SYNOPSIS CR012289

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Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Name of Finished Product	To be decided
Name of Active Ingredient(s)	Paliperidone Palmitate

Protocol No.: CR012289

Title of Study: A Randomized, Double-Blind, Parallel-Group, Comparative Study of Flexible Doses of Paliperidone Palmitate and Flexible Doses of Risperidone Long-Acting Intramuscular Injection in Subjects With Schizophrenia

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Publication (Reference): None

Study Period: 26 March 2007 to 01 July 2009

Phase of Development: 3

Objectives: The primary objective of this study was to demonstrate that paliperidone palmitate is not less effective than RISPERDAL CONSTA. The safety and the tolerability of paliperidone palmitate in the treatment of schizophrenia were also assessed.

Secondary objectives were to assess the global improvement in severity of illness associated with the use of paliperidone palmitate compared with RISPERDAL CONSTA; to explore the effects on personal and social functioning associated with the use of paliperidone palmitate compared with RISPERDAL CONSTA; and to explore the effects of paliperidone palmitate compared with RISPERDAL CONSTA on improvement in sleep quality and reduction of daytime sleepiness.

Methods: This was a randomized, double-blind, double-dummy, active-controlled, parallel-group, multicenter comparative study consisting of 2 periods: a 7-day screening or washout period and a 13-week double-blind treatment period. After completing the screening/washout period, subjects were randomly assigned in a 1-to-1 ratio to receive either paliperidone palmitate or RISPERDAL CONSTA for 13 weeks.

Subjects who were randomly assigned to the paliperidone palmitate group received 4 injections of paliperidone palmitate (150 mg eq. in the deltoid muscle on Day 1, 100 mg eq. in the deltoid muscle on Day 8, and 50 to 150 mg eq. in the deltoid or gluteus muscle on Days 36 and 64); 6 injections of RISPERDAL CONSTA placebo (in the gluteus muscle on Days 8, 22, 36, 50, 64, and 78); mandatory oral placebo supplementation on Days 1 to 28; and optional oral placebo supplementation thereafter with dose increases.

Subjects who were randomly assigned to the RISPERDAL CONSTA group received 6 injections of RISPERDAL CONSTA (25 mg on Days 8 and 22, 25 or 37.5 mg on Days 36 and 50, and 25 to 50 mg on Days 64 and 78, all in the gluteus muscle); 4 injections of paliperidone palmitate placebo (in the deltoid muscle on Days 1 and 8, and in the deltoid or gluteus muscle on Days 36 and 64); mandatory oral risperidone supplementation on Days 1 to 28 (1 to 6 mg/day); and optional oral risperidone supplementation (1 to 2 mg/day) thereafter with dose increases.

End-of-study (EOS) assessments were done 2 weeks after the last dose of study drug (Day 92) for all subjects completing the study. For subjects withdrawing from the study early, early withdrawal assessments (same as EOS assessments) were done at the time of withdrawal.

A blood sample for pharmacogenomic research was collected from subjects who gave consent. Participation in pharmacogenomic research was optional. Blood samples were also collected for (population) pharmacokinetic (PK) analysis.

Number of Subjects (planned and analyzed): Originally, the planned enrollment was 700 subjects, and the initial doses of paliperidone palmitate were: Day 1, 150 mg eq. in the deltoid muscle; Day 8, 50 mg eq. in the deltoid or gluteus muscle. Based on the results of other studies that became available after this study was initiated, an enhanced initiation dosing regimen for paliperidone palmitate (dose of 100 mg eq. on Day 8; injections in the deltoid muscle on both Day 1 and Day 8) was implemented with the approval of protocol Amendment INT-4. At that time, 298 subjects had been enrolled. The planned enrollment was then changed to 700 subjects enrolled after approval of Amendment INT-4. Subsequently, an interim analysis was performed for sample size reestimation, and the planned enrollment was increased to 871 subjects enrolled after approval of Amendment INT-4. A total of 1400 subjects were screened for the study, 1220 subjects were randomly assigned to a treatment group (607 to paliperidone palmitate and 613 to RISPERDAL CONSTA), and 1214 subjects (606 and 608, respectively) received at least 1 dose of double-blind medication and were included in the safety analysis set. The latter included 919 subjects enrolled after approval of Amendment INT-4. The intent-to-treat (ITT) analysis set included 913 subjects, and the per-protocol analysis set included 765 subjects.

Diagnosis and Main Criteria for Inclusion: Men and women who were 18 years of age or older, who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for schizophrenia for at least 1 year, and who had a total Positive and Negative Syndrome Scale for Schizophrenia (PANSS) score of 60 to 120, inclusive.

Test Product, Dose and Mode of Administration, Batch No.: Paliperidone palmitate was supplied as 50, 100, and 150 mg eq. injectable suspensions. The batch/lot numbers for all dose strengths were 06K22/F13, 07D23/F13, and 8GB4G/I/J.

Reference Therapy, Dose and Mode of Administration, Batch No.: RISPERDAL CONSTA was supplied as risperidone depot microspheres in 25, 37.5, and 50 mg injectable dose strengths. The batch/lot numbers for all dose strengths were 164-3749/0775, 164-3714/0775, 164-3714/3796, 164-3749/3795/3796.

The sponsor supplied matching paliperidone palmitate placebo and RISPERDAL CONSTA placebo injections, risperidone tablets for oral supplementation, matching placebo tablets for oral supplementation, and paliperidone extended-release tablets for oral tolerability testing.

Duration of Treatment: The duration of the double-blind treatment period was 13 weeks.

Criteria for Evaluation: Pharmacokinetics: Venous blood samples of 5 mL were collected for studying paliperidone concentration-time profiles. PK samples were collected before the injection of study drug (predose) at Visits 2 (baseline), 4, 6, 7, 8, 9, 10, and about the same time as previous injection at Visits 3, 5, and 11.

Efficacy: Efficacy assessments included the PANSS, Clinical Global Impression-Severity (CGI-S) scale, Personal and Social Performance (PSP) scale, Schedule for Deficit Syndrome (SDS), Pittsburgh Sleep Quality Index (PSQI), and Sleep Visual Analog Scale (VAS).

Safety: Safety was evaluated based on the changes from baseline in clinical laboratory testing (hematology, serum chemistry, urinalysis); vital sign measurements; measurements of weight gain; electrocardiograms (ECGs); monitoring for adverse events, including extrapyramidal symptoms (EPS) using the Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and Simpson-Angus Rating Scale (SAS); evaluation of the injection site and subject's assessment of injection pain; and Global Impressions of Sexual Function (GISF).

Statistical Methods: Primary endpoint: The primary efficacy endpoint was the change in the PANSS total score from baseline to the last postrandomization assessment in the double-blind treatment period. The primary population for the efficacy analyses was the per-protocol analysis set. An analysis of covariance (ANCOVA) model with factors for treatment and country, and baseline PANSS total score as a covariate, was used to analyze the primary endpoint. To take into account the sample size reestimation that was performed, the method described by Proschan (Proschan 2003) and Liu (Liu 2008) was used to determine the point estimate and the 95% confidence interval (CI)

for the difference between RISPERDAL CONSTA and paliperidone palmitate. Noninferiority of paliperidone palmitate to RISPERDAL CONSTA was to be concluded if the lower limit of the 2-sided 95% CI exceeded -5. Additional analyses with the ITT analysis set were performed to evaluate the consistency of the results.

Secondary endpoints: The changes from baseline for CGI-S, PSP score, SDS global categorization, PSQI score, sleep VAS, and PANSS factors and subscales were analyzed using an ANCOVA model with factors for treatment and country and baseline score as a covariate. PSP responders (ie, PSP score of 71 or greater at end point) and responder rates (ie, percentage of subjects with a 30% or more reduction in PANSS total score) were analyzed using a Mantel-Haenszel test.

Safety results: Descriptive statistics and frequencies distributions were used to summarize the results of most of the safety evaluations. The change from baseline in GISF was analyzed separately by sex using an ANCOVA model with factors for treatment and country, and baseline value as a covariate.

RESULTS: Of the subjects randomly assigned to a treatment group, 75% in the paliperidone palmitate group and 77% in the RISPERDAL CONSTA group completed the study. The most common reasons for early withdrawal were withdrawal of consent (9% and 8%, respectively) and lack of efficacy (7% in each group). In the per-protocol analysis set, 84% of the subjects in the paliperidone palmitate group and 85% of those in the RISPERDAL CONSTA group completed the study. Similar percentages of subjects (5% or 6%) in the 2 groups were withdrawn due to withdrawal of consent or lack of efficacy.

A majority of subjects in this study were male, white, between the ages of 26 and 50 years, current smokers, and in the BMI categories of overweight or obese. Most had a diagnosis of paranoid schizophrenia, had moderate or marked severity of illness based on CGI-S, and had been hospitalized at least twice. The 2 treatment groups were comparable with respect to baseline characteristics.

EFFICACY RESULTS: In the per-protocol analysis set, the mean change from baseline to end point in the PANSS total score was -18.6 in the paliperidone palmitate group and -17.9 in the RISPERDAL CONSTA group. Using LOCF, the weighted estimate of the treatment difference was 0.4 (95% CI: -1.62, 2.38). The lower limit of the 95% CI was greater than the prespecified noninferiority margin of -5 and, therefore, paliperidone palmitate was shown to be noninferior to RISPERDAL CONSTA. The results for the ITT analysis set were consistent with those for the per-protocol analysis set.

A test for heterogeneity of treatment effect revealed a statistically significant interaction between treatment and baseline BMI group (normal, overweight, and obese). Efficacy was comparable for the 2 treatments in normal and overweight subjects. In obese subjects, the treatment effect was smaller with paliperidone palmitate than with RISPERDAL CONSTA (difference in LS mean changes of -2.2). However, the overall degree of clinical improvement in obese subjects treated with paliperidone palmitate was considered clinically meaningful.

Results for most of the secondary efficacy variables (ITT analysis set) are presented in the following table.

Summary of Results for Selected Secondary Efficacy Variables (ITT Analysis Set)

	Mean Change From Baseline to End Point		Difference in LS Mean Changes
Variable	Paliperidone Palmitate	RISPERDAL CONSTA	(95% CI)[a]
CGI-S Score	-0.9	-0.9	0.0 (-0.07, 0.17)
PSP Score	8.5	8.8	0.2 (-1.22, 1.69)
SDS Rating	-1.9	-1.8	0.0 (-0.36, 0.38)
PSQI Score	-2.3	-2.4	-0.2 (-0.66, 0.34)
Quality of Sleep (VAS)	8.2	7.5	0.1 (-3.13, 3.33)
Daytime Drowsiness (VAS)	-7.2	-5.1	1.2 (-1.55, 3.94)

[a] RISPERDAL CONSTA minus paliperidone palmitate

In addition, >91% of the subjects in each group had PSP scores <71 at baseline. At end point, the percentages decreased to 68.1% in the paliperidone palmitate group and 64.2% in the RISPERDAL CONSTA group. The percentage of subjects who were considered nondeficit using the SDS global categorization was similar in the paliperidone palmitate and RISPERDAL CONSTA groups at baseline (23.1% and 24.2%, respectively) and at end point (28.3% and 30.4%, respectively). At end point, 53.0% of the subjects in the paliperidone palmitate group and 48.5% of those in the RISPERDAL CONSTA group achieved a 30% or higher reduction in PANSS total score. The

point estimate (95% CI) of the relative risk (ie, the ratio of the probability of achieving at least a 30% reduction in PANSS total score at end point with paliperidone palmitate relative to RISPERDAL CONSTA) was 1.1 (0.97, 1.25). Thus, the results of the secondary efficacy variables were similar for the 2 treatment groups, supporting the comparable efficacy of paliperidone palmitate and RISPERDAL CONSTA.

PHARMACOKINETIC RESULTS: For subjects randomly assigned to receive paliperidone palmitate, plasma concentrations during the recommended initiation regimen (150 mg eq. on Day 1 and 100 mg eq. on Day 8, both administered in the deltoid muscle) were consistent with historical data. The mean plasma paliperidone concentrations for the subgroups that received the highest possible doses (150-100-100-100 mg eq. and 150-100-100-150 mg eq.) rose gradually from Day 1 to approximately 20 ng/mL on Day 8 and approximately 35 ng/mL by Day 15, and subsequently decreased to approximately 18 ng/mL on Day 36 when the next monthly injection was administered. Mean plasma paliperidone concentrations on Day 15 and Day 36 were approximately 5 ng/mL lower when administering a 50 mg eq. dose on Day 8. The plasma concentration-time profiles for paliperidone, from Day 4 onwards, were comparable across all BMI categories for different subgroups (based on the paliperidone palmitate dose strength of each injection).

For subjects randomly assigned to receive RISPERDAL CONSTA, plasma concentrations of the active moiety were consistent with historical data but regular changes in dose limit the interpretation, as steady state for the changed regimen may not have been reached in some subjects.

Overall, when including all possible dose combinations, the plasma exposure (active moiety) in subjects randomly assigned to receive RISPERDAL CONSTA was similar to the paliperidone exposure in subjects randomly assigned to receive paliperidone palmitate.

SAFETY RESULTS: Treatment-emergent adverse events (TEAEs) occurred in 57.9% of the subjects in the paliperidone palmitate group and 52.8% of those in the RISPERDAL CONSTA group. Psychiatric disorders and general disorders/administration site conditions occurred in higher percentages of subjects in the paliperidone palmitate group than the RISPERDAL CONSTA group. The most commonly occurring adverse events (occurring in ≥5% of the subjects in either treatment group) were insomnia (paliperidone palmitate = 9.4%; RISPERDAL CONSTA = 6.7%), headache (7.1% and 7.2%, respectively), somnolence (5.6% and 3.9%, respectively), and injection site pain (5.1% and 0.8%, respectively). With the exception of injection site pain, the percentages of subjects with individual adverse events (preferred terms) were similar in the paliperidone palmitate and RISPERDAL CONSTA groups.

There were 3 deaths: 2 in subjects in the paliperidone palmitate group (suicide and unknown cause) and 1 in a subject in the RISPERDAL CONSTA group (post-study pulmonary embolism). None of these deaths was considered related to study treatment by the investigator. Serious TEAEs occurred in 6.8% of the subjects in the paliperidone palmitate group and 4.8% of those in the RISPERDAL CONSTA group. TEAEs leading to discontinuation of study drug occurred in 3.0% and 1.6% of the subjects, respectively. In the paliperidone palmitate group, schizophrenia was the most common SAE (2.5%) and the TEAE most often leading to discontinuation (0.5%).

The incidence of treatment-emergent EPS-related adverse events was low. Events grouped under the term hyperkinesia were the most frequently reported EPS-related adverse events and were reported at similar incidences in the paliperidone palmitate group (4.8%) and the RISPERDAL CONSTA group (4.9%). One subject in each group experienced tardive dyskinesia. The frequency of use of anticholinergic medications was higher in the paliperidone palmitate group (11%) than the RISPERDAL CONSTA group (8%).

Consistent with the known pharmacology of risperidone and paliperidone, mean increases in prolactin levels were observed in both treatment groups; the increases were larger in the paliperidone palmitate group than in the RISPERDAL CONSTA group. The percentages of subjects with treatment-emergent prolactin values above the normal range were similar in the 2 groups. The incidence of potentially prolactin-related adverse events was low (≤2% in each group).

At the end of the 13-week study, there was a mean increase in weight of 1.1 kg in the paliperidone palmitate group and 1.0 kg in the RISPERDAL CONSTA group, a mean increase in BMI of 0.4 and 0.3 kg/m^2, respectively, and a mean increase in waist circumference of 0.7 and 0.5 cm, respectively.

Occurrences of induration, redness, or swelling at the injection site as assessed by the investigators were infrequent, generally mild, and similar in incidence for the paliperidone palmitate and RISPERDAL CONSTA groups. Mean values for subject ratings of injection pain were higher, indicative of greater pain, for injections of paliperidone palmitate than for injections of RISPERDAL CONSTA.

STUDY LIMITATIONS: Because this study was designed to demonstrate the noninferiority of paliperidone palmitate to RISPERDAL CONSTA, and included no placebo group, assay sensitivity can only be inferred based on the known efficacy of RISPERDAL CONSTA. This study investigated the efficacy and safety of paliperidone palmitate over 13 weeks and does not provide information about longer-term efficacy and safety.

CONCLUSION: The results from this study demonstrated that paliperidone palmitate has comparable efficacy to RISPERDAL CONSTA in the treatment of subjects with schizophrenia. Additionally, the changes from baseline in CGI-S, PSP score, SDS global categorization, PSQI score, sleep VAS, and PANSS factors and subscales were similar in the 2 treatment groups, further supporting the comparable efficacy of paliperidone palmitate to RISPERDAL CONSTA in the treatment of subjects with schizophrenia. Paliperidone palmitate was generally safe and tolerable in these subjects.

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