CLINICAL STUDY REPORT 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(s)	Paliperidone	

Protocol No.: CR003562

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., 50 mg eq., and 100 mg eq.) of Paliperidone Palmitate in Subjects With Schizophrenia

Coordinating Investigator: Henry Nasrallah, M.D., University of Cincinnati, Cincinnati, Ohio USA

Publication (Reference): None.

Study Period: 15 December 2004 to 1 March 2006	**Phase of Development:** 3

Objectives: The primary objective of this study was to evaluate the efficacy and safety of 3 fixed dose levels of paliperidone palmitate, when administered at 4-week intervals after 2 single doses given 1 week apart, as compared with placebo in adult subjects with schizophrenia. Secondary objectives were to assess the global improvement in severity of illness associated with the use of paliperidone palmitate compared with placebo, to assess the benefits to personal and social functioning associated with the use of paliperidone palmitate compared with placebo, to assess the dose-response relationship of paliperidone palmitate, and to explore the pharmacokinetics of paliperidone palmitate and the relationship between its pharmacokinetics and the results of the efficacy parameters (Positive and Negative Syndrome Scale for Schizophrenia [PANSS]) and safety parameters (e.g., extrapyramidal symptoms [EPS], adverse events) of interest.

Methodology: This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-response study of men and women aged at least 18 years with a DSM-IV diagnosis of schizophrenia for at least one year before screening and severely symptomatic (PANSS total score between 70 and 120, inclusive). The study was comprised of a screening period of up to 7 days (including up to 5 days to wash out disallowed psychotropic medications and 4 days for tolerability testing, if needed) and a 13-week double-blind treatment period. To identify any subject who may have a severe tolerability problem or allergic reaction to paliperidone palmitate, subjects without documented previous exposure to at least 4 doses of oral risperidone or paliperidone, or to 1 dose of i.m. RISPERDAL® CONSTA, underwent an oral tolerability test during the screening period. At the start of the double-blind treatment period, each subject was randomly assigned to 1 of 4 treatment groups (3 fixed doses of paliperidone palmitate [25, 50, or 100 mg eq.] or placebo). Each subject received a single gluteal i.m. injection of paliperidone palmitate or placebo on Days 1, 8, 36, and 64. End-of-study assessments were scheduled for Day 92. Subjects were hospitalized for at least 7 days after the first injection of study medication and could be discharged from the study center on Day 8, after receiving their second injection of study medication if, in the opinion of the investigator, they were ready for discharge.

Number of Subjects (planned and analyzed): Approximately 480 subjects (120 in each treatment group) were planned for enrollment. Of the 620 subjects who were screened, 518 were eligible for randomization to double-blind treatment. eq. A total of 517 randomized subjects who received study medication were analyzed for safety. A total of 514 randomized subjects received study medication and had both the baseline and a post baseline efficacy assessments.

Diagnosis and Main Criteria for Inclusion: Men or women aged at least 18 years with a DSM-IV diagnosis of schizophrenia for at least 1 year and a PANSS total score between 70 and 120, inclusive. Subjects were otherwise healthy based on medical history, physical examination, clinical laboratory evaluation, and electrocardiogram (ECG).

Test Product, Dose and Mode of Administration, Batch No.: Paliperidone palmitate (F011 and F013 formulations) fixed doses of 25-, 50-, and 100--mg eq. injectable suspension administered by i.m. injection into the gluteal muscle. The following lot numbers were used: 25 mg eq.: 04F01, 04D13, 04E05, 05C24; 50 mg eq.: 04E05, 05C24, 05E12; 100 mg eq.: 04D13, 04E05, 05C24.

Subjects without documented previous exposure to risperidone or paliperidone underwent an oral tolerability test using a daily dose of ER OROS® paliperidone 3 mg/day (lot number MV0332891) for 4 days before randomization to study treatment.

Reference Therapy, Dose and Mode of Administration, Batch No.: Matching placebo 25, 50, and 100 mg eq. injectable emulsion (20% Intralipid) administered by i.m. injection into the gluteal muscle (lot numbers: 04F07,

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05D19).

Duration of Treatment: Four administrations of study medication: single i.m. gluteal injection on Days 1, 8, 36, and 64.

Criteria for Evaluation:

Pharmacokinetics: Paliperidone plasma concentration data (sparse sampling) were obtained for evaluation of the plasma concentration versus time profiles and pharmacokinetic/pharmacodynamic evaluations. The Sponsor plans to perform a population pharmacokinetic analysis across all paliperidone palmitate studies.

Efficacy:

Efficacy variables included the PANSS total score; PANSS Positive, Negative, and General Psychopathology subscales; PANSS factor scores according to Marder et al.; Personal and Social Performance Scale (PSP); and Clinical Global Impression Scale - Severity (CGI-S). The primary efficacy end point was the change from baseline to end point (Day 92 or last post baseline double-blind assessment) in PANSS total score. Secondary end points were changes from baseline to end point in PSP and CGI-S scales. Other efficacy end points included changes from baseline to end point for the positive, negative and general psychopathology PANSS subscale scores and PANSS factor scores, the change from baseline to each post baseline assessment time point for the PANSS total score, onset of therapeutic effect, and the treatment responder rate.

Safety: Safety was based on the incidence, severity, and relationship of treatment-emergent adverse events and on changes from baseline in clinical laboratory tests (including prolactin), vital sign measurements, ECGs, body weight and body mass index (BMI), physical examinations, and extrapyramidal symptom (EPS) scale scores. Investigator evaluation of the injection site was performed. Subject evaluation of injection site pain and injection pain were done using a visual analog scale (VAS).

Other: The Healthcare Resource Use Questionnaire (HRUQ) was used to collect information on hospitalization not required by the protocol, emergency room visits without hospitalization, day or night clinic stays, and outpatient treatment, as well as information on subjects' daily living; data from this questionnaire will be summarized in a separate report.

Statistical Methods: Primary and secondary efficacy analyses were performed for the primary efficacy analysis set using the last observation carried forward (LOCF) approach. For the primary end point (change in PANSS total score from baseline to last post-randomization assessment in double-blind period), the least squares (LS) means were estimated and compared between the active treatment group versus placebo using an analysis of covariance (ANCOVA) model with treatment and country as factors and baseline PANSS total score as a continuous covariate. The overall type I error rate for testing all paliperidone palmitate dose groups versus placebo was controlled at the 2-sided 0.05 level, separately, for the family of primary efficacy hypotheses and for the family of hypotheses for the secondary efficacy end points.

A closed testing procedure using Dunnett's test was used to adjust for multiple comparisons in testing the 3 paliperidone palmitate doses against placebo for the primary efficacy variable (change in PANSS total score at end point). Unadjusted 95% confidence intervals were presented for the difference in LS mean change between each paliperidone palmitate treatment group and placebo. A dose-response comparison was performed using pairwise comparisons between the 3 active doses, each at the 5% significance level with no adjustment for multiplicity and using the same model as for the primary efficacy analysis. Change from baseline over time (observed case) was explored using longitudinal mixed effects models with time, treatment, and country as factors and baseline score as a covariate. Terms for the treatment-by-country and treatment-by-baseline PANSS total score interactions were included in the ANCOVA model for the primary end point; if either term was statistically significant at the predefined 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. If the results were positive for one or more paliperidone palmitate dose groups on the primary end point, the secondary variable (change in PSP score at end point) again used the closed testing procedure with Dunnett's test in order to control the type I error when comparing each paliperidone palmitate dose group that was found superior in the primary efficacy variable analysis with placebo. An additional analysis of the secondary variables, the change from baseline to end point (LOCF) in the PSP and CGI-S scores, was performed using the Bonferroni-Holm step-down testing procedure.

The number and percentage of subjects with treatment-emergent adverse events were summarized overall, by severity, and by relationship to treatment. 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 identified 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

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evaluation of injection site pain and injection pain.

SUMMARY - CONCLUSIONS

Results are presented for the primary efficacy analysis set unless otherwise stated. The percentage of subjects in the paliperidone palmitate treatment groups who received all 4 injections of study medication ranged from 57% to 64% and was 43% in the placebo group. The completion rates were higher for the paliperidone palmitate 25, 50 and 100 mg eq. groups (53, 54 and 57%, respectively) than for the placebo (38%) group. Lack of efficacy was the most common reason for discontinuation. In total, 25% of subjects discontinued for lack of efficacy (35% in the placebo group, 24% in the paliperidone palmate 25 mg eq. and 50 mg eq. groups, and 16% in the paliperidone palmitate 100 mg eq. group).

DEMOGRAPHIC AND BASELINE CHARACTERISTICS: The double-blind treatment groups were well matched with respect to demographic and baseline disease characteristics and psychiatric history. The 514 subjects who comprised the intent-to-treat analysis set were mainly male (67%), racially diverse (67% white, 29% black, 4% other races), and predominately between the ages of 26 and 50 years. All subjects had a primary DSM-IV diagnosis of schizophrenia and were severely ill as indicated by a mean PANSS score of 90.8 at randomization.

PHARMACOKINETIC RESULTS: Dose-proportionality was observed between the 25 and 50 mg eq. dose. The 100 mg eq. dose resulted in less than a dose-proportional increase in plasma concentrations.

The median inter-subject variability in the observed plasma concentrations from Day 36 onwards was approximately 70%, irrespective of dose. The estimated intra-subject % coefficient of variation (CV) was 44% for the predose plasma concentrations from Day 36 onwards and 46% for the observed maximum plasma concentration (approximately 14 days after paliperidone palmitate injection). The within-subject CV after administration of paliperidone palmitate is similar to the within-subject CV for the PK parameters at steady state (AUC_{τ} and C_{max}) after paliperidone ER administration which was estimated to be less than or equal to 35%.

The median paliperidone plasma concentrations prior to Day 36 were lower in subjects with high baseline BMI (≥ 25 kg/m^2) compared to subjects with lower baseline BMI (<25 kg/m^2) for all treatment groups

EFFICACY RESULTS: Based on the LOCF analysis of the primary efficacy parameter with a closed testing procedure using Dunnett's test to control for multiplicity, adult subjects with schizophrenia achieved an improvement in the PANSS total score with all doses of paliperidone palmitate that was statistically significantly greater than that seen in subjects receiving placebo (25 mg eg.: p=0.015; 50 mg eg.: p=0.017; 100 mg eg.: p<0.001); The mean (SD) change from baseline to end point (LOCF) in PANSS total score was –7.0 (20.07) in the placebo group, -13.6 (21.45) in the paliperidone palmitate 25 mg eq. group, -13.2 (20.14) in the paliperidone palmitate 50 mg eq. group, and -16.1 (20.36) in the paliperidone palmitate 100 mg eq. group, where decreases from baseline represent improvement.

A treatment-by-country interaction was significant at the 10% level for the primary efficacy results; this likely resulted from differences in baseline BMI distribution across countries. The dose response relationship showed a different profile by country, due in part to the lack of sample size balance across countries (South Africa [n=13], Bulgaria [n=37] and Romania [n=19] vs. Russia [n=161] and the U.S. [n=284]), and consequent greater random variation in the treatment effect for countries with smaller sample size. The dose response profile among subjects with normal BMI was more pronounced than that seen in the overweight/obese subjects. Mean improvements in the PSP score from baseline to end point were numerically better with paliperidone palmitate compared to placebo. However, these improvements were not statistically superior to placebo in any of active treatment groups. Significantly more subjects treated with paliperidone palmitate 25 mg eq. (46%; p=0.015) and 100 mg eq. (52%; p<0.001) obtained responder status (30% or larger decrease on PANSS total score) than with placebo (31%). The paliperidone palmitate 50 mg eq. group with 38% responders was numerically higher than placebo but did not achieve statistical superiority (p=0.271). Larger and statistically significant mean changes (improvement) from baseline to end point (LOCF) in the CGI-S were seen for all paliperidone palmitate treatment groups compared with placebo (25 mg eq., p=0.003; 50 mg eq., p=0.006; and 100 mg eq., p=0.002).

The paliperidone palmitate 25 mg eq., 50 mg eq, and 100 mg eq. groups were statistically significantly superior to the placebo group for both the positive (p<0.001, p=0.010, and p<0.001, respectively) and negative symptoms (p=0.003, 0.041, and 0.007, respectively). The improvement in uncontrolled hostility/excitement scores was statistically significantly greater in the paliperidone palmitate 50 mg eq. (p=0.013) and 100 mg eq. (p<0.001) groups compared with placebo, while the improvement in the anxiety/depression scores reached statistical significance in favor of the paliperidone palmitate 25 mg eq. (p=0.041) and 100 mg eq. (p<0.001) groups.

SAFETY RESULTS: Safety results are presented for the safety analysis set.

Overall, the safety and tolerability results were consistent with previous clinical studies involving paliperidone palmitate, and no new safety signals were detected.

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Overall Summary of Treatment-Emergent Adverse Events (TEAE) (Safety Analysis Set)

	Placebo (N=127) n (%)	R092670 25 mg eq. (N=130) n (%)	R092670 50 mg eq. (N=129) n (%)	R092670 100 mg eq. (N=131) n (%)	Total (N=517) n (%)
TEAE	92 (72)	98 (75)	85 (66)	86 (66)	361 (70)
Possibly related TEAE[a]	42 (33)	49 (38)	41 (32)	40 (31)	172 (33)
TEAE leading to death	1 (1)	0	0	1 (1)	2 (<1)
1 or more serious TEAE	23 (18)	18 (14)	17 (13)	11 (8)	69 (13)
TEAE leading to permanent stop	8 (6)	8 (6)	2 (2)	6 (5)	24 (5)

[a] Study drug relationships of possible, probable, and very likely are included in this category.

Two subjects died during the study (paliperidone palmitate 100 mg eq. group: completed suicide on Day 58, 22 days after the third injection of study medication; placebo group: subject died on Day 86 due to pancreatic carcinoma after receiving all 4 doses of study medication). The deaths were considered doubtfully or unlikely to be related to study treatment by the Sponsor. The incidences of serious adverse events and adverse events resulting in treatment discontinuation were lower among subjects receiving paliperidone palmitate compared to those treated with placebo. Most serious adverse events consisted of psychiatric disorders, mainly psychosis and exacerbation of schizophrenia.

Common treatment-emergent adverse events that occurred more frequently in subjects receiving paliperidone palmitate (25, 50, and/or 100 mg eq.) than in those treated with placebo (i.e., ≥3% difference) were agitation, somnolence, weight increase, dizziness, and dry mouth. Common treatment-emergent adverse events that occurred more frequently in the placebo group than in any of the paliperidone palmitate groups (i.e., ≥3% difference) were schizophrenia, insomnia, anxiety, psychotic disorder, and constipation.

An examination of adverse events of potential clinical importance revealed no reports of cerebrovascular disorders, tardive dyskinesia, seizure, ventricular tachycardia or fibrillation, hyperthermia, anaphylactic reaction, convulsion, or dermatologic events.

The incidence of treatment-emergent EPS-related adverse events overall was low. No subject in the paliperidone palmitate treated groups was discontinued for an EPS-related adverse event and none of the EPS-related adverse events reported in subjects receiving paliperidone palmitate were serious. 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.

Orthostatic changes in blood pressure and pulse rate occurred at a similar low rate in the placebo and paliperidone palmitate groups. Tachycardia or sinus tachycardia were reported in 2 subjects receiving paliperidone palmitate 25 mg eq. and 100 mg eq.

Paliperidone palmitate produced an increase in serum prolactin. Adverse events potentially related to increased prolactin levels were reported in 5 (1%) subjects receiving paliperidone palmitate (1 subject in paliperidone palmitate 50 mg eq. group, and 4 subjects in paliperidone palmitate 100mg eq. group) and in 1 (<1%) subject receiving placebo. All of these events were non-serious. Except for severe erectile dysfunction in one paliperidone palmitate 100 mg e.q. subject that caused early withdrawal, all of these events were mild or moderate in severity and did not result in treatment discontinuation.

Assessment of ECG data did not demonstrate evidence of increased cardiovascular risk with paliperidone palmitate at doses up to 100 mg eq. No subject who received paliperidone palmitate had a corrected QTcLD interval value >480 ms.

Mean body weight and BMI were increased during double-blind treatment with paliperidone palmitate. The mean weight increases at the end of the 13-week study in the paliperidone palmitate 25, 50, and 100 mg eq. groups were 0.4, 0.8, and 1.3 kg, respectively, compared with –0.5 kg for placebo-treated subjects. A clinically relevant weight increase of at least 7% relative to baseline was more common among subjects in the paliperidone palmitate groups (25 mg eq.: 6%; 50 mg eq.: 7%, 100 mg eq.: 11% vs 2% placebo). Based on mean changes from baseline to end point and the occurrence of treatment-emergent markedly abnormal values and adverse events related to abnormal findings, the effects of paliperidone palmitate on the results of chemistry (except for prolactin) 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.

Overall, local injection site tolerability was good. Occurrences of induration or swelling as assessed by investigators were infrequent, generally mild, and similar in incidence for the paliperidone palmitate and placebo groups.

CONCLUSION: Data from this Phase 3 clinical trial provides evidence for the efficacy of paliperidone palmitate in the treatment of subjects with schizophrenia. Doses of 25 mg eq., 50 mg eq., and 100 mg eq. were found to be effective based on clinically relevant and statistically significant improvement in total PANSS score and a lower rate of discontinuation for lack of efficacy. Although statistically significant changes in the PSP were absent in

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this particular study of paliperidone palmitate, global improvement was validated by strong favorable CGI change for each of the dose groups. Paliperidone palmitate was also safe and well tolerated at doses of 25 to 100 mg eq. i.m. in gluteal administration. Other than for those few events specifically related to route of administration, no new adverse event findings relative to oral paliperidone ER were identified. The lack of evidence of clinically significant QTc prolongation with paliperidone palmitate at doses up to 100 mg eq. i.m., and no subject showing a maximum QTcLD value >480 ms or a maximal change in QTcLD >60 ms at any timepoint during the study may suggest a favorable cardiovascular profile for paliperidone palmitate.

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