CLINICAL STUDY REPORT SYNOPSIS

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Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development	
Name of Finished Product	Paliperidone palmitate	
Name of Active Ingredient	6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-ethyl]-6,7,8,9-tetrahydro-2-methyl-4-oxo-4H-pyridol[1,2-*a*]pyrimidin-9-yl hexadecanoate	

Protocol No.: CR002350

Title of Study: A Randomized, Crossover Study to Evaluate the Overall Safety and Tolerability of Paliperidone Palmitate Injected in the Deltoid or Gluteus Muscle in Subjects With Schizophrenia

Coordinating Investigator: Jean-Pierre Lindenmayer, M.D. - Manhattan Psychiatric Center, 163 West 125th Street, New York, NY; U.S.A.

Publication (Reference): None

Study Period: 6 July 2005 to 21 November 2006 | **Phase of Development:** 3

Objectives: The primary objectives of this study were to evaluate the safety and tolerability of: (a) Initiating treatment in the deltoid injection site with any of 3 doses of paliperidone palmitate (50, 75, and 100 mg eq.) in subjects with schizophrenia. The evaluation was based on a between-group comparison of the incidence of systemic treatment-emergent adverse events (TEAEs) occurring between the first injection and Week 13 in subjects receiving deltoid injections vs. subjects receiving gluteal injections. (b) Switching from the gluteal to the deltoid (GD) injection site and from the deltoid to the gluteal (DG) injection site at therapeutic plasma concentrations with 3 doses of paliperidone palmitate (50, 75, and 100 mg eq.) in subjects with schizophrenia. The evaluation was based on a within-subject comparison of the incidence of systemic TEAEs occurring during the last 2 injection intervals (8 weeks) of each treatment period (first injection to Week 13 [Period 1] and Week 13 to Week 25 [Period 2]) for each treatment sequence (DG and GD). Secondary objectives of the study included: Exploration of the pharmacokinetics (PK) of paliperidone after i.m. administration of paliperidone palmitate using the injection site as a covariate and the relationship between its PK and the results of safety parameters of interest; evaluation of the incidence of systemic TEAEs that occurred or worsened during the last 2 injection cycles of the study; assessment of the overall safety and tolerability of paliperidone palmitate; exploratory evaluations including the Medication Preference Questionnaire for Patients (MPQP). One unplanned exploratory analysis was performed: The influence of body mass index (BMI) on withdrawal rates and TEAEs was assessed in the DG and GD treatment-sequence groups.

Methodology: The study consisted of a screening period of no more than 7 days and a 25-week treatment period with a crossover of injection sites after the first 13 weeks. The screening period included up to 5 days for the washout of previous disallowed psychotropic medications and up to 4 days for oral tolerability testing with extended-release (ER) OROS® paliperidone, if necessary. Washout and tolerability testing could overlap. During the treatment period, subjects were randomly assigned to 1 of 3 dose groups (50, 75, or 100 mg eq.) and to 1 of 2 treatment sequences. Subjects randomly assigned to Treatment Sequence GD received 4 i.m. gluteal injections of paliperidone palmitate (Days 1, 8, 36, and 64) followed by 3 i.m. deltoid injections of paliperidone palmitate (Days 92, 120, and 148); subjects randomly assigned to Treatment Sequence DG received 4 deltoid injections of paliperidone palmitate (Days 1, 8, 36, and 64) followed by 3 gluteal injections of paliperidone palmitate (Days 92, 120, and 148).

Number of Subjects (planned and analyzed): At least 240 subjects, 40 in each combination of dose and treatment sequence, were to be randomly assigned. A total of 290 subjects were screened and 252 were randomly assigned to treatment with approximately equal allocation ratios (40 to 46 subjects per group) in 6 treatment groups. In all, 249 subjects received at least 1 dose of study medication and were thus in the intent-to-treat (ITT) and safety analysis sets. A total of 185 subjects received at least 2 doses of study drug in each period and thus were in the matched intent-to-treat (MITT) analysis set. Both the ITT and MITT analysis sets were used for the primary safety and tolerability objectives. The MITT analysis set was used for the secondary safety and tolerability objective.

Diagnosis and Main Criteria for Inclusion: Men and women aged 18 years or older with a DSM-IV diagnosis of schizophrenia were eligible for enrollment in the study. Included subjects had a total PANSS score at screening of <70, a BMI of ≥17.0 kg/m², and were otherwise healthy based on medical history, physical examination, laboratory tests, and ECG.

Test Product, Dose and Mode of Administration, Batch No.: Paliperidone ER 3-mg tablets for oral

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administration, batch no. 0426909. Paliperidone palmitate 100mg eq./mL suspension for i.m. administration of 50, 75, or 100 mg eq., batch nos. 05C24/F013, 05E12/F13B, and 05I07/F13B.

Reference Therapy, Dose and Mode of Administration, Batch No.: None

Duration of Treatment: One-week screening, washout, and tolerability period followed by a 25-week double blind period.

Criteria for Evaluation:

Pharmacokinetics: Concentrations of paliperidone (R076477) in plasma were determined using a validated liquid chromatography/dual mass spectrometry method, with a target limit of quantification of 0.1 ng/mL. Venous blood samples were collected on Days 8, 36, 64, 71, 78, 92, 148, 155, and 162, and at End-of-Study/Early Withdrawal. At those visits where study drug was administered (Days 8, 36, 64, 92, and 148), PK samples were obtained before study drug administration (predose). A sparse blood sampling procedure was used while the subjects were receiving deltoid and gluteal injections to study the paliperidone concentration-time profile from each injection site.

Efficacy: The symptoms of schizophrenia were assessed using the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression-Severity (CGI-S) scale. These scales were used primarily to monitor the clinical status of subjects and not as an outcome measure.

Safety: Safety evaluations included adverse events (AEs), clinical laboratory tests, ECGs, vital signs, physical examination, extrapyramidal symptom (EPS) rating scales (Abnormal Involuntary Movement Scale, Barnes Akathisia Rating Scale, and Simpson and Angus Rating Scale), and evaluation of the injection site.

Pharmacogenomics: One 10 mL blood sample was collected from subjects who had given informed consent for this part of the study to allow for the tentative analysis of genes that may have influenced the PK, safety, or tolerability of paliperidone palmitate for the treatment of schizophrenia. No genes were genotyped during this study. Genotyping of any genes in the future will be reported separately. In addition, subjects were asked to consent to storage of a DNA sample for future testing of genes related to paliperidone under investigation in this clinical study or genes related to schizophrenia.

Statistical Methods:

Efficacy: Descriptive statistics on scores and changes from baseline were provided for each treatment group for PANSS and CGI-S assessments.

Safety: For the different dose groups, the point estimate and the 90% confidence interval (CI) for the difference in the incidence of systemic treatment-emergent AEs between injections in the deltoid and the gluteus muscle was calculated using the sample proportions and the corresponding variances. In addition, the difference in systemic treatment-emergent AEs that occurred or increased in severity at the end of the study was estimated using the sample proportions with the corresponding 90% CI. Treatment-emergent AEs that were related to EPS or that may have been associated with changes in glucose or prolactin levels were summarized by treatment group. The frequency of AEs related to the injection site (which were left out of the primary analysis) was tabulated by administration mode The change from baseline in body weight and BMI at each time point and at endpoint was summarized for each treatment sequence. Descriptive statistics were presented at each assessment point and at End-of-Study/Early Withdrawal for change from baseline in orthostatic measures, heart rate, and blood pressure. The effects of treatment on ECGs were evaluated using descriptive statistics and frequency tabulations. Descriptive statistics were provided for each laboratory analyte at baseline and at each scheduled time point. The MPQP was characterized descriptively on all randomized patients who consented to complete the questionnaire and in subgroups by country and by sex.

For the BMI exploratory analysis, 2 subgroups were defined: The “non-obese” category consisted of subjects with baseline BMI values <30 kg/m^2 and the “obese” category consisted of subjects with baseline BMI values ≥ 30 kg/m^2. Study completion and withdrawal information were summarized by BMI category. The difference (90% CI) between gluteus and deltoid administration in the percentage of obese and non-obese subjects reporting at least 1 systemic TEAE event in Period 1 or at least 1 new or worsening systemic TEAE during the last 8 weeks of the study were determined.

Pharmacokinetics: Descriptive statistics (n, mean, SD, %CV, median, minimum, and maximum) were calculated for the actual and dose-normalized (to 50 mg eq.) plasma concentrations of paliperidone at each sampling time for all treatment groups. Actual and dose-normalized paliperidone predose plasma concentrations were graphically displayed as a function of time, in order to explore the achievement of steady state. Within-subject ratios of gluteal to deltoid plasma concentrations (predose and postdose) and between-group gluteus-to-deltoid ratios of the mean and median plasma concentrations for all sampling times were calculated. A scatterplot of plasma concentrations at Day 8 vs. BMI was generated for all treatment groups.

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SUMMARY - CONCLUSIONS

PHARMACOKINETICS: When starting treatment in the deltoid, median paliperidone plasma concentrations during the first days of treatment (Day 8) were higher compared to starting treatment in the gluteus. When switching from deltoid to gluteal injection at Day 92, the median predose plasma concentration remained largely constant up to Day 176, except for the 100 mg eq. treatment group, where there was still an increase in predose plasma concentrations. When switching from gluteal to deltoid injection at Day 92, median plasma concentrations continued to increase at all doses. Median predose plasma concentrations at apparent steady state (Day 148 to Day 176) for the 50 mg eq. dose group were approximately 10 ng/mL in the DG treatment-sequence group and approximately 12 ng/mL in the GD treatment-sequence group. Median predose plasma concentrations at apparent steady state (Day 176) for the 100 mg eq. dose group were 23.5 ng/mL in the DG treatment-sequence group and 21.5 ng/mL in the GD treatment-sequence group. Maximum plasma concentrations were observed 7 days after injection of paliperidone palmitate, both for the gluteus and the deltoid. In the last injection interval (Day 148 to Day 176) at the end of the 6-month study, dose-normalized paliperidone plasma concentrations were similar at all doses.

EFFICACY RESULTS: The efficacy of treatment was not an end point of this study, and the study was not powered to assess changes in symptom scores from baseline to end point.

SAFETY RESULTS:

(a) Safety and tolerability of deltoid injection site: Based on the 90% CI, the proportion of subjects reporting a systemic TEAE in Period 1 was similar between gluteal and deltoid administration and between dosages.

Proportion of Subjects Reporting at Least One Treatment-Emergent Systemic Adverse Event Occurring in the First Study Period (Study R092670-PSY-3005: Intent-to-treat Analysis Set)

	DG	GD	'GD' minus 'DG'	
Treatment Group	n/N (%)	n/N (%)	Diff. (%)	90% CI[a]
R092670 50 mg eq.	28/42 (67)	24/40 (60)	-6.7	(-23.5; 10.7)
R092670 75 mg eq.	25/38 (66)	28/43 (65)	-0.7	(-17.6; 16.5)
R092670 100 mg eq.	28/46 (61)	23/40 (58)	-3.4	(-20.4; 13.8)
Total	81/126 (64)	75/123 (61)	-3.3	(-13.3; 6.7)

[a] CIs based on Wald's improved method.
Diff.=difference

(b) Safety and tolerability of switching injection sites: The proportion of each subject group reporting a systemic TEAE was similar whether the switch of injection site was from deltoid to gluteus or vice versa, and there was no dosage-dependent increase in the proportion of subject groups reporting a systemic TEAE following the switch of injection sites.

Proportion of Subjects Reporting at Least One Treatment-Emergent Systemic Adverse Event Occurring in the Last 8 Weeks of any Study Period (Study R092670-PSY-3005: Matched Intent-to-treat Analysis Set)

	Period 1	Period 2	'GD' minus 'DG'	
Treatment Group	n/N (%)	n/N (%)	Diff. (%)	90% CI[a]
R092670 50 mg eq. DG	14/31 (45)	10/31 (32)	-12.9	(-26.7; 2.4)
R092670 50 mg eq. GD	10/27 (37)	11/27 (41)	-3.7	(-21.4; 14.5)
R092670 75 mg eq. DG	13/31 (42)	13/31 (42)	0.0	(-15.0; 15.0)
R092670 75 mg eq. GD	10/32 (31)	10/32 (31)	0.0	(-18.7; 18.7)
R092670 100 mg eq. DG	11/34 (32)	10/34 (29)	-2.9	(-17.2; 11.7)
R092670 100 mg eq. GD	12/30 (40)	9/30 (30)	10.0	(-6.6; 25.4)
Total DG	38/96 (40)	33/96 (34)	-5.2	(-13.6; 3.4)
Total GD	32/89 (36)	30/89 (34)	2.2	(-8.2; 12.6)

[a]CIs based on improved CIs for matched proportions.
Diff.=difference.

For the secondary safety and tolerability objective, based on the 90% CI, the proportion of subjects reporting any systemic TEAE at the end of the study was similar between treatment sequences and between dosages. For the exploratory BMI analysis, the withdrawal rate due to lack of efficacy was slightly higher in obese subjects, while the number of TEAEs was similar in obese and non-obese subjects.

The incidence of injection-site related TEAEs was low and was similar for the 2 injection sites (6% deltoid, 4% gluteus). Pain was the most commonly reported injection site-related TEAE. Both investigators and subjects reported more pain at the deltoid injection site. There was a notable difference between regions in injection site preference: 77% of U.S. subjects and 30% of non-U.S. subjects preferred deltoid to gluteus.

The overall incidence of AEs in this study was similar following injection in the deltoid or gluteus muscle. Serious TEAEs or TEAEs leading to a permanent stop were infrequent. The most common treatment-emergent adverse

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events reported were insomnia, headache, anxiety, and agitation. They were typically mild or moderate in severity. Extrapyramidal symptom-related adverse events were uncommon and most were mild. Prolactin levels increased from baseline to the end of the study in both males and females, as expected. There were only 2 prolactin-related adverse events. There were slight increases in mean body weight (0.04 to 1.74 kg) and BMI (–0.01 to 0.62 kg/m^2) from baseline to the end of the study for subjects with normal baseline BMI (<25 kg/m^2), but not for overweight or obese subjects.

CONCLUSION: Initiating treatment with paliperidone palmitate at doses of 50, 75, and 100 mg eq. is well tolerated following injection in both the deltoid and gluteus. Switching between the injection sites (deltoid to gluteus and vice versa) is safe and well tolerated.

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