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.: CR002353

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Response Study to Evaluate the Efficacy and Safety of 3 Fixed Doses (50 mg eq., 100 mg eq., and 150 mg eq.) of Paliperidone Palmitate in Subjects With Schizophrenia

Coordinating Investigator: David Brown, M.D., Community Clinical Research, Austin, TX, U.S.

Publication (Reference): None.

Study Period: 30 June 2005 to 20 June 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 (monthly) intervals after 2 initial doses given 1 week apart, as compared with placebo in 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, 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, and to explore healthcare resource utilization information in a select group of subjects.

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 Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) diagnosis of schizophrenia for at least one year before screening and severely symptomatic (PANSS total score between 70 and 120, inclusive at screening and at baseline). 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 [50, 100, or 150 mg eq.] or placebo). Each subject received an i.m. injection in the gluteal muscle 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, 2 or more hours 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 376 subjects (94 in each treatment group) were planned for enrollment. Of the 473 subjects who were screened, 388 were eligible for randomization to double-blind treatment. In the course of the study, a mismatch occurred between some of the medication kits to be assigned and the originally loaded randomization file. The impact of this error was that a total of 88 subjects in the placebo and paliperidone palmitate 150 mg eq. groups were either assigned medication that did not match their original randomization group or were erroneously switched to a different medication at some time during the study. This resulted in fewer subjects treated throughout the double-blind period with paliperidone palmitate 150 mg eq. (N=30), and more subjects treated throughout the double-blind period with placebo (N=135), than planned. The number of eligible subjects randomly assigned and treated with paliperidone palmitate 50 mg eq. or 100 mg eq. was 94 and 97, respectively. Each of the 387 randomized subjects who received study medication were analyzed for safety, including the 31 subjects who received mixed double-blind treatment with paliperidone palmitate 150 mg eq. and placebo during the double-blind period. As specified in the statistical analysis plan prior to database lock, the 31 subjects who were switched from active to placebo treatment or vice versa for one or more doses were excluded from the primary efficacy analysis set. A total of 349 randomized subjects received study medication, had baseline and post baseline efficacy assessments, and received the same study treatment for the duration of the study (primary efficacy analysis set).

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 before screening and a PANSS total score between 70 and 120, inclusive at

SYNOPSIS (CONTINUED)

screening and at baseline. 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 (F013 formulation) fixed doses of 50-, 100-, and 150-mg eq. injectable suspension administered by i.m. injection into the gluteal muscle. The following lot numbers were used: 50 mg eq.: 05C24, 05E12, 05I07; 100 mg eq.: 05C24; 150 mg eq.: 05C24.

Subjects without documented previous exposure to risperidone or paliperidone underwent an oral tolerability test using a daily dose of extended-release (ER) OROS® paliperidone 3 mg/day (lot numbers MV0332891, 0426909) for 4 days before being randomly assigned to study treatment.

Reference Therapy, Dose and Mode of Administration, Batch No.: Matching placebo 50, 100, and 150 mg eq. injectable emulsion (20% Intralipid) administered by i.m. injection into the gluteal muscle (lot number: 05D19). The volume of placebo was matched to the volumes for each of the 3 active doses of study drug.

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-Severity scale (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, 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, physical examinations, body weight and body mass index (BMI), ECGs, and extrapyramidal symptom (EPS) scale scores. Investigator evaluation of the injection site for redness, pain, swelling, and induration was performed using a 4-point scale and subject evaluation of injection site pain and injection pain was done using a visual analog scale (VAS).

Other: The Brief Assessment of Cognition in Schizophrenia (BACS) was used as an exploratory tool to measure cognitive deficits in a subset of native English-speaking subjects at centers in the United States. 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) adjusted means were estimated and compared between each 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.

A stepwise procedure was used to identify effective doses while adjusting for multiplicity in testing the paliperidone palmitate doses versus placebo for the primary efficacy variable (change in PANSS total score at end point). In Step 1, a closed testing procedure using Dunnett's test was used to identify effective doses in testing the paliperidone palmitate 50 mg eq. and 100 mg eq. doses against placebo. The paliperidone palmitate 150 mg eq. dose was to be tested against placebo at the 5% level only if both paliperidone palmitate 50 mg eq. and 100 mg eq. doses were significantly different from placebo in Step 1. Otherwise, the testing was stopped at Step 1. The nominal 95% confidence intervals without adjustment for multiplicity 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) in PANSS total score was explored using longitudinal mixed effects models with time, treatment, and country as factors and baseline PANSS total 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

SYNOPSIS (CONTINUED)

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.

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 site pain and injection pain.

SUMMARY - CONCLUSIONS

Results are presented for the primary efficacy analysis set unless otherwise stated. In the safety analysis set, the percentage of subjects in the paliperidone palmitate treatment groups who received all 4 injections of study medication ranged from 47% to 55% and was 41% in the placebo group. Among all randomized subjects, completion rates were higher for the paliperidone palmitate 50 mg eq. and 100 mg eq. groups (50% and 55%) than for the placebo (38%) or paliperidone palmitate 150 mg eq. groups (40%). Lack of efficacy was the most common reason for discontinuation. In total, 30% of subjects discontinued for lack of efficacy (35% in the placebo group, 27% in the paliperidone palmitate 50 mg eq. group, 27% in the paliperidone palmitate 100 mg eq. group, and 43% in the paliperidone palmitate 150 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 349 subjects who comprised the primary efficacy analysis set were mainly male (69%), racially diverse (40% white, 39% black, 21% other races), and predominantly 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 total score of 91.1 at baseline. There were notable differences between countries with respect to BMI and baseline disease severity, with subjects enrolled at centers in the U.S. being more likely to be overweight/obese (i.e., BMI $\geq$25 kg/m^2) than those from centers in other countries and have greater psychopathology as reflected by higher mean PANSS total scores at baseline.

PHARMACOKINETIC RESULTS: The mean and median paliperidone plasma concentrations for the paliperidone palmitate 100 mg eq. and 150 mg eq. treatment groups were higher than those for the 50 mg eq. treatment group at all time points from Day 8 onward. The increase, however, appeared to be less than dose proportional. The data from the 150 mg eq. treatment group should be interpreted with caution given the limited number of observations for this treatment group due to the medication kit allocation error.

The median paliperidone plasma concentrations prior to Day 36 were lower in subjects with high BMI ($\geq$25 kg/m^2) compared with subjects with low BMI ($<$25 kg/m^2), except for the 150 mg eq. treatment group at Day 22. The median inter-subject variability in the observed plasma concentrations from Day 36 onwards was approximately 67%, irrespective of dose. The estimated intra-subject coefficient of variation was 25% for the predose plasma concentrations from Day 36 onwards and 32% for the observed maximum plasma concentration.

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 the 100 mg eq. dose of paliperidone palmitate that was statistically significantly greater than that seen in subjects receiving placebo (p=0.019); the improvement in the 50 mg eq. group did not reach statistical significance (p=0.193). Since only the paliperidone palmitate 100 mg eq. group reached statistical significance, no statistical comparison was performed for the 150 mg eq. group as prespecified. The mean (SD) change from baseline to end point (LOCF) in PANSS total score was –4.1 (21.01) in the placebo group, –7.9 (18.71) in the paliperidone palmitate 50 mg eq. group, -11.0 (19.06) in the paliperidone palmitate 100 mg eq. group, and -5.5 (19.78) in the paliperidone palmitate 150 mg eq. group, where decreases from baseline represent improvement.

Treatment-by-baseline PANSS total score and treatment-by-country interactions were significant at the 10% level for the primary efficacy results; these likely resulted from differences in baseline disease severity and BMI distribution across countries. 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 statistically significantly larger in the paliperidone palmitate 50 mg eq. (p=0.004) and 100 mg eq. (p<0.001) groups compared to placebo.

Significantly more subjects treated with paliperidone palmitate 100 mg eq. (39%; p=0.012) obtained responder status (30% or larger decrease on PANSS total scores) than with placebo (24%). The paliperidone palmitate 50 mg eq. group with 34% responders was numerically higher than placebo but did not achieve statistical significance (p=0.076). Larger mean changes (improvement) from baseline to end point (LOCF) in the CGI-S

SYNOPSIS (CONTINUED)

were seen for the paliperidone palmitate 50 mg eq. and 100 mg eq. treatment groups compared with placebo, and the difference was significant for the 100 mg eq. group (p=0.010) but not for the 50 mg eq. group (p=0.069).

The paliperidone palmitate 100 mg eq. group was statistically significantly superior to placebo for the mean change from baseline to end point (LOCF) in the PANSS positive symptoms (p=0.012), negative symptoms (p=0.017), disorganized thoughts (p=0.032), uncontrolled hostility/excitement (p=0.027), and anxiety/depression (p=0.009) factor scores.

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.

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

	Placebo (N=135) n (%)	R092670 50 mg eq. (N=94) n (%)	R092670 100 mg eq. (N=97) n (%)	R092670 150 mg eq. (N=30) n (%)	R092670 150 mg eq./Pbo (N=31) n (%)
TEAE	103 (76)	70 (74)	79 (81)	25 (83)	27 (87)
Possibly related TEAE [a]	55 (41)	46 (49)	45 (46)	21 (70)	20 (65)
TEAE leading to death	0	0	0	0	0
1 or more serious TEAE	25 (19)	16 (17)	10 (10)	6 (20)	5 (16)
TEAE leading to permanent stop	13 (10)	8 (9)	2 (2)	2 (7)	0

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

There were no deaths in this study. 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 50 and 100 mg eq. than in those treated with placebo (i.e., ≥3% difference) were headache, dizziness, insomnia, vomiting, abdominal discomfort, constipation, injection site pain, injection site induration, pain in extremity, weight increased, blood pressure increased, urinary tract infection, auditory hallucination, and abdominal pain upper.

An examination of adverse events of potential clinical importance revealed no reports of cerebrovascular disorders, ventricular tachycardia or fibrillation, or anaphylactic reaction.

The incidence of treatment-emergent EPS-related adverse events overall was low. The one report of tardive dyskinesia in this study occurred in a subject with a history of this adverse event, and was not considered serious or treatment limiting. No subject was discontinued for an EPS-related adverse event, and other than a single report of akathisia in the paliperidone palmitate 150 mg eq. group, 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, and tachycardia, sinus tachycardia, or tachyarrhythmia were reported for a similar number of subjects receiving paliperidone palmitate and placebo (n=2 each).

Paliperidone palmitate produced an increase in serum prolactin. Adverse events potentially related to increased prolactin levels were reported in 2 (1%) subjects receiving paliperidone palmitate 50, 100, or 150 mg eq. and in 2 (1%) subjects receiving placebo. All of these events were non-serious, 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 150 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 50, 100, and 150 mg eq. groups were 1.0, 1.5, and 0.9 kg, respectively, compared with –0.7 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 (50 mg eq.: 12%; 100 mg eq.: 10%, 150 mg eq.: 4%). 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 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 in the gluteal muscle was good. While adverse event reports of injection

SYNOPSIS (CONTINUED)

site pain and injection site induration occurred at higher rates in the paliperidone palmitate 100 and 150 mg eq. groups compared with placebo, none of these events were serious or resulted in treatment discontinuation.

Of the treatment-emergent adverse events identified to be of clinical interest among subjects receiving paliperidone palmitate, the Sponsor assessed 25 as related or possibly related to study treatment following medical review.

CONCLUSION: This Phase 3 clinical trial provided evidence for the efficacy of paliperidone palmitate 100 mg eq. in reducing the severity of psychopathology and improving social functioning among subjects with schizophrenia. Paliperidone palmitate 50 mg eq. was numerically superior to placebo for the primary efficacy end point, but the difference was not statistically significant. Paliperidone palmitate was safe and well tolerated at doses up to 100 mg eq. and in the limited number of subjects who received the 150 mg eq. dose.

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