SYNOPSIS

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Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Name of Finished Product	Paliperidone palmitate
Name of Active Ingredient	Paliperidone

PROTOCOL NO.: R092670-PSY-3007

TITLE OF STUDY: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Response Study to Evaluate the Efficacy and Safety of 3 Fixed Doses (25 mg eq., 100 mg eq., and 150 mg eq.) of Paliperidone Palmitate in Subjects With Schizophrenia

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PUBLICATION (REFERENCE): None

STUDY PERIOD: 08 March 2007 to 24 March 2008

PHASE OF DEVELOPMENT: Phase 3

OBJECTIVES: The primary objectives of this study were to evaluate the efficacy and safety of 3 fixed doses of paliperidone palmitate administered intramuscularly (i.m.) after an initial dose of 150 mg equivalent (eq.) in the deltoid muscle followed by either deltoid or gluteal injections for a total of 13 weeks of treatment as compared with placebo in subjects with schizophrenia.

The secondary objectives were to:

- Assess the benefits in personal and social functioning (key secondary endpoint) associated with the use of paliperidone palmitate compared with placebo;
- Assess the global improvement in severity of illness associated with the use of paliperidone palmitate compared with placebo;
- Assess the dose-response and exposure-response relationships of paliperidone palmitate.

METHODS: This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter, dose-response study of men and women, 18 years of age and older, who had a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnosis of schizophrenia. The study included a screening period of up to 7 days and a 13-week double-blind treatment period. The screening period included a washout of disallowed psychotropic medications.

Subjects without source documentation of previous exposure to at least 2 doses of oral risperidone or paliperidone extended-release (ER), at least 1 dose of i.m. RISPERDAL® CONSTA® or paliperidone palmitate, or who were not currently receiving an antipsychotic medication were given 4 to 6 days of paliperidone ER 6 mg/day (or the option of oral risperidone 3 mg/day for subjects in Malaysia) for tolerability testing. Subjects who had source documentation of previous exposure to the above medications and were currently taking another antipsychotic regimen continued their current treatment through Day –1. At the beginning of the double-blind treatment period, subjects were randomly assigned in a 1:1:1:1 ratio to 1 of 4 treatment groups: placebo or paliperidone palmitate 25 mg eq., 100 mg eq., or 150 mg eq. Study medication was administered as 4 doses: an initial i.m. injection of 150 mg eq. of paliperidone palmitate or placebo followed by 3 fixed i.m. doses of placebo or paliperidone palmitate [25, 100, or 150 mg eq.] on Days 8, 36, and 64. The initial injection of study medication was given in the deltoid muscle. Subsequent injections were given either in the deltoid or gluteal muscle at the discretion of the investigator. Randomized subjects were to remain in the study for 28 days after the last injection on Day 64 with the end of study visit scheduled for Day 92 during

the double-blind period. The entire study, including the screening period, lasted approximately 14 weeks.

Samples for pharmacokinetic (PK) evaluation were collected on Day 1, prior to the first injection and on Days 2, 4, 6, 8, 15, 22, 36, 64 and 92. Efficacy and safety were evaluated regularly throughout the study. A pharmacogenomic blood sample (10 mL) was collected from subjects who gave separate written informed consent for this part of the study. Participation in the pharmacogenomic research was optional. Approximately 105 to 115 mL of whole blood was collected during the study.

Number of Subjects (Planned and Analyzed): It was planned to include approximately 644 men and women in this study. A total of 652 eligible subjects from 72 centers in 8 countries were randomized and received at least 1 dose of double-blind study medication (safety analysis set); 636 subjects had both baseline and post baseline efficacy data (intent-to-treat analysis set).

Diagnosis and Main Criteria for Inclusion: Male or female subjects ≥18 years of age who met the DSM-IV diagnostic criteria for schizophrenia for at least 1 year before screening, had a Positive and Negative Syndrome Scale (PANSS) total score at screening of between 70 and 120, inclusive, and at baseline of between 60 and 120, inclusive, and had a body mass index (BMI) of >17.0 kg/m^2 to <40 kg/m^2 were eligible.

Test Product, Dose and Mode of Administration, Batch No.: Paliperidone ER was supplied as a 6-mg capsule-shaped tablet for the oral tolerability test (batch number 0617714/F40). Paliperidone palmitate was supplied as 25, 100, or 150 mg eq. injectable suspension (batch numbers 06K22/F13 and 07D23/F13). For the oral tolerability test, a 6-mg tablet of paliperidone ER (or the option of oral risperidone 3 mg/day for subjects in Malaysia) was administered daily for 4 to 6 days. On Day 1 of the double-blind treatment period, 150 mg eq. of paliperidone palmitate was injected in the deltoid muscle followed by 25, 100, or 150 mg eq. i.m. injections of paliperidone palmitate on Days 8, 36, and 64, injected into the deltoid or gluteal muscle at the investigator's discretion.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo was supplied as 20% Intralipid (200 mg/mL) injectable emulsion (batch numbers 06K14/F00 and 07F12/F00). An injection was given on Days 1, 8, 36 and 64.

Duration of Treatment: The study consisted of a screening and washout phase of 7 days and a double-blind treatment period of 13 weeks, starting with the first injection in the deltoid muscle followed by a second injection 1 week later. All injections after Day 1 were given in either the deltoid or the gluteal muscle at the discretion of the investigator. Two subsequent injections were given at 4-week intervals.

CRITERIA FOR EVALUATION:

Pharmacokinetic Evaluations: A sparse blood sampling procedure was followed to study the paliperidone concentration-time profiles. Paliperidone plasma concentration-time data were subject to population PK analysis using nonlinear mixed-effects modeling, and details are described in a separate report.

Efficacy Evaluations/Criteria: The primary endpoint was the change in the PANSS total score from baseline (i.e., the start of double-blind treatment, Day 1) to the end of the double-blind treatment period (i.e., Day 92 or the last post baseline assessment). The key secondary efficacy endpoint was the change in the Personal and Social Performance Scale (PSP) from baseline to the end of the double-blind treatment period. The other secondary efficacy endpoint was the change in the Clinical Global Impression-Severity (CGI-S) scores from baseline to the end of the double-blind treatment period. Other endpoints included the change from baseline in subject ratings of sleep quality and daytime drowsiness using a visual analogue scale (VAS), the onset of therapeutic effect, responder rate, and the change from baseline to end point in PANSS subscales and Marder factors.

Safety Evaluations: Safety was monitored by the evaluation of adverse events, extrapyramidal symptom (EPS) rating scales (Abnormal Involuntary Movement Scale [AIMS], Barnes Akathisia Rating Scale [BARS], Simpson and Angus Rating Scale [SAS]) scores, clinical laboratory test results, vital signs measurements, electrocardiograms (ECGs), and physical examination findings. In addition,

the tolerability of injections was assessed; the investigators evaluated injection sites and the subjects assessed injection pain.

STATISTICAL METHODS: All randomized subjects who received at least 1 dose of double-blind study drug and had both baseline and at least one post baseline efficacy measurement (PANSS, PSP, or CGI-S) during the double-blind treatment period were included in the intent-to-treat efficacy analyses. The overall type I error rate for testing all paliperidone palmitate doses versus placebo for both the primary endpoint (change in PANSS total score at end point) and the key secondary efficacy endpoint (change in PSP total score at end point) was controlled at the 2-sided 0.05 significance level. The 2 families of hypotheses (in each family, 3 comparisons for each of the paliperidone palmitate doses versus placebo) were tested using a parallel gatekeeping procedure that adjusts for multiplicity using Dunnett's method in each family of hypotheses and using Bonferroni's inequality between different families of hypotheses. This procedure is referred to as the Dunnett-Bonferroni-based parallel gatekeeping procedure.

The change from baseline in PANSS total score at each visit and at end point was analyzed using an analysis of covariance (ANCOVA) model. The last observation carried forward (LOCF) method was used. The model included treatment and country as factors and baseline PANSS total score as a covariate. Treatment effect was based on the difference in least-squares mean change. Dunnett's test was used to adjust for multiple comparisons of the 3 paliperidone palmitate dosages versus placebo. Unadjusted 2-sided 95% confidence intervals were presented for the difference in least-squares mean change of each paliperidone palmitate dosage group compared with placebo. Treatment-by-country and treatment-by-baseline PANSS total score interactions were explored using the same ANCOVA model as the one for the analysis of the primary endpoint. If either term was statistically significant at the predefined 2-sided significance level of 0.10, further evaluations of the effect of other covariates were to be performed to assess the nature of the interaction and identify possible causes. In addition, to address the dose-response relationship and to facilitate the discussion of dosage selection, an analysis to compare the 3 active paliperidone palmitate dosages with each other was performed without adjustment for multiple comparisons.

The analysis of the key secondary endpoint, change in PSP score at end point, was conducted by means of an ANCOVA model with treatment and country as factors and the baseline score as the covariate. The Dunnett-Bonferroni-based parallel gatekeeping approach was used to adjust for multiple testing.

Between-group comparisons of CGI-S were performed by using an ANCOVA model on the ranks of change from baseline, with treatment and country as factors and the baseline score as the covariate.

Change from baseline over time (observed case) in the PANSS total score was explored using mixed effects linear models for repeated measures with time, treatment, country, and treatment-by-time as factors and baseline score as a covariate.

The number and percentage of subjects with treatment-emergent adverse events were summarized. Adverse events of potential clinical interest were summarized separately, including events related to EPS or changes in serum glucose or prolactin levels.

Changes from baseline in clinical laboratory tests, vital sign measurements, ECGs, body weight, BMI, and EPS scale scores were summarized by treatment group. Prolactin levels were summarized by sex. Subjects with potentially abnormal values or changes in clinical laboratory tests, vital signs, orthostatic parameters, and ECG parameters were summarized based on predefined criteria. Frequency distributions were presented for the investigator's evaluation of the injection site, and descriptive statistics were presented for VAS scores corresponding to the subject's evaluation of injection pain.

RESULTS:

The majority of subjects in the paliperidone palmitate treatment groups (56% - 61%) received all 4 injections compared with 48% of the placebo-treated subjects. Completion rates were also higher for the paliperidone palmitate groups (52% - 55%) than for the placebo group (43%). More subjects were discontinued for lack of efficacy in the placebo group (27%) compared with the paliperidone palmitate groups (14% - 19%).

Demographic and Baseline Characteristics: The double-blind treatment groups were well matched with respect to demographic and baseline disease characteristics and psychiatric history. The 636 subjects who comprised the intent-to-treat analysis set were mainly male (67%), racially diverse (54% White, 30% Black, 14% Asian, 1% other races), and predominately between the ages of 26 and 50 years (75%). Most subjects had a primary diagnosis of paranoid schizophrenia (88%), and were highly symptomatic as indicated by a mean PANSS total score of 87.1 at baseline. There were notable differences between countries with respect to BMI and gender, with subjects enrolled at centers in the U.S. being more likely to be male and obese (i.e., BMI ≥30 kg/m^2) than those from centers in other countries.

Pharmacokinetics: A total of 488 subjects who were randomly assigned to receive paliperidone palmitate treatment had scheduled pharmacokinetic blood samples taken over the course of the study. The median paliperidone predose concentration for the 25 mg eq. treatment group was highest on Day 8, which is the result of the initial 150 mg eq. dose on Day 1. After Day 8, paliperidone concentrations decreased and seemed to reach steady state levels on Day 92 based on visual inspection. The median paliperidone predose concentration for the 100 mg eq. treatment group remained in the same range from Day 8 onwards. The median predose concentration for the 150 mg eq. treatment group seemed to increase up to the last study day, Day 92. The median paliperidone plasma concentrations on Day 8 were lower in subjects with high BMI (≥25 to <30 kg/m² and ≥30 kg/m^2; overweight/obese) compared to subjects with low BMI (<25 kg/m²) for the 3 dose groups. After Day 8, no consistent trends were observed for the 3 paliperidone palmitate dose groups with respect to paliperidone plasma concentrations as a function of baseline BMI classification.

The mean and median paliperidone plasma concentrations on Day 64 for the 100 mg eq. treatment group were approximately 2-fold higher than those for the 25 mg eq. treatment group. Thus, the PK profile for the 25 mg eq. and 100 mg eq. dose groups appeared to be less than dose proportional, which is the result of the initial paliperidone palmitate 150 mg eq. injection on Day 1 in all active treatment groups. The mean and median paliperidone plasma concentrations on Day 64 for the 100 mg eq. dose were apparently dose proportional compared to the 150 mg eq. dose. A high inter-subject variability was observed in the paliperidone plasma concentrations on Days 1 and 2 with a %CV of 118.9% (Day 1) and 153.1% (Day 2). After Day 2, the inter-subject variability decreased and the %CV ranged from 50.4 to 83.4%.

Primary Efficacy Analysis: Adult subjects with schizophrenia achieved statistically significant improvements in the PANSS total score (primary efficacy endpoint) with all 3 doses of paliperidone palmitate compared to placebo (25 mg eq.: p=0.034; 100 mg eq.: p<0.001; 150 mg eq.: p<0.001) based on the intent-to-treat LOCF analysis and the Dunnett's test to control for multiplicity.

Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Total Score -Change from Baseline to End Point-LOCF with the Dunnett-Bonferroni-Based Parallel Gatekeeping Procedure
(Study R092670-PSY-3007: Intent-to-Treat Analysis Set)

	Placebo (N=160)	R092670 25 mg eq. (N=155)	R092670 100 mg eq. (N=161)	R092670 150 mg eq. (N=160)
Baseline Mean (SD)	86.8 (10.31)	86.9 (11.99)	86.2 (10.77)	88.4 (11.70)
End point Mean (SD)	83.9 (21.44)	78.8 (19.88)	74.6 (18.06)	75.2 (18.59)
Change from Baseline				
Mean (SD)	-2.9 (19.26)	-8.0 (19.90)	-11.6 (17.63)	-13.2 (18.48)
P-value (minus Placebo)[a]		0.034	<0.001	<0.001
Diff. of LS Means (SE)		-5.1 (2.01)	-8.7 (2.00)	-9.8 (2.00)

[a] Based on analysis of covariance (ANCOVA) model with treatment (Placebo, R092670 25 mg eq., R092670 100 mg eq., R092670 150 mg eq.) and country as factors, and baseline value as a covariate. P-values were adjusted for multiplicity for comparison with placebo using Dunnett's test.

Note: Negative change in score indicates improvement.

Other Efficacy Results: There was a dose-response pattern with respect to the primary efficacy variable, with the mean decreases (improvement) in the PANSS total score at end point (LOCF).

Prespecified treatment-by-country and treatment-by-baseline PANSS total score interactions in the primary efficacy model were not statistically significant at the 0.10 level. An exploratory analysis additionally provided no statistical evidence for a BMI effect on treatment.

All 3 paliperidone palmitate dose groups showed a statistically significant improvement over placebo in the change in PANSS total score as of Day 22 and at every subsequent time point, and as early as Day 8 in the paliperidone palmitate 25 mg eq. and 150 mg eq. groups.

The mean improvements in the PSP score from baseline to end point, the key secondary efficacy outcome measure, showed a dose response among the 3 paliperidone palmitate groups (25 mg eq.: 2.9; 100 mg eq.: 6.1; 150 mg eq.: 8.3); all were numerically higher than the mean improvement in the PSP score seen in the placebo group (1.7). Based on the intent-to-treat LOCF analysis of this key secondary efficacy variable, using the Dunnett-Bonferroni-based parallel gatekeeping procedure to adjust for multiplicity, the improvement in the paliperidone palmitate 100 and 150 mg eq. treatment groups reached statistical significance (100 mg eq.: p=0.007; 150 mg eq.: p<0.001) when compared with the placebo group.

The paliperidone palmitate 100 mg eq. and 150 mg eq. groups were statistically significantly superior to placebo in improving the CGI-S scores from baseline to end point (LOCF) (without multiplicity adjustment, 100 mg eq.: p=0.005; 150 mg eq.: p<0.001). Significantly more subjects treated with paliperidone palmitate 25 mg eq. (33.5%; p=0.007), 100 mg eq. (41.0%; p<0.001), and 150 mg eq. (40.0%, p<0.001) achieved responder status (30% or larger decrease on PANSS total scores) than with placebo (20.0%).

Based on the intent-to-treat LOCF analysis of the change from baseline to end point without statistical adjustment for multiplicity, the paliperidone palmitate 100 and 150 mg eq. groups were statistically significantly superior to the placebo group for all 5 PANSS Marder factors (p≤0.010). The improvements in both negative symptoms and disorganized thoughts factor scores were statistically significantly greater in the paliperidone palmitate 25 mg eq. group compared with placebo (p=0.032).

Based on the intent-to-treat LOCF analysis using an ANCOVA model with no adjustment for multiplicity, the mean improvement in sleep quality in the paliperidone palmitate 100 mg eq. and 150 mg eq. groups were statistically significant (p<0.001 and p=0.026, respectively) when compared with placebo. The mean changes in daytime drowsiness in the paliperidone palmitate treatment groups were not statistically significantly different from that in the placebo group (25 mg eq.: p=0.541; 100 mg eq.: p=0.340; 150 mg eq.: p=0.261).

Safety Results: Paliperidone palmitate, injected at a dose of 150 mg eq. into the deltoid muscle followed by 3 i.m. injections at fixed doses of 25 mg eq., 100 mg eq., or 150 mg eq. on Days 8, 36, and 64, was generally well tolerated by adult subjects with schizophrenia during this 13-week study. Overall, the safety and tolerability results were consistent with previous clinical studies involving paliperidone palmitate, and no new safety signals were detected.

The overall summary of treatment-emergent adverse events is given below.

Overall Summary of Treatment-Emergent Adverse Events
(Study R092670-PSY-3007: Safety Analysis Set)

	Placebo (N=164) n (%)	R092670 25 mg eq. (N=160) n (%)	R092670 100 mg eq. (N=165) n (%)	R092670 150 mg eq. (N=163) n (%)	Total (N=652) n (%)
TEAE	107 (65.2)	101 (63.1)	99 (60.0)	103 (63.2)	410 (62.9)
Possibly related TEAE[a]	47 (28.7)	45 (28.1)	49 (29.7)	51 (31.3)	192 (29.4)
TEAE leading to death	0	0	0	1 (0.6)	1 (0.2)
1 or more serious TEAE	23 (14.0)	15 (9.4)	22 (13.3)	13 (8.0)	73 (11.2)
TEAE leading to permanent stop	11 (6.7)	10 (6.3)	10 (6.1)	13 (8.0)	44 (6.7)

[a] Study drug relationships of possible, probable, and very likely are included in this category.
Adverse events are coded using MedDRA version 10.1

There was 1 death in a subject in the paliperidone palmitate 150 mg eq. group after withdrawal from the study due to an adverse event (cerebrovascular accident) that began during the study. This subject received 2 injections of study medication, with the last injection administered approximately 2 weeks before the subject died. While this event was assessed as doubtfully related to study treatment by the investigator, an unblinded review by the sponsor assessed this event to be possibly related to study treatment.

The number of subjects who experienced treatment-emergent serious adverse events was higher in the placebo group than in any of the paliperidone palmitate groups (see table above). Most serious adverse events in all treatment groups were psychiatric disorders (e.g., schizophrenia, psychotic disorder) that were likely the result of the natural course of the underlying schizophrenia. Adverse events leading to study discontinuation occurred at a similar low incidence across treatment groups.

Common treatment-emergent adverse events (≥2% of subjects in any treatment group) that occurred more frequently in the total paliperidone palmitate group (all 3 active dose groups combined) than in the placebo-treated subjects (i.e., ≥1% difference between the combined paliperidone palmitate group and the placebo group) were: injection site pain, dizziness, sedation, pain in extremity, and myalgia. An examination of treatment-emergent adverse events of potential clinical importance revealed no reports of seizure or convulsion, tardive dyskinesia, dermatologic events, neuroleptic malignant syndrome, hyperthermia, anaphylactic reaction, rhabdomyolysis, syndrome of inappropriate secretion of antidiuretic hormone, ventricular tachycardia, ventricular fibrillation, or torsades de pointes.

In general, the type and incidence of treatment-emergent adverse events did not differ as a function of baseline BMI categories (normal: <25 kg/m^2; overweight: ≥25 to <30 kg/m^2; obese: ≥30 kg/m^2).

The incidence of treatment-emergent EPS-related adverse events was low and comparable to placebo. Akathisia was the most frequently reported EPS-related adverse event (4.9% for the placebo group and 1.3%, 4.8%, 5.5% for the paliperidone palmitate 25, 100, and 150 mg eq. groups, respectively). None of the EPS-related adverse events reported in subjects receiving paliperidone palmitate were serious or treatment limiting, and only 1 was severe (musculoskeletal stiffness). Results of EPS rating scales and use of anti-EPS medication were consistent in indicating that paliperidone palmitate was associated with a low incidence of EPS.

No clinically relevant mean changes from baseline to end point in supine or standing pulse rates were apparent for any of the paliperidone palmitate doses. A similar, low percentage of subjects had pulse rate of ≥100 bpm with an increase of ≥15 bpm in the placebo and paliperidone palmitate groups (6% to 11% for standing measurements; 2% to 5% for supine measurements).

Assessment of ECG data did not demonstrate evidence of clinically significant QTc prolongation with paliperidone palmitate at doses up to 150 mg eq. No subject had a maximum QTcLD value >480 ms or a maximal change in QTcLD >60 ms during the study.

The increases in body weight with paliperidone palmitate over the 13-week double-blind treatment period were modest in a dose-related manner, averaging 0.4, 0.7, and 1.4 kg for the 25 mg eq., 100 mg eq., and 150 mg eq. groups, respectively (-0.2 kg for placebo); corresponding mean changes in BMI from baseline to end point were 0.1, 0.3, and 0.5 kg/m^2, respectively (-0.1 kg/m^2 for placebo). A clinically relevant weight increase of at least 7% relative to baseline was seen in 13% of subjects receiving the highest dose of paliperidone palmitate (compared with 5% for placebo).

Consistent with the known pharmacology of paliperidone, increases in prolactin levels were observed with greater frequency in subjects who received paliperidone palmitate, with the largest increase seen in the 150 mg eq. group. Overall, there was a low incidence of potentially prolactin-related adverse events, despite the known propensity of paliperidone palmitate to increase serum prolactin levels. This suggests that the clinical importance of this increase in serum prolactin levels is of questionable clinical significance.

Based on mean changes from baseline to end point and the occurrence of treatment-emergent markedly abnormal laboratory test values and adverse events related to abnormal laboratory analyte findings, except for prolactin, the effects of paliperidone palmitate on the results of chemistry and hematology

laboratory tests (including liver and renal function tests, serum lipid levels, and glucose levels) did not show clinically relevant differences from those of placebo.

Local injection site tolerability was good. Occurrences of induration, redness, or swelling as assessed by blinded study personnel were infrequent, generally mild, decreasing over time, and similar in incidence for the paliperidone palmitate and placebo groups. Investigator ratings of injection pain were similar for the placebo and paliperidone palmitate groups.

STUDY LIMITATIONS: This study investigated the efficacy and safety of paliperidone palmitate for acute treatment of schizophrenia over 13 weeks and does not provide information on longer term treatment. The study was not designed to detect differences between doses of paliperidone palmitate; thus, dose-related trends in efficacy and safety can only be described descriptively. The study was also not designed to demonstrate efficacy for specific subgroups of subjects, such as those from a particular country. An independent, centralized blinded rating service was used for performing all ratings of PANSS, PSP and CGI-S for all subjects enrolled at U.S. sites. The investigators at these sites did not complete any of the ratings, which would have provided a reference for ratings provided by the rating service. Thus, data from this study cannot be used to fully evaluate the utility of using blinded independent raters for detecting treatment differences.

CONCLUSION: All 3 doses of paliperidone palmitate tested in this study - 25, 100, and 150 mg eq. - were efficacious in adult subjects with schizophrenia who were experiencing acutely exacerbated schizophrenia. Specifically, the results of the primary efficacy endpoint (change from baseline to end point in PANSS total score) demonstrated statistical superiority of paliperidone palmitate 25 mg eq., 100 mg eq., and 150 mg eq. over placebo. Significantly greater improvement in subjects' personal and social functioning (as measured by the PSP score) was also seen for the paliperidone palmitate 100 mg eq. and 150 mg eq. doses compared with placebo, and global improvement was validated by a favorable and statistically significant CGI-S change for these 2 dose groups. There was a dose response in the primary and secondary efficacy endpoints (PANSS, PSP, and CGI-S). All 3 doses of paliperidone palmitate, including the highest dose of 150 mg eq., were well tolerated, suggesting a positive benefit-risk ratio across the dose range currently studied. No new safety signal was detected.

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