-up period. Overall, all doses of PP3M were generally tolerable following injections in either the deltoid or gluteal muscle, and there were no new safety signals detected, compared with PP1M. The proportion of TEAEs noted in this study is also consistent with that of PP1M.[7] The majority of TEAEs were mild to moderate in severity across panels. In total, 35 patients reported serious TEAEs; there was 1 death in the study due to malignant melanoma. The injection-site-related TEAEs were also similar (~8%) to those observed in PP1M studies.[2,12,18] These TEAEs were slightly higher in patients receiving a deltoid injection, consistent with a previous report on PP1M.[14] Results from a subsequent phase-3 clinical study confirmed these safety and tolerability results in addition to demonstrating efficacy of PP3M in patients with schizophrenia.[20]

Following intramuscular injection of PP3M, paliperidone exhibited a dose-proportional PK across a dose range of 75–525 mg eq. Overall, the novel PP3M formulation was generally tolerable following injection in either deltoid or gluteal muscle and at all doses evaluated. The safety and tolerability profiles of PP3M were similar to those of the PP1M formulation, and the slower profile of PP3M supports a dosing interval of 3 monthly administrations in patients with schizophrenia or schizoaffective disorder.

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Sites and Principal Investigators

Belgium: Ignace Demeyer, OLV Ziekenhuis Moorselbaan OLV Research Unit, Aalst Oostvlaanderen; Firmin Janssen, VZW St Annendael Vestenstraat, Diest Vlaamsbrabant. **Bulgaria:** Vesselin Palazov, Mental Health Center Prof Ivan Temkov, Bourgas; Loris Sayan, Mental Health Center Prof Ivan Temkov, Bourgas. **Croatia:** Igor Francetic, KBC Zagreb Kispaticeva, Zagreb. **Israel:** Asaf Caspi, Sheba MC Tel Hashomer, Ramat Gan; Sergio Marchevsky, Beer Yaakov Mental Health Center, Beer; Yehiel Levkovich, Shalvata Mental Health Center, Hod Hasharon. **Korea:** Jong-Il Lee, Asan Medical Center, Seoul; Yongmin Ahn, Seoul National University Hospital, Seoul; Yong Sik Kim, Seoul National University Hospital, Seoul; ChulEung Kim, Inha University Hospital, Incheon; YoungChul Chung, Chonbuk National University Hospital, Chonju. **Malaysia:** Ahmad Hatim Sulaiman, University Malaya Medical Centre, Kuala Lumpur; Suarn Singh, Jasmit Singh, Hospital Bahagia, Perak; Abdul Kadir Abu Bakar, Hospital Permai, Johor. **Slovakia:** Peter Molcan, NsP Ruzinov, Bratislava; Peter Korcsog, Vseobecna Nemocnica Rimavska Sobota, Sobota; Monika Biackova, Psychiatricka Nemocnica, Michalovce. **South Africa:** Paul Pretorius, Free State Psychiatric Complex Research Unit, Bloemfontein Free State; Juan Schronen, Cape Trial Centre, Cape Town. **Spain:** Marcela Manriquez, Hospital Universitario De Bellvitge, Barcelona; Clara Rosso, Hospital Universitario De Bellvitge, Barcelona; Joan Costa, Hospital Universitari Germans Trias I Pujol, Barcelona; Ana Maria Barriocanal, Hospital Universitari Germans Trias I Pujol, Barcelona; Gonzalez Antonio, Hospital Infanta Cristina, Badajoz; Clara Rosso, H Virgen del Rocio, Sevilla; Manuel Franco, Complejo Asistencial De Zamora, Zamora. **Taiwan:** Hung Yu Chan, Taoyuan Mental Hospital, Taoyuan; JiahnJyh Chen, Taoyuan Mental Hospital, Taoyuan; JenYeu Chen, Yu Li Veterans Hospital, Hua Lian; Tzu Ting Chen, Yu Li Veterans Hospital, Hua Lian; TsungMing Hu, Yu Li Veterans Hospital, Hua Lian; ShihKu Lin, Taipei City Hospital, Taipei. **United States:** Mohammed Bari, Synergy Clinical Research Center, National City, CA; Larry Ereshefsky, California Clinical Trials Medical Group, Glendale, CA; Donald Garcia, FutureSearch Trials, Austin, TX; Gregory Kaczenski, KS Professional Services Research Services, Little Rock, AR; Morteza Marandi, Comprehensive NeuroScience, Cerritos, CA; Mark Novitsky, CRI Worldwide, Philadelphia, PA; Rajinder Shiwach, InSite Clinical Research, Desoto, TX; Vicky Spratlin, BioPharm Medical Research, Atlanta, GA; David Walling, CNS Network, Garden Grove, CA; Robert Riesenberg, Atlanta Center for Medical Research, Atlanta, GA.

Previous Presentations

A poster of some of these data was presented at American Psychiatric Association (APA) 168th Annual Meeting, Toronto, Canada, 16–20 May 2015.

Declaration of Conflicting Interests

All authors are employees of Janssen Research & Development, LLC, or of Janssen Research & Development, a division of Janssen Pharmaceutica NV. All authors except Dr. Ravenstijn and Mr. De Meulder hold stock in the company.

Author Contributions

Dr. Ravenstijn and Mr Remmerie were the clinical pharmacology leaders, contributing to the study design, data analysis, and interpretation. Dr. Savitz was the safety physician for the study and was also involved in data analysis and interpretation. Dr. Samtani had primary role in the study design and data interpretation. Dr. Nuamah was the statistical lead, and Dr. Chang was the statistician for the study, and both had primary roles in the statistical analyses and data interpretation. Mr. De Meulder was the bioanalytical scientist responsible for sample analyses. Drs. Hough and Gopal were the clinical leaders for paliperidone palmitate 3-month formulation and had primary roles in the study design, analyses and data interpretation.

All authors met ICMJE criteria, and all those who fulfilled those criteria are listed as authors. All authors had access to the study data and made the final decision about where to present these data.

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