A Randomized, Placebo-Controlled Study to Assess the Efficacy and Safety of 3 Doses of Paliperidone Palmitate in Adults With Acutely Exacerbated Schizophrenia

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Abstract: This study assessed the efficacy and the safety of a dosing regimen that was revised from earlier studies for the investigational injectable atypical antipsychotic paliperidone palmitate (approved in the USA, August 2009) for adult patients with acutely exacerbated schizophrenia. The patients (N = 652) were randomly assigned (1:1:1:1) to paliperidone palmitate at 25, 100, or 150 mg eq. or placebo in this 13-week double-blind study. The patients received an injection of paliperidone palmitate at 150 mg eq. or placebo in the deltoid muscle on day 1 and the assigned fixed dose or placebo in the deltoid or muscle on day 8 and then once monthly (days 36 and 64). No oral supplementation was used. Target plasma levels were achieved by day 8 in all paliperidone palmitate groups. The mean change in Positive and Negative Syndrome Scale total score from baseline to end point improved significantly (P ≤ 0.034) in all the paliperidone palmitate dose groups versus placebo. Paliperidone palmitate treatment with this revised dosing regimen led to the achievement of rapid and consistent therapeutically effective plasma levels that were maintained by once-monthly dosing in either the deltoid or gluteal muscle. Common treatment-emergent adverse events (≥2% of patients in any of the treatment groups) that occurred more frequently in the total paliperidone palmitate group versus the placebo group (within 21% difference) were injection-site pain (7.6% vs 3.7%), dizziness (2.5% vs 1.2%), sedation (2.3% vs 0.6%), pain in the extremity (1.6% vs 0.0%), and myalgia (1.0% vs 0.0%). The paliperidone palmitate treatment was efficacious and generally tolerated across the dose range (25, 100, or 150 mg eq.) in adult patients with acutely exacerbated schizophrenia.

Key Words: atypical antipsychotic, deltoid, initiation dose, long-acting injectable, paliperidone palmitate, schizophrenia

Abbreviations: BMI - body mass index, CGI-S - Clinical Global Impression—Severity, EPS - extrapyramidal symptoms, ER - extended release, ITT - intent-to-treat, LAI - long-acting injectable, PANSS - Positive and Negative Syndrome Scale, PK - pharmacokinetic, PSP - Personal and Social Performance Scale, TEAE - treatment-emergent adverse events, VAS - Visual Analogue Scale

Schizophrenia is a recurrent and chronic disease requiring continuous, long-term treatment with antipsychotic medications. Treatment nonadherence and high discontinuation rates are common problems associated with long-term treatment strategies. However, the intramuscular (IM) long-acting injectable (LAI) formulations of antipsychotic medications due to their sustained delivery and the regular treatment monitoring by health care professionals of the clinical team may enhance treatment adherence in patients with schizophrenia.

Paliperidone extended release (ER) is an approved oral atypical antipsychotic agent for treatment of schizophrenia. Paliperidone palmitate is the palmitate ester of paliperidone, which is the principal metabolite of risperidone (9-OH-risperidone). Paliperidone palmitate is an investigational once-monthly atypical antipsychotic LAI (approved in the USA, August 2009) for the acute and maintenance treatment of schizophrenia in adults. It has extremely low water solubility and provides sustained plasma concentrations of paliperidone, the pharmacologically active fraction. Paliperidone palmitate administered as gluteal or as deltoid and gluteal injections was effective and tolerated in the treatment of schizophrenia in several randomized, double-blind, controlled studies.

This was the first phase 3 study designed (1) to evaluate a dosing regimen of paliperidone palmitate revised from earlier studies with initiation at 150 mg eq. in the deltoid muscle to increase the initial exposure to paliperidone, (2) to fully assess the efficacy and safety of a higher paliperidone palmitate dose of 150 mg eq., and (3) to confirm the efficacy and safety of the 25- and 100-mg eq. doses previously tested. As in other studies of paliperidone palmitate oral antipsychotic agent supplementation of paliperidone palmitate was prohibited.

METHODS

Patients
Men and women with an acute exacerbation of an established diagnosis of schizophrenia (defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [DSM-IV]), whose disease diagnosis was able to be documented as present for at least 1 year before study screening, who demonstrated a Positive and Negative Syndrome Scale (PANSS) total score between 70 and 120 (inclusive) at screening and between...
60 and 120 at baseline (inclusive), and who were 18 years or older and able to consent to study participation were enrolled.

The main exclusion criteria included primary DSM-IV Axis I diagnosis other than schizophrenia, DSM-IV diagnosis of active substance dependence within 3 months before screening, history of treatment resistance (failure to respond to 2 adequate courses of different antipsychotic medications with a minimum of 4 weeks' duration at the patient's maximum tolerated dose), history of neuroleptic malignant syndrome, a relevant history of any significant or unstable systemic disease, morbid obesity (body mass index [BMI] ≥ 40 kg/m²), and circumstances that could increase the risk of the occurrence of Torsade de Pointes or sudden death. Other exclusion criteria were a significant risk of suicidal, homicidal, or violent ideation or behavior, use of the disallowed medications or hypersensitivity or intolerance to risperidone, paliperidone, or any of their excipients. Women were excluded if pregnant, breast-feeding, or planning to become pregnant.

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 applicable regulatory requirements. The study protocol was reviewed by an independent ethics committee or an institutional review board of each investigator site, and all the patients provided written informed consent before entering the study.

Study Medication

Because doses of paliperidone palmitate can be expressed either in milligram equivalents (mg eq.) of the pharmacologically active fraction, paliperidone, or in milligrams of paliperidone palmitate, the doses expressed as 25, 100, and 150 mg eq. equate to 39, 156, and 234 mg, respectively, of paliperidone palmitate. The study medication was provided as wrapped, prefilled syringes containing paliperidone palmitate 25, 100, or 150 mg eq. (0.25, 1.0, or 1.5 mL, respectively) injectable suspensions or matching placebos (20% Intralipid, 200 mg/mL; Fresenius Kabi AB, Uppsala, Sweden) that did not require reconstitution or refrigeration. Delirial injections were administered with a 1-1 needle to patients weighing less than 90 kg and with a 1.5-in needle to patients weighing 90 kg or greater. All gluteal injections were administered with a 1.5-in needle.

Study Design, Randomization, and Blinding

This study was a randomized, double-blind, placebo-controlled, multicenter, phase 3 study conducted from March 2007 through March 2008 at 72 centers in 8 countries in the USA, Europe, and Asia.

The study consisted of a screening period of up to 7 days for washout of disallowed psychotropic medications and for oral tolerability testing (patients without documented previous exposure to risperidone or paliperidone were administered 6-mg paliperidone ER tablets once daily for 4 to 6 days), followed by a 13-week double-blind treatment period. Eligible patients were randomly assigned (1:1:1:1) to fixed doses of paliperidone palmitate (25, 100, or 150 mg eq.) or placebo based on a computer-generated randomization schedule balanced by using permuted blocks of treatments and stratified by center. On day 1, all the patients received a deltoid injection of paliperidone palmitate 150 mg eq. or matching placebo; on day 8 and then on days 36 and 64, the patients received their assigned treatment per the randomization schedule, injected in the deltoid or the gluteal muscle at the discretion of the investigator. The side of each injection was alternated at each visit. The patients were hospitalized from day 1 (first injection) until at least after the second injection of the study drug on day 8. All oral and injectable antipsychotic agents except the study drug were prohibited during the double-blind treatment period.

Concomitant Medications

Antiparkinsonian medications (trihexyphenidyl, benztrpine, and biperidin) or antihistamines with anticholinergic properties (if extrapyramidal symptoms [EPS] emerged or worsened during the study), antidepresants (except for nonselective or irreversible monoamine oxidase inhibitors) if they had been used at a stable dose for at least 30 days before screening, and oral benzodiazepines (as rescue medication for agitation, anxiety, or sleep difficulties) at the permitted maximum daily doses were allowed.

Study Assessments

Efficacy Assessments

The primary efficacy end point was the change in the PANSS total score from baseline to the end of the double-blind treatment period (day 92 or last postbaseline assessment). The key secondary efficacy end point was the change in Personal and Social Performance (PSP) Scale score from baseline to the end of the double-blind treatment period. Other efficacy end points included the change in Clinical Global Impression—Severity (CGI-S) score, onset of therapeutic effect assessed by change in the PANSS total score, responder rate (defined as the number of patients with a 30% or more reduction from baseline in the PANSS total score at endpoint), sleep visual analogue scale (VAS) scores (patient administered, to assess quality of sleep and daytime sleepiness), and changes in the PANSS Marcar factor scores.

Trained professionals performed all the efficacy assessments (a professional was defined as a psychiatrist, psychiatric resident, psychologist, a master's level mental health professional, or a bachelor's level mental health professional with a recognized degree and license to practice [eg, psychology or counseling]). For sites in the USA, remote central blinded raters from MedAvante, Inc (Hamilton, NJ) performed the ratings for PANSS, PSP, and CGI-S via live high-definition audio and video interviewing at each defined time point. Raters from sites outside the USA participated in training on all the rating scales and in a qualification program for PANSS ratings. The described clinical interview for the PANSS was used for all the PANSS ratings globally.

Safety Assessments

Safety assessments included recording and monitoring of treatment-emergent adverse events (TEAEs), clinical laboratory tests, vital sign measurements, physical examination findings, 12-lead electrocardiograms, EPS rating scales (Simpson and Angus Rating Scale, Barnes Akathisia Rating Scale, and Abnormal Involuntary Movement Scale), evaluation of the injection site, and patient's evaluation of injection pain.

Pharmacokinetic Assessments

Blood samples were taken for pharmacokinetic (PK) analysis on days 1, 2, 4, 6, 8, 15, 22, 36, 64, and 92. On study days when study drug was administered, the PK blood sample was collected before study drug administration. The plasma concentrations of paliperidone were determined using a validated liquid chromatography coupled to the tandem mass spectrometry method, with a target limit of quantification of 0.1 ng/mL, at the Frontage Laboratories Co, Ltd, Shanghai, China.
The analytical method consisted of protein precipitation followed by reversed-phase high-performance liquid chromatography coupled to tandem mass spectrometry using Turbolonspray (AB Sciex, Foster City, Calif) ionization (positive ion mode). A Polaris C18-A (Varian, Palo Alto, Calif) 3-μm 4.6-mm ID × 30-mm column was used as analytical column; the mobile phase was a mixture of 0.01 mol/L ammonium formate/acetoniitrile/methanol. Paliperidone was monitored at transition m/z 427.2 to 207.0, and the stable isotope labeled internal standard at transition m/z 431.2 to 209.0. The calibration range of the assay was 0.1 to 250 ng/mL. Plasma. The intrabatch accuracy expressed as percentage bias ranged from −11.3% to 9.2% and intrabatch precision (percent coefficient of variation) ranged from 0.0% to 12.1%. Interbatch accuracy and precision ranged from −3.2% to 1.3% and from 4.3% to 5.5%, respectively.

Sample Size Determination
A sample size of 161 patients per group provided 90% power at a 2-sided overall significance level of 0.05 after adjusting for multiplicity to detect a clinically meaningful difference of at least 9 points in the mean change from baseline to end point in PANSS total score between any paliperidone palmitate dose group and placebo, assuming a standard deviation of 21 points, and adjusting for a dropout rate of 8% of patients not expected to have either baseline or postbaseline efficacy assessments.

Analysis Sets
All efficacy analyses were performed on the intent-to-treat (ITT) analysis set, which included all randomized patients who received at least one dose of double-blind study medication and had both the baseline and at least one postbaseline efficacy assessment (PANSS, PSP, or CGI-S). The safety analysis set included all patients who were randomized and received at least one dose of double-blind study medication. The PK analysis set included all patients randomly assigned to receive paliperidone palmitate treatment, having evaluable samples at the time of the respective PK assessments.

Statistical Evaluations
The overall type I error rate for testing all paliperidone palmitate doses versus placebo for both the primary end point (change in PANSS total score at end point) and the key secondary end point (change in PSP at end point) was controlled at the 2-sided 0.05 significance level. The last observation carried forward (LOCF) approach was used to impute missing visit data for the efficacy variables.

For the change in PANSS total score at end point (LOCF), the least squares (LS) means were estimated and compared between each active treatment group and placebo using an analysis of covariance (ANCOVA) model with treatment and country as factors and baseline PANSS total score as a covariate. The Dunnett-Bonferroni-based parallel gatekeeping procedure was used to adjust for multiplicity in testing the 3 doses of paliperidone palmitate versus placebo for both the change in PANSS total score and SPS scores. The change from baseline to end point (LOCF) in PSP, PANSS Marder factor and PANSS subscale scores, and sleep VAS scores were analyzed using an ANCOVA model with treatment and country as factors, and the respective baseline score as a covariate. As a sensitivity analysis, a mixed-model repeated measures analysis was performed on the observed case data for the change from baseline in PANSS total score with time, country, treatment, and the time-by-treatment interaction as factors and baseline PANSS total score as a covariate.

The analysis of the change in the CGI-S score at end point (LOCF) was performed using an ANCOVA model on the ranks of the change in score at end point with treatment and country as factors and (nonranked) baseline CGI-S score as a covariate. Differences in the percentage of responders at end point between each treatment group and placebo were evaluated using the Cochran-Mantel-Haenszel test, controlling for country. The onset of effect for a given dose was defined as the first time point at which the treatment groups (each dose of paliperidone palmitate vs placebo) were different (at the 2-sided nominal 5% level of significance) and remained different thereafter until end point based on the change from baseline in the PANSS total score (LOCF).

The TEAEs were summarized according to Medical Dictionary for Regulatory Activities system organ class and preferred term. Descriptive statistics at each visit and changes from baseline for clinical laboratory analyte values, vital sign measurements, and electrocardiograms were summarized.

Post hoc Analyses
A post hoc analysis of the change from baseline in the PANSS total score at end point was performed for subgroups based on baseline BMI, with the treatment-by baseline BMI group interaction added to the ANCOVA model that included treatment, country, and the baseline BMI group (≤25, >25 to <30, and ≥30 kg/m²) as factors and the baseline PANSS total score as a covariate. Effect sizes (vs placebo) were calculated for the 3 paliperidone palmitate treatment groups for the change from baseline in PANSS total score at end point. A posthoc analysis was also done to explore the discontinuations due to adverse events associated with the 150 mg eq. initiation dose of paliperidone palmitate.

Pharmacokinetics Analyses
Descriptive statistics were calculated for the plasma concentrations of paliperidone. No formal statistical comparison of PK results between dose groups was performed.

RESULTS
Patient Characteristics and Disposition
Of the 855 patients screened, 652 (76%) were randomly assigned to 1 of 4 treatment groups. The ITT analysis set consisted of the total paliperidone palmitate (n = 476 [98%]), placebo (n = 160 [98%]); and the safety analysis set, total paliperidone palmitate (n = 488 [100%]) and placebo (n = 164 [100%]). Out of the randomly assigned patients, 333 patients (51%) completed the study; 262 (54%) in the total paliperidone palmitate group and 71 (43%) in placebo group. The most common reasons for premature discontinuation from the study were lack of efficacy, patient choice, and adverse event. Throughout the study, the cumulative dropout rate in the placebo group was consistently higher than in the total paliperidone palmitate group (Table 1). In the first week after the initiation dose, the rates of discontinuation due to adverse events were 0.8% (4/476) for the total paliperidone palmitate group and 1.3% for the placebo group (2/160) for the ITT analysis set. More patients in the paliperidone palmitate groups received all 4 injections of double-blind study medication (25 mg eq., 56%; 100 mg eq., 61%; and 150 mg eq., 59%) than in the placebo group (48%). Among those administered more than 1 injection of the study drug (n = 585), 43% (n = 250) received all subsequent injections in the deltoid muscle and an equivalent percentage (43%; n = 250) received all subsequent injections in the glutus muscle. The mean duration of exposure was similar (ranging from
65 to 67 days) for the 3 paliperidone palmitate treatment groups versus 58 days for the placebo group.

Demographics and baseline characteristics were comparable among the groups. The patients (ITT analysis set) had a mean age of 39 years; 67% were men, and 54% were white. Atypical antipsychotic agents were the most commonly used (70%) psychotropic medications before the double-blind treatment period, with oral risperidone being used by 34% to 41% of patients across all the treatment groups. Only 3% of the patients had received prior treatment with LAIs. Approximately one third of the patients were using an anti-EPS medication, nearly two thirds of the patients were using a benzodiazepine, and nearly one fourth of the patients were using antidepressants at baseline.

Efficacy Findings

Primary Efficacy Parameter

There was a significant (P ≤ 0.034) and dose-related change in PANSS total score (mean baseline score, 87.1) for each of the 3 paliperidone palmitate groups compared with placebo (Fig. 1). The mixed-model repeated measures analysis corroborated these findings (paliperidone palmitate at 25 mg eq., P = 0.02 vs placebo; 100 and 150 mg eq., P < 0.001 vs placebo on day 92).

The estimated effect sizes (vs placebo) based on the standardized difference in LS mean values between the groups were 0.28 (25 mg eq.), 0.49 (100 mg eq.), and 0.55 (150 mg eq.). The prespecified treatment-by-country (P = 0.27) and treatment-by-baseline PANSS total score (P = 0.21) interactions were not statistically significant at the prespecified 0.10 significance level nor was the post hoc treatment-by-baseline BMI group (P = 0.15) interaction.

Key Secondary Efficacy Parameter

Mean PSP scores showed a dose-related improvement in the paliperidone palmitate treatment groups, which was significant for the 100 and 150 mg eq. groups (Table 2).

Other Efficacy Parameters

The paliperidone palmitate 100 and 150 mg eq. groups showed significant improvements in CGI-S scores (P ≤ 0.005), in all the 5 PANSS Marder factor scores (P ≤ 0.01), and in the 3 PANSS subscale scores (P ≤ 0.03; Table 2). A significant change in PANSS total score was observed as early as day 8, reflecting of the initial 150 mg eq. dose on day 1 in the assigned 25 and 150 mg eq. treatment groups, and from day 22 in all the 3 paliperidone palmitate groups and maintained until end point (Fig. 1). Significantly more patients on paliperidone palmitate responded to treatment (25 mg eq. group: 33.5%, P = 0.007; 100 mg eq. group: 41.0%, P < 0.001; 150 mg eq. group: 40.0%, P < 0.001) compared with placebo (20.0%). The quality of sleep VAS scores significantly improved from baseline to end point in the paliperidone palmitate 100 and 150 mg eq. groups (P ≤ 0.03) compared with placebo. Daytime drowsiness VAS scores did not differ from placebo for any of the paliperidone palmitate groups (P ≥ 0.26).

Safety and Tolerability Findings

All the 3 doses of paliperidone palmitate were tolerated. The overall incidence of TEAEs was similar among the paliperidone palmitate (60.0%–63.2%) and placebo groups (65.2%); most were mild to moderate in severity. Among the most common TEAEs (≥2% of the patients in any of the 4 treatment group; Fig. 2), events that occurred more frequently in the total paliperidone palmitate group than in the placebo group (with ≥1% difference) were injection site pain (7.6% vs 3.7%), dizziness (2.5% vs 1.2%), sedation (2.3% vs 0.6%), pain in extremity (1.6% vs 0.0%), and myalgia (1.0% vs 0.0%; Fig. 2). The incidence of TEAEs leading to study discontinuation was similar across the treatment groups (placebo, 6.7%; paliperidone palmitate, 6.1% to 8.0%). Incidence of serious TEAEs was higher in the placebo group (14.0%) than in any of the paliperidone palmitate groups (9.4%, 25 mg eq.; 13.3%, 100 mg eq.; and 8.0%, 150 mg eq.). Overall, schizophrenia (worsening or exacerbation of illness;
FIGURE 1. Mean change from baseline in the PANSS total score over time (LOCF; intent-to-treat analysis set). The doses expressed as paliperidone palmitate 25, 100, and 150 mg eq. equate to 39, 156, and 234 mg of paliperidone palmitate, respectively. The differences from placebo in LS mean change at end point were −5.1 in the 25 mg eq. group, −8.7 in the 100 mg eq. group, and −9.8 in the 150 mg eq. group. *All unadjusted \( P < 0.05 \) as early as day 8 for assigned paliperidone palmitate 25 and 150 mg eq. groups versus the placebo group and as early as day 22 for the paliperidone palmitate 100 mg eq. group versus the placebo group. The day 8 findings are reflective of the initial 150 mg eq. dose on day 1.

4.9% vs 6.1% placebo) and psychotic disorder (2.9% vs 4.3% placebo) were the most commonly reported serious TEAEs for paliperidone palmitate. One patient died 1 week (day 22) after premature discontinuation from the study on day 15 (the last dose of 150 mg eq. paliperidone palmitate was received on day 8). The investigator assessed the death (cerebrovascular accident) as doubtfully related to study treatment.

Akathisia was the most frequently reported EPS-related adverse event across all the treatment groups (<6% of patients). The use of anti-EPS medication decreased from baseline during the study and was similar between the placebo and paliperidone palmitate groups during the last week of the double-blind period (safety analysis set): placebo group, 9%; paliperidone palmitate groups, 8% to 12%. There were no adverse event reports of tardive dyskinesia.

Benzodiazepine usage was similar among the 4 treatment groups during the double-blind period (placebo group, 61%; paliperidone palmitate groups, 56%–63%; safety analysis set) and generally similar to the baseline values (59%–67%). Lorazepam was the most commonly used benzodiazepine (43%–50% across the 4 groups).

There were no glucose-related TEAEs reported for paliperidone palmitate. Three patients in the paliperidone palmitate group and 1 patient in the placebo group had potentially prolactin-related TEAEs: ejaculation disorder (placebo, 25 mg eq.), loss of libido (100 mg eq.), and galactorrhea (150 mg eq.). The mean increases in prolactin levels from baseline to end point were seen in all the paliperidone palmitate groups; increases were larger in women (change from baseline, 4.72–37.24 ng/mL) compared with those in men (change from baseline, 3.73–13.15 ng/mL). The mean prolactin levels decreased in the placebo group irrespective of the sex.

Weight increase of 7% or higher was dose-related and more common among patients in the paliperidone palmitate groups (6% [25 mg eq.], 8% [100 mg eq.], and 13% [150 mg eq.]) compared with that in the placebo group (5%).

There were no clinically relevant changes from baseline in vital signs, ECG recordings, or other clinical laboratory parameters (including fasting glucose levels and serum lipids) in any of the paliperidone palmitate groups. No patient had a maximum linear-derived QT correction formula (QTcLD) value more than 480 milliseconds or a maximal change in QTcLD greater than 60 milliseconds during the study. Local injection site tolerability was good, and investigator ratings of injection site pain were similar for the placebo and paliperidone palmitate groups.

Pharmacokinetic Findings

Samples from 488 patients randomized to paliperidone palmitate were included for the PK analysis. With an initiation dose of paliperidone palmitate 150 mg eq., the mean predose paliperidone concentrations on day 8 were similar (22.6–23.3 ng/mL) for all the treatment groups (Fig. 3). After day 8, the mean predose paliperidone plasma concentrations (ie, those sampled on injection days 36 and 64) gradually declined in the 25 mg eq. treatment group compared with those in the 100 and 150 mg eq.
<table>
<thead>
<tr>
<th>Efficacy Measure</th>
<th>Placebo (n = 160)</th>
<th>Paliperidone Paltimate 25 mg eq. (39 mg) (n = 155)</th>
<th>Paliperidone Paltimate 100 mg eq. (156 mg) (n = 161)</th>
<th>Paliperidone Paltimate 150 mg eq. (234 mg) (n = 160)</th>
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<tr>
<td><strong>PSP score, mean (SD)</strong></td>
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<tr>
<td>Baseline</td>
<td>49.7 (12.3)</td>
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<td>-1.0 (-4.2)</td>
<td>-1.0 (-4.3)</td>
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<td><strong>PANSS Marber factor scores</strong></td>
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<td>Positive symptoms factor, mean (SD)</td>
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<td>Baseline</td>
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<td>26.1 (5.1)</td>
<td>26.4 (5.1)</td>
<td>26.4 (4.9)</td>
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<td>0.0 (4.6)</td>
<td>-0.9 (4.0)</td>
<td>-1.4 (3.9)</td>
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<td>10.7 (3.4)</td>
<td>10.4 (3.4)</td>
<td>10.6 (3.2)</td>
</tr>
<tr>
<td>Change from baseline§</td>
<td>-0.9 (4.0)</td>
<td>-1.2 (3.8)</td>
<td>-1.8 (3.8)</td>
<td>-1.8 (3.8)</td>
</tr>
<tr>
<td>P value (minus placebo)§</td>
<td>0.45</td>
<td>0.004</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td><strong>PANS subscales</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive subscale, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>22.4 (5.4)</td>
<td>21.9 (4.7)</td>
<td>22.3 (4.5)</td>
<td>22.5 (5.1)</td>
</tr>
<tr>
<td>Change from baseline§</td>
<td>-1.1 (6.4)</td>
<td>-2.2 (6.6)</td>
<td>-4.1 (5.8)</td>
<td>-4.4 (6.3)</td>
</tr>
<tr>
<td>P value (minus placebo)§</td>
<td>0.06</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Negative subscale, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>21.5 (4.8)</td>
<td>21.5 (4.8)</td>
<td>21.4 (4.9)</td>
<td>22.4 (5.2)</td>
</tr>
<tr>
<td>Change from baseline§</td>
<td>-0.6 (5.5)</td>
<td>-1.2 (5.3)</td>
<td>-1.9 (4.9)</td>
<td>-2.5 (5.6)</td>
</tr>
<tr>
<td>P value (minus placebo)§</td>
<td>0.25</td>
<td>0.02</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>General psychopathology, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>42.9 (6.1)</td>
<td>43.4 (6.6)</td>
<td>42.5 (6.0)</td>
<td>43.6 (5.9)</td>
</tr>
<tr>
<td>Change from baseline§</td>
<td>-1.3 (10.2)</td>
<td>-4.6 (10.6)</td>
<td>-5.6 (9.5)</td>
<td>-6.4 (9.3)</td>
</tr>
<tr>
<td>P value (minus placebo)§</td>
<td>0.003</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CGI-S indicates Clinical Global Impression-Severity; PANNS, Positive and Negative Syndrome Scale; PSP, Personal and Social Performance Scale. Factor scores are derived from the Marber criteria.²³

*Positive change in score indicates improvement.

¹Based on the ANCOVA model with treatment (placebo and paliperidone palmitate 25, 100, and 150 mg eq.) and country as factors and baseline value as a covariate.

²P values were adjusted for multiplicity between the PANSS total score (primary efficacy end point) and the PSP (key secondary efficacy end point), as well as different dose levels in comparison with placebo, using the Dunnett-Bonferroni–based parallel gatekeeping method.

³Negative change in score represents improvement in the severity of neuropsychiatric symptoms.

⁴Based on the ANCOVA model on ranks with treatment (placebo and paliperidone palmitate 25, 100, and 150 mg eq) and country as factors and baseline value as a covariate.

⁵Comparisons with placebo without multiplicity adjustment.
FIGURE 2. Treatment-emergent adverse events experienced by at least 2% of patients in any treatment group (safety analysis set). The doses expressed as paliperidone palmitate 25, 100, and 150 mg eq. equate to 39, 156, and 234 mg of paliperidone palmitate, respectively. All the groups are plotted for each adverse event; some groups overlap in incidence rate.

The mean predose paliperidone plasma concentration for the 100 mg group remained within the range of 19.0 to 23.3 ng/mL from day 8 onward, whereas an upward trend was evident for the 150 mg group after day 36 (Supplemental Table A, Supplemental Digital Content 1, which shows actual plasma concentrations of paliperidone descriptive statistics, http://links.lww.com/JCP/A19). The patients with high baseline BMI (overweight and obese categories) in all the 3 paliperidone palmitate treatment groups had lower median paliperidone plasma concentrations on day 8 than patients with normal baseline BMI. After day 8, no consistent trends were observed for the 3 dose groups with respect to paliperidone plasma concentrations as a function of the baseline BMI classification.

DISCUSSION

Treatment with the investigational injectable antipsychotic agent paliperidone palmitate in patients with acutely exacerbated schizophrenia resulted in statistically significant, dose-related improvements in the PANSS total score when injected as an initial dose of 150 mg eq. in the deltoid and subsequently at

FIGURE 3. Median actual paliperidone plasma concentration in the 3 treatment groups by visit (pharmacokinetic analysis set). The doses expressed as paliperidone palmitate 25, 100, and 150 mg eq. equate to 39, 156, and 234 mg of paliperidone palmitate, respectively. On the day of injection (days 1, 8, 36, and 64), the samples were taken predose. The 25th and 75th quartiles are depicted in the figure.
doses of either 25, 100, or 150 mg eq. initially after 1 week and then as once-monthly injections in either the deltoid or gluteal muscle. Secondary efficacy parameters (PSP and CGI-S scale scores) also showed statistically significant, dose-related improvements versus placebo after treatment with paliperidone palmitate 100 and 150 mg eq. paliperidone palmitate but not with the 25 mg eq. dose. The onset of antipsychotic effect (ie, a significant difference in paliperidone palmitate compared with placebo) occurred as early as day 8.

The median apparent half-life of paliperidone after paliperidone palmitate single-dose administration over the dose range of 25 to 150 mg eq. ranges from 25 to 49 days. Population PK modeling data from previous paliperidone palmitate trials helped identify injection site, needle length, and BMI as among the factors important to optimizing early and effective plasma concentrations of paliperidone palmitate. The initial median paliperidone plasma concentrations (on day 8) were higher on starting treatment in the deltoid muscle than in the gluteal muscle and also with the use of a longer (1.5-in) needle length. At the deltoid site, the likelihood of a true IM injection is higher compared with the gluteal site, whereas the hypovascularity of subcutaneous adipose tissue may result in a slower uptake of paliperidone from the gluteal muscle compared with the deltoid muscle. Hence, in the present study treatment was initiated with a 150 mg eq. dose in the deltoid muscle to increase the initial exposure to the drug and to more rapidly (by day 8) and consistently achieve effective plasma levels across body types. However, this high initiation dose of 150 mg eq. was not associated with any new safety concerns.

The paliperidone palmitate dosing regimen used in this study seems to have mitigated previously observed treatment-by-BMI effects. This observation was confirmed by the PK results, which showed that there was no substantial difference in paliperidone plasma concentration profiles between normal, overweight, and obese patients. Although apparent steady state was achieved by day 36 in another paliperidone palmitate study, the paliperidone plasma concentrations in this study were continuing to increase at day 92 for patients receiving the 100 and 150 mg eq. doses and were declining for the 25 mg eq. group.

The initiation dose of paliperidone palmitate 150 mg eq. (16.5 ng/mL) resulted in slightly lower median plasma concentrations of paliperidone than the steady-state concentrations previously observed using the recommended starting dose of the oral formulation (ie, 6-mg paliperidone ER; 19.3 ng/mL). A population PK simulation approach was used to compare plasma concentrations of paliperidone after multiple IM injections of paliperidone palmitate (dose range, 25–150 mg eq.) with the paliperidone plasma concentrations for oral paliperidone ER (dose range, 2–12 mg). The simulations indicated that monthly maintenance dosing of paliperidone palmitate 25, 100, and 150 mg eq. provided sustained steady-state paliperidone plasma concentrations within the exposure window for 2 and 12 mg doses of paliperidone ER, respectively.

As deficits in psychosocial domains are a core feature of schizophrenia, efficient long-term treatment of patients with schizophrenia must consider a successful psychosocial reintegration in addition to reduction in psychopathological symptoms. The PSP is a validated, reliable tool for quickly assessing personal and social functioning of patients with schizophrenia. The significant improvements in PSP score that resulted with paliperidone palmitate treatment may be important clinical considerations for selection of an antipsychotic treatment. The improved quality of sleep results in the paliperidone palmitate 100 and 150 mg eq. groups are consistent with data from studies of the oral formulation, paliperidone ER; including a study that specifically investigated the effects of paliperidone ER on the sleep architecture and sleep continuity in patients with schizophrenia experiencing insomnia.

The incidence of discontinuations across treatment groups in this study (45%–48% in the paliperidone palmitate groups, 57% in the placebo group) is consistent with rates reported in other drug studies in schizophrenia and with rates observed in previous paliperidone palmitate studies. One limitation of this study is that an active comparator was not included; hence, the relative efficacy of paliperidone palmitate compared with other active treatments is not known.

In the population studied here, the 25 mg eq. dose may represent a minimally effective dose in the initial and maintenance treatment of acutely exacerbated psychosis, whereas the higher doses investigated may represent more relevant doses for most individuals with acutely symptomatic schizophrenia, as is evident from this and other studies.

Consistent with the known pharmacology of paliperidone, dose-related mean increases in prolactin levels were observed, larger in women than men. The overall proportion of EPS-related TEAs in patients receiving paliperidone palmitate was 9%, and none were serious or resulted in treatment discontinuation. These results too are consistent with earlier phase 2 and 3 studies. There were no reports of tardive dyskinesia, although development of tardive dyskinesia may not be expected in a short duration study of 13 weeks. All 3 doses, including the 150 mg eq. dose, were tolerated with no new safety signals emerging.

In the present study, as in other paliperidone palmitate studies, no oral supplementation was used during the switch from the previous oral antipsychotic agent; the unique formulation of paliperidone palmitate allows the immediate gradual release of the active fraction and rapid achievement of therapeutic plasma levels of paliperidone. The findings of this study could be of particular clinical relevance, as typically, patients in the acute stages of psychosis are not initiated on LAI antipsychotic agents in inpatient settings.

These results indicate that initiating paliperidone palmitate treatment with a 150 mg eq. injection in the deltoid muscle, followed by a fixed dose (25, 100, or 150 mg eq.) injection in either the deltoid or gluteal muscle on day 8, allows for rapid achievement of target plasma levels that can be further maintained by once-monthly dosing. As this was a short-term study in acutely exacerbated patients, it does not address long-term maintenance dosing. However, paliperidone palmitate treatment at doses of 25, 100, or 150 mg eq. was efficacious and generally tolerated across the dose range. This may present an effective treatment paradigm for adult patients with acutely exacerbated schizophrenia.

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