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A Single-Dose, Open-Label, Parallel, Randomized, Dose-Proportionality Study of Paliperidone After Intramuscular Injections of Paliperidone Palmitate in the Deltoid or Gluteal Muscle in Patients With Schizophrenia

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Abstract

Paliperidone palmitate (PP) is a long-acting injectable (LAI) antipsychotic, developed for monthly intramuscular (i.m.) administration into deltoid/gluteal muscle, approved for the treatment of schizophrenia in many countries. To assess the options for i.m. injection sites, dose-proportionality of PP was investigated after injection of a single dose (25–150 mg eq.) of PP in either gluteal (n = 106) or deltoid (n = 95) muscle of schizophrenic patients. Overall, mean (geometric) area under plasma concentration–time curve from time zero to infinity (AUC_∞) of paliperidone increased proportionally with increasing PP doses, regardless of injection site. Mean maximum plasma concentration (C_{max}) was slightly less than dose-proportional for both injection sites at PP doses >50 mg eq. Mean C_{max} was higher after injection in the deltoid compared with the gluteal muscle, except for the 100 mg eq. dose, while AUC_∞ for both injection sites was comparable at all doses. Median time to reach C_{max} (t_{max}) ranged from 13–14 days after deltoid and 13–17 days after gluteal injection across all doses. Single PP injections in deltoid and gluteal muscles in the dose range of 25–150 mg eq. were generally tolerable both locally and systemically.

Keywords

dose-proportionality, long-acting injectable, paliperidone palmitate, schizophrenia

Oral antipsychotic medications are considered effective for the management of schizophrenia, but poor patient adherence which is often observed with oral medications that require dosing on a daily basis, remains common in patients with schizophrenia.[1–3] However, long-acting injectable formulations (LAIs) can promote compliance during long-term treatment.[2,4–6] Because healthcare professionals administer each LAI dose, they can follow up with the patient if a dose is missed to ensure timely administration and aid better compliance. Additionally, LAIs provide a slow initial absorption of the dose and less peak-to-trough variability in plasma concentrations at steady state, thus offering the potential to reduce treatment-emergent adverse events (TEAEs) sometimes associated with the relatively high peak plasma drug concentrations of oral immediate-release formulations. Several first and second generation LAI antipsychotics are currently available. The drawback of first generation LAIs is that they are associated with movement disorders, including extrapyramidal symptoms (EPS) and tardive dyskinesia.[7,8]

Paliperidone palmitate (PP) is the palmitate ester of paliperidone (9-hydroxy-risperidone), which is the major

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[Correction added on April 30, 2014 after first online publication: Dr. Rosso's name was originally provided as "Clara M. Rosso Fernandez."]

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active metabolite of risperidone and is a racemic mixture of the enantiomers R078543 (+) and R078544 (−). Paliperidone is a selective monoaminergic antagonist that exhibits the characteristic dopamine type 2 and serotonin (5-hydroxytryptamine) type 2A antagonism of the second-generation antipsychotic drugs. Once daily paliperidone extended-release (ER) tablet (Invega®) is effective in patients with schizophrenia and is generally tolerable.[9–12] The LAI of paliperidone, PP for 4-weekly i.m. administration, has been approved in the United States, European Union, Japan and many other countries for the treatment of schizophrenia in adults (INVEGA® SUSTENNA®, XEPLION® [in Europe]).[13] It is an aqueous nanosuspension that slowly dissolves at the intramuscular (i.m.) injection site and releases paliperidone into the systemic circulation over an extended period of time. PP at doses of 25–150 mg equivalent (mg eq.) was efficacious and generally safe and tolerable in phase II/III trials in adult patients with schizophrenia.[14–17] The approved recommended initiation regimen of i.m. PP 150 mg eq on day 1 and 100 mg eq. on day 8 (both deltoid muscle), followed by a monthly maintenance dose in the range of i.m. PP 25–150 mg eq. (deltoid or gluteal muscle) provides relatively constant therapeutic plasma concentrations over several weeks and hence eliminates the need for oral supplementation and enhances compliance.[13,18,19] PP (50, 100, or 150 mg eq.) i.m. without oral supplementation has demonstrated non-inferiority and comparable safety and tolerability to risperidone-LAI (RIS-LAI) (25, 37.5, 50 mg) i.m. with oral risperidone supplementation in the treatment of schizophrenia.[20]

The safety and tolerability of once-monthly PP was generally comparable irrespective of the injection site (deltoid or gluteal) in a cross-over study evaluating injection sites.[21] In that study, although median plasma paliperidone concentrations were higher with deltoid muscle injection compared with the gluteal muscle during the first week of treatment, at apparent steady state, there was little difference in plasma paliperidone concentrations between both sites for a given dose. However, injection site pain (patient and investigator evaluation) was more frequently observed in patients who received the deltoid injection compared with those who received the gluteal injection.[21] Doses of PP are expressed in terms of milligram equivalents (mg eq.) of the active moiety, paliperidone. The doses expressed as PP 25, 50, 100, and 150 mg eq. in this study correspond to 39, 78, 156, and 234 mg of PP, respectively. To allow patients the choice between different injection sites, pharmacokinetics and the dose-proportionality of PP at doses equivalent of 25, 50, 100, and 150 mg paliperidone (referred in the study as, PP 25, 50, 100, and 150 mg eq.) when injected in the deltoid or gluteal muscles were evaluated in the present study. Furthermore, the safety and tolerability of PP i.m. injections at the two muscle sites were compared.

Methods

Patients and Study Design

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and in compliance with local regulations. Before the start of the study, the protocol was reviewed and approved by the Institutional Review Boards or independent ethics committee. Prior to any study procedures, patients provided written informed consent to participate in the study after having been informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits of treatment.

Voluntary inpatients or outpatients between 18 and 65 years of age with a body mass index (BMI) between 17 and 35 kg/m^2, diagnosed with schizophrenia of any subtype (disorganized, catatonic, paranoid, residual, or undifferentiated) for more than 1 year (specific requirement in Israel: had at least 1 prior hospitalization for schizophrenia) according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) were included in the study. In addition, the patients were clinically stable with no change in antipsychotic medication for 3 months before screening and had a Positive and Negative Syndrome Score (PANSS) total score $\leq$70 at screening. Patients were excluded from the study if they had DSM-IV diagnosis of alcohol or substance dependence within 12 months before screening, or had history of neuroleptic malignant syndrome, or had moderate or severe tardive dyskinesia at the time of screening. Women who were pregnant, breastfeeding, or who planned to become pregnant during the study period were also excluded.

This single-dose, open-label, randomized, parallel-group study was designed to evaluate the dose proportionality (for each injection site) of four fixed doses of PP (25, 50, 100, 150 mg eq.) following an i.m. injection in the gluteal or deltoid muscle. The study consisted of a screening period of up to 21 days, and an open-label treatment period during which patients received a single injection of PP (25, 50, 100, or 150 mg eq.) in the deltoid or gluteal muscle followed by a 126-day post-treatment observation period. Injections were administered with a 22G 1.5-in. needle (gluteal injection) or a 23G 1-in. needle (deltoid injection) and the exact site and side of injection (right or left deltoid or gluteal muscles) and date, time, and dosage of the injection were documented. An end-of-study visit was completed on Day 126 or at early withdrawal.

Prior and Concomitant Medication

Patients who had been treated with an antipsychotic medication before study entry could continue using their medication throughout the study except for the specific previous use of PP within 10 months of randomization, RIS-LAI within 100 days before screening, long-acting

formulations of other antipsychotic drugs within 1 treatment cycle before screening, clozapine within 6 weeks before randomization, oral risperidone and oral paliperidone within 2 weeks before randomization, thioridazine and ziprasidone within 1 week before randomization. In addition, barbiturates and any anticonvulsant medications had to be discontinued within 2 weeks before randomization. All concomitant antipsychotic medications were tapered to the lowest possible dose as clinically indicated according to the investigator's judgment. Patients without source documentation of previous treatment with risperidone, paliperidone, PP, or RIS-LAI underwent an oral tolerability testing wherein they received 4 daily doses of oral paliperidone ER (3 mg/day). This 4-day testing period was completed at least 8 full days before the first i.m. injection of PP, which was long enough for the washout of paliperidone. The oral tolerability test was meant to prevent any potential problems with tolerability and allergic or hypersensitivity reactions that might be related to systemic exposure to paliperidone. Examples of problems that could have resulted in exclusion of the patient concerned included intolerable sedation, clinically symptomatic orthostatic hypotension, torticollis or other severe extrapyramidal symptoms, or evidence of an allergic reaction.

Treatment

PP was provided as a suspension in prefilled syringes (100 mg/mL eq.). At baseline (day 1), eligible patients were randomly assigned to 1 of 8 treatment groups based on a computer-generated randomization scheme prepared by the sponsor before the study. The randomization was balanced using permuted blocks of treatments and stratified by Body Mass Index classification (<25, 25–30, $>30\,kg/m^2$) and sex.

Assessments

Venous blood samples were collected via venipuncture for determination of plasma concentrations of paliperidone enantiomers at the following time points: immediately before the i.m. injection on day 1, at 6, 24, 48, and 96 hours after injection and on days 7, 9, 11, 13, 15, 17, 19, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84, 98, 112, and 126. On Days 7–126, plasma samples were collected at about the same time of the day.

Neuropsychiatric evaluations of schizophrenia included PANSS[22] and the Clinical Global Impression-Severity (CGI-S) scale[23] which were completed at screening, predose on day 1, on day 28 and on day 126 (end of study).

Safety assessments included reported treatment-emergent adverse events (TEAEs) and serious TEAEs, extrapyramidal symptom rating scales (Simpson-Angus Scale [SAS],[24] Abnormal Involuntary Movement Scale [AIMS][25] and Barnes Akathisia Rating Scale [BARS]),[26] clinical laboratory evaluations, electrocardiogram, vital signs, and body weight. Injection site tolerability was evaluated by the investigator by scoring for redness, pain, swelling, and induration. Injection site pain was rated by patients using a 0–100 mm VAS score.

Bioanalytical Methods

Blood samples were collected in heparinized tubes. After centrifugation, the plasma aliquots were frozen and stored at $-20°C$ until analyzed. All sample handling and storage conditions are consistent with the available stability information. Plasma concentrations of the paliperidone enantiomers were determined using a validated liquid chromatography coupled to tandem mass spectrometry method.[27] The analytical range was 0.200–100 ng/mL, with a precision (expressed as percentage of coefficient of variation) within 7.6% and accuracy of 98.4–101.9%.

Pharmacokinetic Evaluations

The total paliperidone plasma concentration was calculated as the sum of both enantiomers. From the paliperidone and enantiomer plasma concentrations, the following pharmacokinetic parameters were calculated, with non-compartmental analysis (WinNonlin, Version 4.0.1b): observed maximum plasma concentration (C_{max}); time to reach C_{max} (t_{max}); apparent elimination half-life ($t_{1/2}$); area under the plasma concentration–time curve from time zero to last observation (AUC_{last}); AUC from time zero to infinity (AUC_{∞}). Enantiomer ratios of (+)/(−) paliperidone were calculated for C_{max} and AUC_{∞}.

Data Analysis

Sample Size. Based on a previous study (Clinicaltrials.gov, NCT00073320) with PP i.m. injections in the deltoid and gluteal muscle at dose levels of 25 and 150 mg eq., the standard deviation of log-transformed (after dose-normalization) C_{max} and AUC_{∞} was estimated to be ≤ 0.5 for paliperidone. Linear regression on log-transformed variables allows interpretation of the slope as a deviation from dose-proportionality. Using a standard deviation of 0.55, a sample size of 192 patients (i.e., 24 patients per group, and four groups per injection site) was sufficient to estimate by injection site the slope of the regression line to within 0.16 of the true value with 95% confidence. To allow for a 4% dropout rate, 200 patients (approximately 25 per group) were planned to be enrolled.

Dose-proportionality after PP i.m. injections was evaluated by fitting a linear regression model to the logarithm of the dose-normalized (to 50 mg eq.) pharmacokinetic parameters (C_{max} and AUC_{∞}) for paliperidone with logarithm of dose as a predictor. For each injection site, the assumption of dose-proportionality was rejected on a 5% significance level if the corresponding slope was significantly different from zero, evaluated by the corresponding two-sided 95% confidence interval from the regression model. In addition, an analysis-of-variance

(ANOVA) model was fitted for each injection site separately (deltoid, gluteal) on log-transformed dose-normalized pharmacokinetic parameters with dose as a factor and comparing each dose. For each dose the ratio of geometric mean (GM) of pharmacokinetic parameters versus the 150 mg eq. dose (reference) with associated 90% confidence intervals was determined. To compare exposure in the deltoid muscle with the gluteal muscle, an ANOVA model was fitted for each dose separately on the log-transformed pharmacokinetic parameters with injection site as a factor. The ratios of GM pharmacokinetic parameters after deltoid versus gluteal injection with associated 90% CIs were estimated for each dose.

Results

Patient and Treatment Information

A Total of 201 patients with schizophrenia were randomized between June 2005 and September 2006, to receive a single PP injection (25 [n = 48], 50 [n = 50], 100 [n = 51], or 150 [n = 52] mg eq.) in either the deltoid or the gluteal muscle, at 28 study sites in eight countries (Canada, Israel, Romania, Slovakia, Sweden, Spain, United States of America, and Poland). Demographic and baseline characteristics were comparable between all treatment groups, (Table 1). Majority of the patients (72%) were men and the age of the patients ranged from 20 to 65 years. Majority of the patients had a diagnosis of paranoid schizophrenia (78.6%). Overall, 170 patients (85%) completed the study. The percentage of completers ranged from 67% (150 mg eq. deltoid group) to 96% (100 mg eq. deltoid group) among the treatment groups. Withdrawal from the study was due to safety concerns (n = 5), lost to follow up (n = 6), withdrawal of consent (n = 9), pregnancy (n = 1) and other reasons (n = 10).

Pharmacokinetics of Paliperidone

Median dose-normalized (to 50 mg eq.) paliperidone plasma concentration–time profiles per injection site are presented in Figure 1. Upon deltoid injection of 150 mg eq., the median paliperidone plasma concentrations was 4.1 (range: 1.7–9.8, n = 22) ng/mL at 24 hours and 10 (range: 3.6–28.6, n = 22) ng/mL at 48 hours after administration.

Pharmacokinetic parameter values are summarized by group in Table 2 (actual pharmacokinetic parameter values are presented in supplemental Table S1). The maximum exposure (median C_{max}) dose-normalized to 50 mg eq. decreased slightly with increasing dose and ranged from 8.8 to 11.0 ng/mL. The median C_{max} was generally higher after deltoid i.m. injection compared to gluteal injection. The total exposure (median AUC_{∞}) dose-normalized to 50 mg eq. was comparable across all doses, independent of the injection site, and ranged from 9311 to 11,271 ng h/mL. The median t_{max} of paliperidone

Table 1. Demographic and Baseline Characteristics

	25 mg		50 mg		100 mg		150 mg	
	Deltoid i.m. (N = 24)	Gluteal i.m. (N = 24)	Deltoid i.m. (N = 24)	Gluteal i.m. (N = 26)	Deltoid i.m. (N = 23)	Gluteal i.m. (N = 28)	Deltoid i.m. (N = 24)	Gluteal i.m. (N = 28)
Sex, n (%)								
Men	17 (71)	18 (75)	18 (75)	19 (73)	17 (74)	19 (68)	18 (75)	19 (68)
Women	7 (29)	6 (25)	6 (25)	7 (27)	6 (26)	9 (32)	6 (25)	9 (32)
Race, n (%)								
Asian	0	0	0	0	0	0	2 (8)	0
Black	2 (8)	10 (42)	6 (25)	4 (15)	5 (22)	5 (18)	7 (29)	10 (36)
Other	1 (4)	1 (4)	0	2 (8)	1 (4)	2 (7)	2 (8)	1 (4)
White	21 (88)	13 (54)	18 (75)	20 (77)	17 (74)	21 (75)	13 (54)	17 (61)
Age (years)								
Mean (SD)	37.7 (9.1)	43.8 (9.5)	42.8 (8.6)	39.9 (9.5)	37.4 (10.1)	42.6 (12.6)	41.4 (9.2)	42.8 (10.0)
Weight (kg)								
Mean (SD)	85.6 (18.2)	86.1 (19.0)	87.3 (15.9)	82.8 (15.6)	87.1 (14.8)	85.8 (14.1)	83.4 (15.0)	84.5 (17.9)
Height (cm)								
Mean (SD)	172.8 (8.4)	175.2 (10.2)	175.2 (8.6)	171.5 (12.1)	175.9 (10.8)	173.0 (10.8)	170.5 (8.1)	173.6 (9.5)
Body mass index (kg/m^2)								
Mean (SD)	28.5 (5.0)	27.9 (4.9)	28.4 (4.4)	28.2 (4.5)	28.1 (3.8)	28.7 (4.1)	28.6 (4.3)	27.9 (4.7)
Schizophrenia type, n (%)								
Catatonic	0	0	0	0	0	1 (4)	0	0
Disorganized	0	1 (4)	0	1 (4)	0	0	1 (4)	0
Paranoid	19 (79)	21 (88)	20 (83)	17 (65)	18 (78)	22 (79)	17 (71)	24 (86)
Residual	3 (13)	1 (4)	2 (8)	4 (15)	4 (17)	3 (11)	4 (17)	3 (11)
Undifferentiated	2 (8)	1 (4)	2 (8)	4 (15)	1 (4)	2 (7)	2 (8)	1 (4)

i.m., intramuscular; SD, standard deviation.

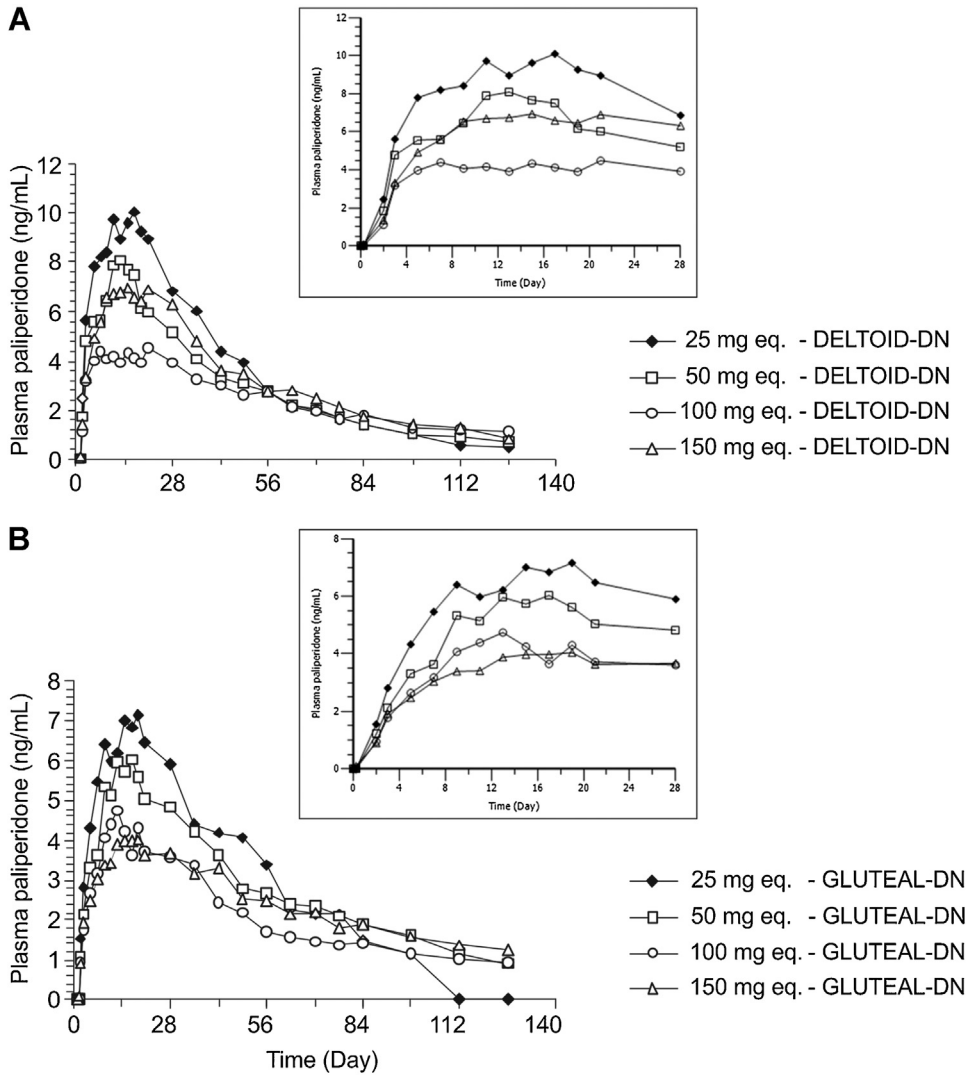

Figure 1. Median dose-normalized (to 50 mg eq.) paliperidone plasma concentration–time profile after i.m. injection of paliperidone palmitate in the deltoid (A) and gluteal (B) muscle. Inset shows absorption and distribution phase only from t = 0 to 28 days. DN, dose-normalized.

was comparable, at both the injection sites and for the different doses (13–17 days). After i.m. injection in the deltoid as well as the gluteal muscle, the median apparent $t_{1/2}$, increased with dose from 25 days after administering the 25 mg eq. dose to 40–49 days after administering the 100 and 150 mg eq. doses. For all doses, the apparent $t_{1/2}$ was comparable between injection sites.

Plasma concentrations of the R078543(+) enantiomer were consistently higher than those for the R078544(−) enantiomer. The median R078543(+)/R078544(−) C_{max} and AUC_{∞} ratios were approximately 1.7 for both injection sites.

Evaluation of Dose-Proportionality

In Figure 2, the individual log-transformed dose-normalized (to 50 mg eq.) paliperidone C_{max} and AUC_{∞} estimates are depicted versus the log-transformed dose with the estimated linear relationship based on the linear regression model. The slopes of the linear regression for C_{max} were significantly different from zero for the deltoid (slope −0.22; $P = 0.0062$) and gluteal (slope −0.31; $P < 0.0001$) injection sites, indicating a less than dose-proportional increase in C_{max} (Figure 2A). Specifically, the geometric means for C_{max} (after dose-normalization) were significantly lower for PP 100 mg eq. injection in the deltoid muscle, and for the 100 and 150 mg eq. doses injected in the gluteal muscle, when compared with other dose groups (Table 3). The slopes of the linear regression for AUC_{∞}, however, were not significantly different from zero for both the deltoid (slope −0.06; $P = 0.36$) and gluteal (slope −0.02; $P = 0.76$) injection sites, and as such, dose-proportionality for AUC was concluded for both injection sites (Figure 2B). The pairwise comparisons of the pharmacokinetic parameters for each dose with the

Table 2. Median (Range) Dose-Normalized (to 50 mg eq.) Pharmacokinetic Parameters of Paliperidone After a Single Injection of Paliperidone Palmitate Administered Into the Deltoid or Gluteal Muscle

Parameters	n	25 mg eq.	n	50 mg eq.	n	100 mg eq.	n	150 mg eq.
Deltoid injection								
t_{max}, days	22	13.0 (4.0–35.0)	23	13.0 (4.0–48.0)	22	12.5 (4.0–56.0)	21	14.0 (4.1–48.0)
C_{max}, ng/mL	22	11.0 (4.6–23.2)	23	8.8 (3.1–29.5)	22	5.3 (3.5–18.2)	21	9.2 (3.6–17.0)
AUC_{last}, ng h/mL	22	10,266 (5870–20,998)	19	9445 (5005–23,339)	22	7754 (2605–14,526)	17	9574 (7098–14,568)
AUC_{∞}, ng h/mL	20	11,271 (6566–22,294)	18	11,162 (5492–24,693)	16	9311 (2882–17,120)	18	11,170 (8336–22,105)
$t_{1/2}$, days	20	24.9 (12.8–53.0)	18	29.1 (16.7–72.4)	16	43.7 (18.8–73.4)	18	40.6 (20.6–62.7)
CL/F, L/h	20	4.4 (2.2–6.7)	18	4.5 (2.0–9.1)	16	5.4 (2.9–16.5)	18	4.5 (2.3–6.0)
Gluteal injection								
t_{max}, days	21	16.0 (4.0–55.2)	24	13.4 (6.0–41.0)	25	14.1 (6.0–62.0)	24	17.0 (4.0–75.9)
C_{max}, ng/mL	21	8.7 (4.1–19.3)	24	6.9 (2.6–14.8)	25	5.4 (2.2–15.4)	24	5.1 (2.9–14.9)
AUC_{last}, ng h/mL	20	9779 (2388–18,452)	21	8978 (5164–13,893)	21	5966 (2509–14,557)	20	7329 (4320–14,992)
AUC_{∞}, ng h/mL	19	10,557 (2681–19,708)	19	10,088 (8018–14,338)	18	9652 (3864–19,511)	16	10,442 (5640–17,942)
$t_{1/2}$, days	19	25.1 (10.2–76.6)	19	31.2 (12.5–60.6)	18	40.0 (18.7–56.7)	16	49.1 (16.0–82.2)
CL/F, L/h	19	4.6 (2.5–17.7)	19	5.0 (3.5–6.2)	18	5.2 (2.6–12.9)	16	4.8 (2.8–8.8)

AUC_{∞}, area under the plasma concentration–time curve from time zero to infinite time; AUC_{last}, area under the plasma concentration–time curve from time zero to the time of the last quantifiable concentration; CL/F, apparent plasma clearance; C_{max}, observed maximum plasma concentration; $t_{1/2}$, elimination half-life; t_{max}, time to reach observed maximum plasma concentration.

150 mg reference dose (all dose normalized to 50 mg eq.) are presented in Table 3. In addition, for each injection site the estimated ratio of geometric mean AUC_{∞} (dose-normalized) between each dose and 150 mg eq. varied from 83% to 107% (Table 3). Both analyses indicate that the total paliperidone exposure (AUC_{∞}) increases proportionally with increasing PP dose.

Deltoid Versus Gluteal Injection Site

A summary of the comparison of the geometric mean exposure (C_{max} and AUC_{∞}) of paliperidone for each dose between deltoid and gluteal muscle is shown in Table 4. Geometric mean C_{max} was estimated to be higher after deltoid injection compared to gluteal injection (ratios of deltoid versus gluteal ranging from 109% to 165%). Geometric mean AUC_{∞} of paliperidone was slightly higher after deltoid injection compared with gluteal injection (ratios of deltoid versus gluteal ranging from 103% to 118%) (see Table 4).

Psychiatric Evaluations

Mean changes from baseline in total PANSS scores and PANSS factor scores were comparable between doses and the two injection sites (range of mean $\pm$ SD PANSS total scores for deltoid group at baseline: 49.1 ± 11.0 to 55.4 ± 11.3, end-of-study 50.6 ± 11.8 to 56.3 ± 11.9; for the gluteal group: baseline 54.1 ± 9.8 to 54.4 ± 11.0, end-of-study 54.1 ± 11.9 to 56.4 ± 13.6). An assessment of CGI-S did not reveal any apparent changes over time across doses or either site of injection. For each dose and injection site, the median score for CGI-S was mild at each postbaseline time point.

Safety Results

TEAEs were observed in 120/201 (60%) patients (Supplemental Table S2). The majority of the TEAEs were mild to moderate in severity. There were no deaths and 18 (9%) patients experienced serious TEAEs. Five patients prematurely withdrew from the study due to TEAEs

The most common TEAEs were tachycardia (n = 20), headache (n = 15), worsening of schizophrenia (n = 13), weight increased (n = 11), and insomnia (n = 10) (Supplemental Table S2). The incidence of TEAEs was similar across all dose groups, regardless of injection site and it did not increase with increasing dose of PP. Nine patients (4%) reported an injection site-related TEAE (six in the gluteal group and three in the deltoid group), including injection site mass (n = 2), injection site phlebitis (n = 1), induration (n = 3), injection site pain (n = 2) and injection site anesthesia (n = 1). All injection site-related TEAEs were mild in severity.

No ratings of moderate or severe induration/redness in the injection site evaluation by the investigators were reported at either injection sites. The proportion of patients experiencing pain after injection was higher in the deltoid group compared with the gluteal group (39% vs. 25%, respectively); the majority of these cases were mild in severity. After deltoid injection, injection site swelling was reported in nine patients, compared with six patients receiving gluteal injections. The mean $\pm$ SD injection site pain VAS score at 30 minutes after injection was low overall and lowest for the 25 mg eq. gluteal injection (6.6 ± 7.5 mm) and highest for the 100 mg eq. deltoid injection (17.0 ± 22.7mm).

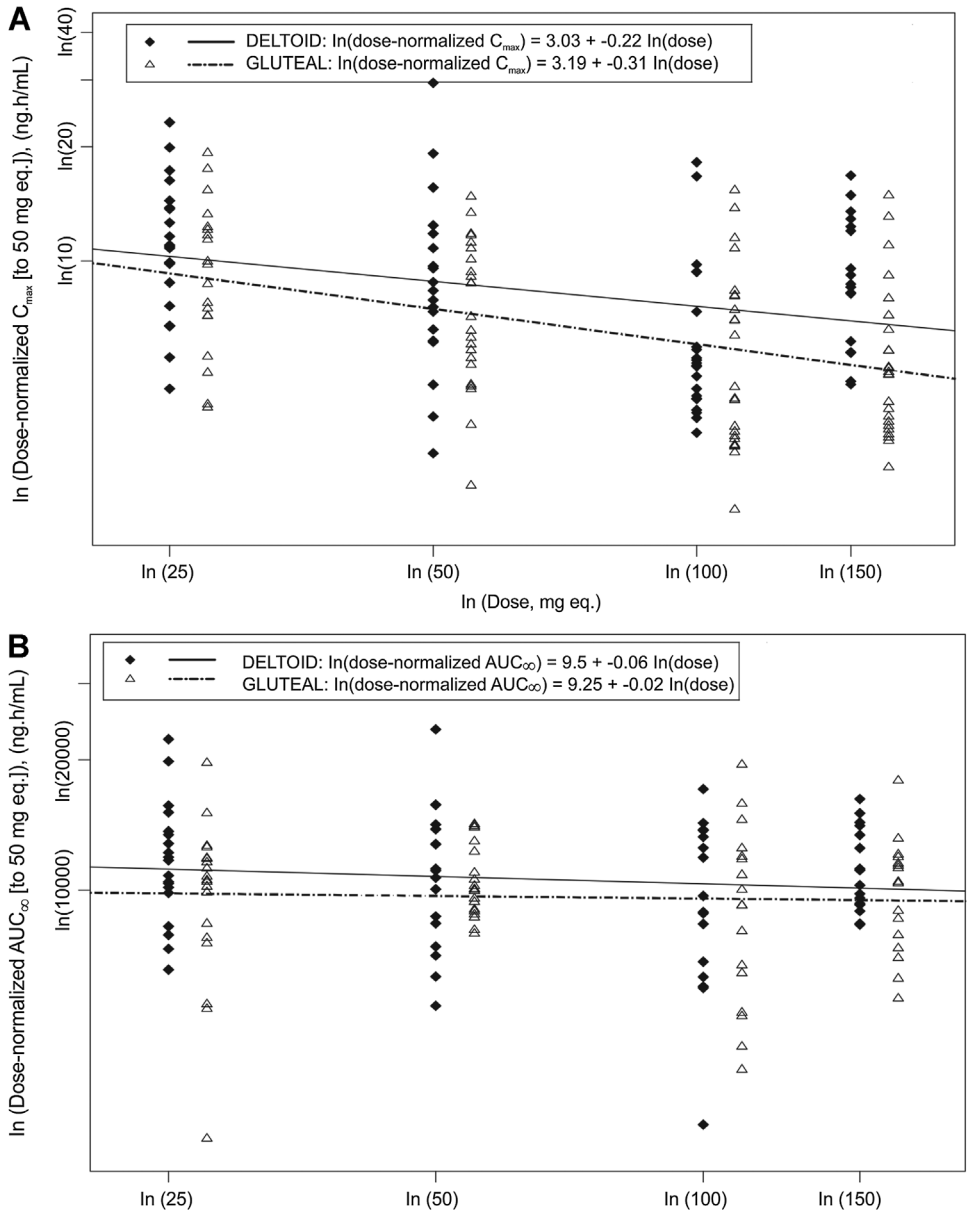

Figure 2. Linear regression model of paliperidone C_{max} (A) and AUC_{∞} (B) parameters (dose-normalized to 50 mg eq.).

There were no clinically relevant changes in any of the hematology and urinalysis parameters evaluated. Relevant changes in clinical chemistry parameters were limited to dose-dependent increases in prolactin (ng/mL) in the deltoid and gluteal muscle injection groups.

Twenty (10%) patients (10 in the gluteal group and 10 in the deltoid group) experienced treatment-emergent orthostatic hypotension (sustained decrease in systolic or diastolic blood pressure [>20 or >10 mmHg, respectively] upon standing for ≥2 minutes, associated with an increase in pulse >15 bpm) at least once during the study with no dose-dependent increase in the incidence in either muscle injection group. No patients had population-specific linear-derived corrected QT intervals exceeding 500 milliseconds. The maximum postbaseline QTcLD interval ranged from 431 to 452 milliseconds in the deltoid muscle injection group and from 418 to 471 milliseconds in the gluteal muscle injection group.

There were no clinically relevant changes from baseline in mean total BARS and SAS scores for all doses and for both injection sites. At the end of the study, mean (SD) total AIMS score had increased from baseline in patients receiving PP 150 mg eq. in the deltoid (0.2 ± 0.82 to 0.7 ± 1.7) but not in the gluteal muscle (0.2 ± 0.8 to 0.2 ± 0.8).

Table 3. Pairwise Comparisons of Geometric Least-Square Mean Between Doses (Dose-Normalized to 50 mg eq.) After a Single Injection of Paliperidone Palmitate into the Deltoid or Gluteal Muscle

Injection Site	Parameter	Dose (Test) mg eq.	Dose (Reference) mg eq.	Ratio, % (Test/Reference) [90% CI]
Deltoid	C_{max} (ng/mL)	25	150	123.1 [96.8–156.6]
		50	150	98.3 [76.8–125.7]
		100	150	67.5 [53.0–85.8]
	AUC_{∞} (ng h/mL)	25	150	103.1 [84.8–125.5]
		50	150	96.5 [78.7–118.3]
		100	150	82.7 [67.3–101.8]
Gluteal	C_{max} (ng/mL)	25	150	169.1 [133.3–214.6]
		50	150	135.1 [107.4–169.9]
		100	150	102.3 [81.3–128.6]
	AUC_{∞} (ng h/mL)	25	150	98.3 [80.0–120.9]
		50	150	106.8 [86.9–131.3]
		100	150	92.4 [75.0–113.9]

AUC_{∞}, area under the plasma concentration–time curve from time zero to infinite time; CI, confidence interval; C_{max}, observed maximum plasma concentration.

Discussion

This study was designed to characterize the pharmacokinetics, safety and tolerability of PP after i.m. administration of a single dose in the deltoid or gluteal muscle with particular focus on the dose-proportionality of systemic paliperidone exposures at 25, 50, 100, and 150 mg eq. The data indicate that the AUC_{∞} of paliperidone increased proportionally with dose after a single injection of PP 25–150 mg eq. in both the deltoid and gluteal muscle. The somewhat lower dose-normalized AUC_{∞} of the 100 mg eq. dose after i.m. injection in the deltoid muscle compared with the other doses at the same injection site can be the result of the limited number of patients per dose group and the relatively high variability of the paliperidone pharmacokinetic parameters after PP injection. For C_{max} the increase was less than dose-proportional for both injections sites at doses greater than 50 mg eq. Based on median values for AUC_{∞} and AUC_{last}, the percentage AUC extrapolated ($\%AUC_{ex}$) varied from 7% to 38% for the eight treatment groups. For some patients the $\%AUC_{ex}$ was above 20% and the number of patients who experienced this increased with dose due to the longer half-life at higher dose. These patients were used in the statistical analysis as the calculated half-life was consistent with the half-life of patients with a $\%AUC_{ex}$ below 20%.

Table 4. Comparison of Dose-Normalized (to 50 mg eq.) Paliperidone Pharmacokinetic Parameters After a Single Injection of Paliperidone Palmitate Into the Deltoid or Gluteal Muscle

Paliperidone Palmitate Dose (mg eq.)	Parameter	Ratio, % (Deltoid/Gluteal) [90% CI]
25	C_{max} (ng/mL)	119.9 [96.2–149.3]
	AUC_{∞} (ng h/mL)	117.8 [96.6–143.7]
50	C_{max} (ng/mL)	119.9 [93.4–153.9]
	AUC_{∞} (ng h/mL)	104.4 [88.4–123.3]
100	C_{max} (ng/mL)	108.8 [84.6–139.8]
	AUC_{∞} (ng h/mL)	103.0 [79.0–134.3]
150	C_{max} (ng/mL)	164.9 [131.2–207.1]
	AUC_{∞} (ng h/mL)	114.4 [97.6–134.1]

AUC_{∞}, area under the plasma concentration–time curve from time zero to infinite time; CI, confidence interval; C_{max}, observed maximum plasma concentration.

After i.m. injection in both the deltoid as well as in the gluteal muscle, the median apparent $t_{1/2}$ increased with dose from 25 days after injection of the 25 mg eq. dose to 40–49 days after injection of the 100 and 150 mg eq. doses. For all doses, median apparent $t_{1/2}$ was comparable between injection sites. For LAI formulations, it is known that the elimination rate is determined by the absorption rate. Therefore, the observed longer apparent half-life for the higher doses reflects a slower release of PP from the injection site for these doses. Consistent with this, the increase in C_{max} was less than dose-proportional for both injection sites. This was further confirmed by population pharmacokinetic modeling for PP, the results of which showed a significant effect of the administered dose on the absorption related pharmacokinetic parameters.[18] This is also in line with the observations of Hirano et al[28] that in general, a higher volume injected in muscle will result in a less than dose-proportional increase in C_{max}. The median t_{max}, after a single i.m. injection in the deltoid or gluteal muscle, ranged from 13 to 17 days across all doses. This is comparable with a previous PP single-dose study (INT-12, unpublished data) where the median t_{max} ranged from 11 to 21 days.

The initial median paliperidone plasma concentrations (especially 2–3 weeks after injection) after i.m. administration of PP in the gluteal muscle were lower compared with i.m. injection in the deltoid muscle, except for the 100 mg eq. dose. The slower release after injection in the gluteal muscle can likely be explained by the fact that the drug has partly been administered in adipose tissue when administered in the gluteal muscle. The

hypovascularity of subcutaneous adipose compared with muscle tissue may result in a slower absorption of the drug in the gluteal compared with the deltoid muscle.[18] However, the total exposure (AUC_∞) was found to be independent of the injection site. The study was not designed to be powered for a formal bioequivalency comparison and has limitations in terms of the small sample size and parallel-design, in particular given the inter-patient variability. However, the higher C_{max} after deltoid injection, compared to gluteal injection, reflects the 37% higher initial release rate during the zero-order input phase after deltoid injection, as estimated by Samtani et al.[18] The difference in release rate between the injection sites, observed after a single dose, is expected to be reduced at steady-state.

The median paliperidone plasma concentrations (4 ng/mL at 24 hours; 10 ng/mL at 48 hours after dosing) after deltoid injection of 150 mg eq., that is, the first initiation dose of the recommended dosing regimen, suggest that potentially therapeutic concentrations are reached between 1 and 2 days after the initial dose. A paliperidone plasma concentration of 7.5 ng/mL is associated with a central D_2-receptor occupancy of approximately 60%.[29] A central D_2-receptor occupancy of 60–80% is thought to be required for antipsychotic efficacy.[30,31] Furthermore, it was found that between 24 and 48 hours after injection of the first i.m. dose of PP 150 mg eq. in the deltoid muscle, the paliperidone plasma concentrations are comparable to those observed after initiating treatment with 6 mg oral paliperidone extended release (ER) (data not shown). Similarly, it was found that 4 hours after injection, the paliperidone plasma concentrations are similar to those after oral administration of 3 mg paliperidone ER, the lowest effective dose. The comparative exposure data confirm the potential of PP to treat acute symptoms of schizophrenia as demonstrated in other clinical studies.[14–17,20,21] The paliperidone plasma concentration range for PP dosing was within the plasma concentration range observed after oral administration of paliperidone ER, suggesting robust and controlled release of paliperidone from the injection site of PP.

The median R078543(+)/R078544(−) C_{max} and AUC_∞ ratios after i.m. injection in the deltoid or gluteal muscle were around 1.7, independent of dose or injection site. These results are similar to the R078543(+)/R078544(−) C_{max} and AUC_∞ ratios after administration of oral paliperidone ER tablets.

Patients were permitted to continue on their existing oral antipsychotic treatment in addition to the PP injections. Therefore, the psychiatric evaluation should be interpreted with caution considering that patients were receiving 2 or more antipsychotic agents simultaneously. Similarly, for the safety results, some TEAEs may have been due to PP, or concomitant antipsychotics medications, or a combination of PP and the concomitant antipsychotic medications. PP was generally tolerable at doses up to 150 mg eq. The most commonly reported TEAEs were tachycardia (n = 20), headache (n = 15), worsening of schizophrenia (n = 13), weight increased (n = 11), and insomnia (n = 10). Eighteen patients (9%) reported 1 or more serious TEAEs, mostly psychiatric disorders (7%). Five patients prematurely withdrew from the study due to TEAEs. No patient died due to a TEAE. The observed safety profile of PP is consistent with that from other studies.[14–17,20,21] PP was well tolerated at either site of injection and at all doses tested. Although slightly more discomfort (pain and swelling) was reported with deltoid injection, this is not unexpected as the deltoid muscle is smaller than the gluteal muscle and injections of similar volume are thus expected to result in more discomfort due to swelling. Twenty patients (10%) were identified as meeting criteria for treatment-emergent orthostatic hypotension on the basis of vital sign measurements at least once during the study. Patients were permitted to continue on their existing oral antipsychotic treatment in addition to the PP injections. Many of the concomitant antipsychotic medications are known to induce orthostatic hypotension owing to their alpha-1-lytic activity, which may have influenced the occurrence of TEAEs of orthostatic hypotension in the patients in this study.

In conclusion, the results of this study indicate that besides the gluteal muscle, the deltoid muscle also can be used as injection site for the i.m. administration of PP in patients with schizophrenia. Paliperidone pharmacokinetics increased proportionally with PP dose for AUC_∞ and less than dose-proportional for C_{max} at doses above 50 mg eq. Single PP injections in deltoid and gluteal muscles in the dose range of 25–150 mg eq. were well-tolerated locally and systemically.

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Declaration of Conflicting Interests

Dr. Hough, Dr. Gopal, and Dr. Berwaerts are employees of Janssen Research & Development, USA. Dr. Crauwels and Dr. Vandebosch, Mr. Remmerie and De Meulder are employees of Janssen Research & Development, Belgium. Dr. Rossenu, Dr. Cleton, and Dr. Eerdekens were employees of Janssen Research & Development, Belgium at the time this study was conducted. Dr. Cleton is currently an employee of Astrazeneca, Molndal, Sweden. Dr. Rossenu is currently an employee of Merck, Oss, The Netherlands. Dr. Eerdekens is now employed

by Grünenthal GmbH, Aachen, Germany. Dr. Rossenu, Dr. Cleton, Dr. Rosso, and Dr. Eerdekens, have no additional conflict of interest.

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