SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: paliperidone palmitate NAME OF ACTIVE INGREDIENT(S): 9-hydroxy-risperidone palmitate	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: CR004357 **Title of Study:** A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of 50 and 100 mg eq. of Paliperidone Palmitate in Subjects With Schizophrenia		
Coordinating Investigator: Robert E. Litman, M.D. Centers for Behavioral Health, L.L.C., 14915 Broschart Road, Suite 250, Rockville, MD; U.S.A.		
Publication (Reference): None.		
Study Initiation/Completion Dates: 27 October 2003 to 09 July 2004 **Sample Analysis:** 18 May 2004 to 07 September 2004		**Phase of development:** 2/3
Objectives: The primary objective was to evaluate the efficacy and safety of 2 fixed dosages of long-acting injections of paliperidone palmitate (50 and 100 mg eq.) compared with placebo in subjects with schizophrenia. Secondary objectives were to: 1) assess the global improvement in severity of illness (CGI-S) with the use of paliperidone palmitate relative to placebo and 2) to explore the pharmacokinetic (PK) profiles of ER OROS paliperidone, IR paliperidone, and paliperidone palmitate and to compare the PK profiles of ER OROS paliperidone and IR paliperidone to that of paliperidone palmitate.		
Methodology: This was a randomized, double-blind, placebo-controlled, multicenter study in subjects with schizophrenia. Subject enrollment included a screening period (maximum 5 days, including 3-day washout of psychotropic medications other than antidepressants); a 7-day, open-label, oral run-in period; and a 64-day double-blind treatment period. Total study duration was approximately 11 weeks. During the oral run-in period subjects received either ER OROS paliperidone (6 or 12 mg) or IR paliperidone (2 or 4 mg), Q.D. on each of the 7 oral run-in days. Subjects who met study eligibility criteria at the conclusion of the oral run-in period entered the double-blind phase and were randomized to placebo, paliperidone palmitate 50 mg eq., or paliperidone palmitate 100 mg eq. treatment groups. Double-blind treatment was administered as intramuscular (i.m.; gluteal muscle) injections on Days 1, 8, and 36. All subjects were hospitalized for at least 14 days, including the 7-day oral run-in period and the first 7 days of the double-blind treatment period.		
Number of Subjects (planned and analyzed): The planned sample size was 210 subjects, with 70 subjects randomized to each of 3 double-blind treatment groups. Of the 266 subjects who entered the oral run-in period, 247 continued into the double-blind phase and were randomized to placebo (N=84), paliperidone palmitate 50 mg eq. (N=79), or paliperidone palmitate 100 mg eq. (N=84) treatment groups. Forty-nine randomized subjects from 6 sites were excluded from the primary analyses of efficacy due to major deviations in study drug administration and in using the IVRS system. The primary efficacy analysis set was the intent-to-treat (ITT) population that included 197 randomized subjects who received at least 1 injection of double-blind treatment and had at least 1 postbaseline efficacy measurement. The safety analysis set included any subject who received at least 1 injection of double-blind treatment, including the 49 subjects from the 6 sites excluded for the analyses of efficacy.		
Diagnosis and Main Criteria for Inclusion: Men or women, between 18 and 65 years of age, with a diagnosis of schizophrenia according to DSM-IV criteria were eligible for study enrollment. Subjects were required to have a total PANSS score between 70 and 120 (inclusive) at screening and between 60 and 120 (inclusive) on Day 1 (baseline) prior to start of double-blind treatment. Subjects were otherwise healthy based on pre-enrollment medical history, physical examination, clinical laboratory evaluation, and ECG.		
Test Product, Dose and Mode of Administration, Batch No.: Oral 3 mg or 9 mg ER OROS paliperidone tablets; Batch Nos. ALZA MV0307085 (3 mg tablet) and ALZA MV0301025 (9 mg tablet). Oral 2 mg or 4 mg IR paliperidone capsules; Batch Nos. 03I01/F031 (2 mg capsule) and 03I02/F033 (4 mg capsule). Paliperidone palmitate for i.m. injection was pre-packaged in vials containing 2 mL of drug nano-suspension., equivalent to 200 mg paliperidone (Batch Nos. 01D06/F011 and 01C16/F011; drug substance sterilized by gamma-irradiation.). The appropriate volume (0.5 or 1.0 mL) of suspension was withdrawn from the vial to administer the correct dose.		

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Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo solution (2 mL) was provided in a prefilled syringe for i.m injection, Batch No. 318011.

Duration of Treatment: 1-week oral run-in period followed by 64-day double-blind period.

Criteria for Evaluation:

Pharmacokinetics: Plasma concentrations of the enantiomers of paliperidone [R078543 and R078544], risperidone, and paliperidone palmitate (R092670) were determined. Based on the individual plasma concentration-time data, the following pharmacokinetic parameters were estimated for paliperidone and its enantiomers during the oral run-in phase: $C_{pre\ Day-3}$, $C_{pre\ Day-2}$, $C_{pre\ Day-1}$, C_{max}, t_{max}, C_{min}, AUC_{last}, C_{avg}, CL/F and FI. Based on the individual plasma concentration-time data, the following pharmacokinetic parameters were estimated for paliperidone and its enantiomers during the double blind phase, as applicable: $C_{pre\ Day8}$, $C_{pre\ Day\ 36}$, C_{Day64}, C_{max}, t_{max}, C_{min}, AUC_{last}, C_{avg}, CL/F, λ_z, $t_{1/2}$, FI.

Efficacy: The primary efficacy endpoint was the change in total PANSS score from start of the double-blind treatment period (baseline, Day 1) to the last post-randomization assessment in the double-blind period (last observation carried forward [LOCF] end point). Secondary efficacy variables included changes from baseline to each assessment time point (LOCF) in CGI-S scores and PANSS subscale scores for Positive Symptoms, Negative Symptoms, Disorganized Thoughts, Uncontrolled Hostility/Excitement, and Anxiety/Depression. Treatment responders were subjects having at least a 20% or 30% reduction in the total PANSS score from baseline (Day 1) to LOCF end point.

Safety: Safety parameters monitored included adverse events; clinical laboratory tests; vital signs; ECGs; body weight; body mass index (BMI); investigator ratings of injection site redness, swelling, pain, and induration; subject ratings of injection site pain; and 3 EPS scales for assessing extrapyramidal symptoms (Simpson Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), and Abnormal Involuntary Movement Scale (AIMS).

Statistical Methods:

Pharmacokinetics: Descriptive statistics were calculated for the plasma concentrations of paliperidone, its enantiomers and, if applicable, risperidone at each sampling time. Descriptive statistics for the PK parameters were calculated for each paliperidone formulation (IR paliperidone, ER OROS paliperidone and i.m. paliperidone palmitate), dose and dosing interval, as applicable.

The dose-proportionality of paliperidone administered during the oral run-in phase and double-blind phase was evaluated by an analysis of variance model fitted to log-transformed, dose-normalized C_{max} and AUC with dose as fixed effect to estimate the least square means and inter-subject variance. Using these estimated values, 90% confidence interval for the ratio of mean PK parameters were determined.

Efficacy: Statistical tests were interpreted at the 10% significance level (2-sided). An alpha level of 0.1 was selected to determine sample size due to the limited clinical drug supply at the time of this Phase 2 study. The use of a 10% significance level allowed selection of a sample size that was considered sufficient to meet the primary objective of the study. The change from baseline in PANSS total and subscale scores at end point (LOCF) and at each time point were analyzed using an ANCOVA model that included factors for double-blind treatment group, analysis center, and oral run-in treatment, and the baseline PANSS score as a covariate. Using this model, least squares means of the difference, 90% CI, and p-values were determined for the change from baseline for each paliperidone palmitate treatment group versus placebo. A similar ANCOVA model on ranks was used to analyze the change from baseline in CGI-S scores at end point and each time point (LOCF). The percentages of subjects who demonstrated a ≥20% or 30% reduction in total PANSS score from baseline to LOCF end point were compared between the paliperidone palmitate and placebo groups using a Cochran-Mantel-Haenszel test, controlling for analysis center. A worst rank analysis was performed to assess the robustness of the primary efficacy analysis.

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Safety: For both the oral run-in and double-blind periods, the number and percentage of subjects with treatment-emergent adverse events (by MedDRA preferred terms) were summarized according to treatment group. Descriptive statistics were used to summarize the change from baseline in vital signs, body weight, and BMI measurements, and EPS rating scales (SAS, AIMS, and BARS scores) for each treatment group at each visit. For body weight and BMI, the analysis was repeated by baseline BMI classification. Descriptive statistics were provided for the change from baseline in clinical laboratory values at each time point. Using predefined criteria, the distribution of subjects exhibiting markedly abnormal clinical laboratory, vital sign, and ECG QT interval measurements were summarized according to treatment group. Adverse events of special clinical interest including EPS-, glucose- and potentially prolactin-related, CV-related events (arrhythmias, orthostatic hypotension, QT interval prolongation, ischemic events), injection site reactions, plus other events of clinical interest (dermatologic, rhabdomyolysis-related, SIADH-related and hepatic function abnormalities) were reviewed by clinicians at the Sponsor and summarized.

SUMMARY: The percentage of subjects in the paliperidone palmitate 50 mg eq. (47 of 79, 59%) and 100 mg eq. (51 of 84, 61%) groups who completed the 64-day double-blind period was greater than that in the placebo group (27 of 84, 32%). More subjects were withdrawn for lack of efficacy in the placebo group (43%) than in the paliperidone palmitate 50 mg eq. and 100 mg eq. groups (29% and 17%, respectively). The double-blind treatment groups were well matched with respect to demographic and baseline disease characteristics. Subjects comprising the primary ITT analysis set were predominantly white (81%) with a median age of 40 years, and 62% were male. Most intent-to-treat (ITT) subjects (88%) were diagnosed with paranoid schizophrenia and 75% of subjects had been treated previously with antipsychotic. The mean total PANSS score at baseline was 87. Based on CGI-S scores, 49% of subjects in the ITT analysis set were markedly or severely impaired by their disease. Less than half (42%) of subjects in the placebo group received all 3 scheduled injections of study medication, compared with approximately two thirds of subjects in the paliperidone palmitate 50 mg eq. and 100 mg eq. treatment groups (66% and 65%, respectively).

PHARMACOKINETIC RESULTS:

a) Oral Run-In Phase:

Apparent steady-state was reached before Day 7 during the oral run-in phase for the ER OROS and the IR formulation of paliperidone, consistent with a half-life of 24 hours. After administration of 6 or 12 mg ER OROS paliperidone, mean C_{min} values of paliperidone were 17.8 and 35.4 ng/mL, mean C_{max} values were 30.8 and 58.3 ng/mL and mean AUC_{last} values were 554 and 1107 ng.h/mL, respectively.

After administration of 2 or 4 mg IR paliperidone, mean C_{min} values of paliperidone were 12.2 and 27.3 ng/mL, mean C_{max} values were 31.5 and 64.8 ng/mL and mean AUC_{last} values were 482 and 1013 ng.h/mL, respectively. The fluctuation in plasma concentrations of paliperidone was lower for ER OROS paliperidone than for IR paliperidone (mean FI values were 51.0% and 52.7%, and 96.2% and 92.0%, respectively).

The results indicated dose-proportionality of paliperidone over the dose range studied for both the ER OROS and IR paliperidone formulations. The exposure to paliperidone was comparable between 2 mg IR paliperidone and 6 mg ER OROS paliperidone, and between 4 mg IR paliperidone and 12 mg ER OROS paliperidone and connfirmed an approximately 3 times lower bioavailability of the ER OROS paliperidone formulation compared with the IR paliperidone formulation.

The mean C_{max} ratio of R078543(+)/R078544(-) was 1.62 and 1.65 for 6 and 12 mg ER OROS paliperidone, respectively, and 1.77 and 1.79 for 2 and 4 mg IR paliperidone, respectively. For AUC_{last} these ratios ranged from 1.57 to 1.63.

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PHARMACOKINETIC RESULTS: (cont)

b) Double-Blind Phase:

During the first 7 days following the first i.m. injection of paliperidone palmitate, the median plasma concentrations of paliperidone gradually decreased from 18.9 ng/mL (predose Day 1) to 7.59 ng/mL (predose Day 8) and from 28.7 ng/mL (predose Day 1) to 8.24 ng/mL (predose Day 8) for the 50 and 100 mg eq. dose levels of plaiperidone palmitate, respectively. Following the third i.m. injection (Day 36), plasma concentrations of paliperidone reached a maximum about 4 days after i.m. injection. Median predose concentrations on Day 8, 36 and 64 (end of the study period) were 7.59, 7.30 and 7.90 ng/mL and 8.24, 22.5 and 22.1 ng/mL for the 50 and 100 mg eq. dose, respectively. For the paliperidone palmitate 50 mg eq. dose, the ratio of the median plasma concentration on Day 64 and the median predose on Day 36 and the ratio of the median plasma concentration on Day 64 and the median predose on Day 8 were comparable (1.08 and 1.04, respectively), while for the 100 mg eq. dose, the ratios were 0.98 and 2.68, respectively. These comparable plasma concentrations suggest that for the paliperidone palmitate 50 mg eq. dose, an apparent steady-state was reached as early as Day 8, while for the paliperidone palmitate 100 mg eq. dose, apparent steady-state was reached after the third injection. Median C_{max} values during the last dosing interval (Day 36 to Day 64) were 13.7 and 35.2 ng/mL for the 50 mg eq. and 100 mg eq. paliperidone palmitate doses, respectively. Median AUC_{last} was approximately 2.6-fold higher (7235 vs 18557 ng.h/mL), when the dose was twice as high (50 mg eq. vs. 100 mg eq.). Statistical evaluation indicates that the pharmacokinetics of paliperidone increased proportionally with dose in the 50 mg eq. to 100 mg eq. dosing range of paliperidone palmitate.

The median apparent half-life determined in a limited number of subjects was approximately 20.3 days for the paliperidone palmitate 50 mg eq. dose and 27.4 days for the paliperidone palmitate 100 mg eq. dose. The median FI was 65.7% and 60.4% for the 50 and 100 mg eq. dose of paliperidone palmitate, respectively.

Within each dose group of paliperidone palmitate the exposure to paliperidone was comparable for subjects that previously received either, 2 mg IR paliperidone as compared to 6 mg ER OROS paliperidone, or 4 mg IR paliperidone as compared to 12 mg ER OROS paliperidone, after an initial decrease in predose plasma concentrations during the first 8 days of injection.

The median exposure (AUC_{last}) of 2 mg IR paliperidone or 6 mg ER OROS paliperidone is slightly higher (1.6 to 1.8 fold) compared with the median exposure after the third injection (AUC_{last}/28 days) in the 50 mg eq. dose group (458 and 404 ng.h/mL versus 258 ng.h/mL). In the higher dose group, the exposure was 1.2 to 1.3 fold higher after 4 mg IR paliperidone or 12 mg ER OROS paliperidone compared with the third injection of paliperidone palmitate 100 mg eq. dose group (882 and 827 ng.h/mL versus 663 ng.h/mL).

The mean C_{max} ratios of R078543(+)/R078544(-) in the Day 36 to Day 64 period were 1.64 and 1.63 for the 50 and 100 mg eq. paliperidone palmitate doses, respectively. For AUC_{last} these ratios were 1.62 and 1.59, respectively.

Plasma concentrations of paliperidone palmitate could only be quantified for a total of 32 out of 163 subjects (4.5% of total samples), who received one dose of paliperidone palmitate, with the majority of these samples between Day 1 and Day 10 after initiation of paliperidone palmitate treatment. The highest measured concentration of paliperidone palmitate was 3.90 ng/mL, which was 33.3 times lower compared to the paliperidone concentration (130 ng/mL0 at the same time point.

There was no relationship between CYP450 2D6, CYP450 3A4/5 genotype and paliperidone PK parameters.

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EFFICACY RESULTS: Paliperidone palmitate 50 mg eq. and 100 mg eq. were statistically significantly superior to placebo for the primary efficacy variable, the change from baseline to LOCF end point in total PANSS score.

Positive and Negative Syndrome Scale for Schizophrenia (PANSS) – Change From Baseline to End Point (LOCF) (Primary Intent-to-Treat Analysis Set)

	Placebo (N=66)	R092670 50 mg eq. (N=63)	R092670 100 mg eq. (N=68)
Baseline mean (SD)	87.8 (13.90)	88.0 (12.39)	85.2 (11.09)
End point mean (SD)	94.0 (24.84)	82.8 (24.48)	77.5 (21.42)
Mean (SD) change from baseline to end point	6.2 (18.25)	-5.2 (21.52)	-7.8 (19.40)
p-value (vs Placebo)[a]		0.001	<0.0001

[a] From ANCOVA model with factors for treatment, oral run-in treatment, and analysis center, and with baseline value as covariate. Comparisons with placebo done without multiplicity adjustment.

Onset of activity was demonstrated, with both paliperidone palmitate groups statistically significantly superior to placebo beginning at Day 8 ($p<0.011$). Significantly more subjects in the paliperidone palmitate 50 mg eq. (33%) and 100 mg eq. (37%) compared with the placebo group (14%) experienced at least a 30% improvement from baseline to end point in total PANSS ($p=0.007$ and $p=0.002$, respectively). Similarly, the proportion of subjects who had a 20% or greater improvement in the total PANSS score from baseline to end point was significantly larger ($p<0.001$) in the 2 paliperidone palmitate treatment groups compared to placebo. Approximately 85% of subjects in the placebo group failed to achieve at least a 20% improvement in total PANSS score.

Both the paliperidone palmitate 50 mg eq. and 100 mg eq. groups were statistically significantly superior to placebo for the mean change from baseline to end point (LOCF) in the PANSS Positive Symptoms ($p=0.001$ and $p<0.001$, respectively), Negative Symptoms ($p=0.010$ and $p<0.001$), Anxiety/Depression ($p=0.002$ and $p<0.001$), Disorganized Thoughts ($p=0.012$ and $p<0.001$), and Uncontrolled Hostility/Excitement ($p=0.080$ and $p=0.006$) subscale scores and in the change from baseline in CGI-S scores ($p=0.004$ and $p<0.001$).

SAFETY RESULTS: Treatment-emergent adverse events (TEAEs) during the double-blind period occurred in 64% of placebo subjects, 65% of subjects receiving paliperidone palmitate 50 mg eq., and 60% of subjects treated with paliperidone palmitate 100 mg eq.

There were no deaths during either the 7-day oral run-in period or the 64-day double-blind treatment period. A similar percentage (6-10%) of all randomized subjects (N=247) treated with paliperidone palmitate or placebo had a serious adverse event. The two most common serious adverse events reported were schizophrenia and psychotic disorder. Other notable serious adverse events were singular reports of hepatic enzyme increased, suicidal ideation, and syncopal episode. Few paliperidone palmitate-treated subjects were discontinued from the study due to an adverse event(s) (4 of 163 randomized subjects, 2%), and the rate of discontinuation of double-blind treatment for adverse events was higher among placebo-treated subjects (8 of 84 randomized subjects, 10%). Adverse events resulting in discontinuation of paliperidone palmitate were psychiatric disorders (n=3) and pyelocystitis (n=1).

EPS-related adverse events were infrequent in this study, all were mild or moderate in severity, and none resulted in discontinuation of study treatment. No statistically significant or clinically relevant differences between the paliperidone palmitate and placebo groups were seen in scores for 3 EPS rating scales (AIMS, BARS, SAS). While the percentage of subjects receiving anti-EPS medications during the double-blind period was higher in the paliperidone palmitate 100 mg eq. group than in the placebo or paliperidone palmitate 50 mg eq. group, only 21% of subjects in the 100 mg eq. group required treatment with an anti-EPS drug compared to 7% of placebo-treated subjects.

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There were 4 reports of tachycardia (1 placebo subject and 3 paliperidone palmitate 100 mg eq. subjects); none of these events were identified as clinically noteworthy. The incidence of orthostatic hypotensionwas higher for paliperidone palmitate 50 mg eq. (6%) and 100 mg eq. (11%) than for placebo (4%), but hypotension was not reported as an adverse event in any subject. One paliperidone palmitate-treated subject experienced an episode of syncope. Up to 8% of subjects receiving paliperidone palmitate had a weight increase of 7% or more from baseline to end point compared to 4% of placebo-treated subjects, and most of these weight increases were not associated with a shift in BMI classification. A total of 3 (2%) of subjects treated with paliperidone palmitate and 3 (4%) of placebo-treated subjects experienced a weight decrease of 7% or more.

Adverse events potentially related to increased prolactin levels were reported in 3 (2%) of 163 subjects receiving paliperidone palmitate and in 1 placebo-treated subject. Only 1 of these adverse events (erectile dysfunction) coincided with an increase in serum prolactin above baseline. There were no clinically relevant treatment-related changes in any other laboratory parameter evaluated in this study, including glucose. Mean changes in liver transaminases (ALT and AST) were minimal in all 3 treatment groups in this study, and tended to decrease with time. Marked elevation in CPK levels were noted in 5 subjects, however, based on Sponsor clinician review, these elevations were not associated with rhabdomyolysis.

There were no potentially rhabdomyolysis-related, pancreatitis-related, or syndrome of inappropriate anti-diuretic hormone secretion (SIADH) events during the study.

No subject receiving paliperidone palmitate in this study had a corrected QTc interval (QTcF, QTlc, QTcLD, or QTcB) of 500 ms or higher. When QT was corrected for heart rate using QTcF, QTlc, or QTcLD methods, no subject had an increase in QTc of >60 ms, and only 1 placebo- treated subject had an increase in QTcB of >60 ms. The incidence of changes in QTc of 30-60 ms relative to baseline was comparable for paliperidone palmitate and placebo.

Overall, local injection site tolerability as assessed by blinded study personnel was good. While subject assessments of pain at the injection site were higher after the first injection among those receiving paliperidone palmitate, ratings improved after the second and third injection and were similar to those in the placebo group.

STUDY CONCLUSIONS:

The efficacy and safety of paliperidone palmitate at fixed doses of 50 mg eq. and 100 mg eq. was evaluated in a randomized, double-blind, placebo-controlled, multicenter study in subjects with schizophrenia.

Paliperidone palmitate 50 mg eq. or paliperidone palmitate 100 mg eq., administered as an intramuscular injection in the gluteal muscle on Days 1, 8, and 36 of the double-blind period, demonstrated statistically significantly superior improvement compared to placebo for the primary efficacy variable and for all secondary efficacy variables from baseline to endpoint (Day 64/LOCF).

The safety results of this study indicate that paliperidone palmitate administered as an intramuscular injection was generally well tolerated both locally and systemically at doses of 50 mg eq. and 100 mg eq. There were no deaths during either phase of the study and no unusual or unexpected treatment-emergent adverse events were noted. The frequency of discontinuation from the study due to adverse events was higher in the placebo group than in the paliperidone palmitate groups. Review of ECG data did not demonstrate evidence of increased risk of QTc prolongation with paliperidone palmitate at doses up to 100 mg eq.

The results of this study support the safety, tolerability, and efficacy of paliperidone palmitate in subjects with schizophrenia. Overall, paliperidone palmitate was found to be safe, and no new or unexpected safety signals were identified when compared with phase 1 paliperidone palmitate studies.

Issue Date of the Clinical Study Report: 20 August 2007

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