SYNOPSIS

Issue Date: 15 October 2009
Document No.: EDMS-PSDB-10322382:2.0

Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development*
Name of Finished Product	Paliperidone palmitate
Name of Active Ingredient	Paliperidone

Protocol No.: R092670-PSY-1008

Title of Study: An Open-Label, Long-Term, Multiple-Dose, Safety and Tolerability, Pharmacokinetic Study of 150 mg eq. Paliperidone Palmitate in the Treatment of Subjects With Schizophrenia.

Principal Investigator: Ahmad Hatim Sulaiman, MD, University Malaya Medical Centre, Kuala Lumpur; Malaysia

Publication (Reference): None.

Study Period: 27 September 2007 to 9 June 2009. Database Lock date: 3 July 2009

Phase of Development: Phase 1

Objectives: The primary objectives were: 1) to evaluate the long-term safety and tolerability of flexible doses of paliperidone palmitate in the treatment of subjects with schizophrenia; and 2) to characterize and document the pharmacokinetics (PK) of paliperidone following fixed multiple i.m. injections of paliperidone palmitate 150 mg eq.

Secondary objectives were: 1) to evaluate the long-term changes in positive and negative symptoms of schizophrenia as measured by the Positive and Negative Syndrome Scale (PANSS); 2) to examine the long-term changes in global impression as measured by the Clinical Global Impression Severity of Illness (CGI-S); 3) to record and descriptively summarize changes in personal and social functioning as measured by the Personal and Social Performance Scale (PSP); 4) to assess the quality of sleep and daytime drowsiness as measured by Sleep Visual Analog Scale (Sleep VAS); and 5) to collect health resource use (HRU) data that may be used in future economic modeling.

Methods: This was an open-label, long-term, multiple-dose, multicenter study in men and women who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for schizophrenia for at least 1 year. The study consisted of 2 phases, a screening and washout phase of up to 21 days and a 53-week open-label treatment phase including an end-of-study or early withdrawal visit. There were 2 treatment groups in this study, Treatment A and Treatment B.

Treatment A represents subjects who received paliperidone palmitate 150 mg eq. throughout the study and who participated in intensive PK sampling. Treatment B represents subjects who were unable to tolerate the 150 mg eq. dose or who were unwilling to continue with intensive PK sampling. Subjects in Treatment group B received flexible doses of paliperidone palmitate in the range of 50 to 150 mg eq.

All subjects were initially assigned to Treatment A and received the first dose of paliperidone palmitate 150 mg eq. in the deltoid muscle. One week later, subjects in Treatment group A received a second injection in the deltoid muscle while subjects in Treatment group B received the second injection in either the deltoid or gluteal muscle. The 12 subsequent i.m. injections were administered every 4 weeks in either the deltoid or gluteal muscle (Treatment A and Treatment B).

Including the screening/washout phase, the total duration of the study was approximately 56 weeks.

One pharmacogenomic blood sample (10 mL) was collected from subjects who had given separate written informed consent to allow for pharmacogenomic analysis, as necessary. Subject participation in the pharmacogenomic research was optional.

Number of Subjects (planned and analyzed): Planned: At least 200 subjects were to be enrolled to ensure that at least 100 subjects completed the study. Analyzed: Two hundred and twelve (212) subjects received at least 1 dose of paliperidone palmitate (safety analysis set) and 209 had at least 1 postbaseline psychiatric evaluation. One hundred thirteen (113) subjects completed the study.

Diagnosis and Main Criteria for Inclusion: Men and women, between 18 and 65 years of age, inclusive, with a body mass index (BMI) of ≥17.0 kg/m^2 at screening and a PANSS total score of ≤70, who met the diagnostic criteria for schizophrenia according to the DSM-IV for at least 1 year before screening were included in the study.

Test Product, Dose and Mode of Administration, Batch No.: Paliperidone extended-release (ER) (batch numbers: 0617714 and 0707704) for oral tolerability testing was supplied as a 6-mg capsule-shaped tablet.

Paliperidone palmitate injectable suspensions (50, 100, or 150 mg eq.) (batch numbers: 06K22/F13 and 07D23/F13) were supplied in prefilled syringes.

Reference Therapy, Dose and Mode of Administration, Batch No.: Not Applicable

Duration of Treatment: Treatment A: Subjects in this treatment group received a fixed dose of paliperidone palmitate 150 mg eq. for all injections (maximum of 14 injections) in the study. The first and second injections (Day 1 and Day 8) were administered in the deltoid muscle. All subsequent injections (every 4 weeks) were administered in either the deltoid or gluteal muscle. Subjects in this treatment group underwent intensive PK sampling. Subjects who were unable to tolerate 150 mg eq. or who were unwilling to continue with intensive PK sampling were allowed to continue treatment with flexible doses of paliperidone palmitate for the remainder of the open-label treatment phase (ie, Treatment B). Treatment B: Subjects in this treatment group received lower doses of paliperidone palmitate (50 mg eq. and/or 100 mg eq.) after the initial dose of paliperidone palmitate 150 mg eq. or received paliperidone palmitate 150 mg eq. throughout the study but did not participate in intensive PK sampling.

Criteria for Evaluation:

Psychiatric and Safety Evaluations: The overall safety and tolerability of long-term multiple-dose administration of paliperidone palmitate 150 mg eq. were assessed. Psychiatric evaluations included PANSS, CGI-S, PSP, and Sleep VAS assessments. Safety evaluations included physical examinations, vital signs, clinical laboratory tests, 12-lead electrocardiograms (ECGs), and the recording of adverse events. Extrapyramidal symptoms (EPS) were assessed using the Simpson and Angus Rating Scale (SAS), the Barnes Akathisia Rating Scale (BARS), and the Abnormal Involuntary Movement Scale (AIMS). Injection site pain was assessed by the subject using a VAS, and designated study site personnel evaluated the site(s) of injection for redness, pain, swelling, and induration.

Pharmacokinetic Evaluations: For each subject enrolled in Treatment A, 39 venous blood samples (4 mL each) were obtained for determination of plasma paliperidone at the time points specified in the protocol. For subjects in Treatment B, PK samples were obtained for determination of plasma paliperidone on selected days of study drug injection only.

Plasma concentrations of paliperidone (R076477) were determined in 2 laboratories (the Bioanalytical department of Johnson & Johnson Pharmaceutical Research & Development [J&JPRD], Beerse, Belgium and Frontage Laboratories Co., LTD, Shanghai, China). Validated liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) methods with a target limit of quantification (LOQ) of 0.1 ng/mL were used. Prior to sample analysis in the Bioanalytical department of J&JPRD, a cross-validation using study samples previously analyzed by Frontage Laboratories was performed and is described in the Bioanalytical Study Summary.

The following PK parameters of paliperidone were estimated in subjects with Treatment A: $C_{predose}$, C_{max}, t_{max}, AUC_{τ}, C_{avg}, τ, and FI.

Pharmacogenomic Evaluations: No genes were genotyped in this study.

Statistical Methods: Based on the primary objectives, a sample size of at least 200 subjects was chosen. Assuming a discontinuation rate of approximately 50%, additional subjects could be enrolled to ensure that approximately 100 subjects completed the study.

Psychiatric and Safety Analyses: The safety and tolerability of paliperidone palmitate were evaluated from the signing of the informed consent until completion of the last study-related procedure by examining the incidence, severity, relationship to study medication, and type of adverse events; changes in clinical laboratory results; physical examination and vital signs measurements; concomitant medication/therapy; and 12-lead ECGs. Extrapyramidal (AIMS, BARS, and SAS) and psychiatric (PANSS, CGI-S, PSP, and Sleep VAS) symptoms as well as injection site redness, pain, swelling, and induration were also evaluated. Psychiatric and safety data were summarized using descriptive statistics.

Pharmacokinetic Analysis: For Treatment A, a primary objective of the PK analysis was to estimate the relative bioavailability after the 8^{th} injection with respect to the 2^{nd} injection. The primary parameters of interest for the statistical analysis were the log-transformed estimated AUC_{τ} and C_{max}. Only the data from subjects who completed Day 204 were included in the statistical analysis.

For Treatment B, no formal statistical comparison of PK results was performed. Actual paliperidone plasma concentrations were listed separately.

Paliperidone plasma concentration-time data could be subjected to population PK analysis using nonlinear mixed-effects modeling which will be described in a separate report.

RESULTS:

The majority of all subjects were white, male, and between the ages of 26 to 50 years. Regardless of treatment (Treatment A or Treatment B) approximately half of all subjects completed the study.

Psychiatric and Safety Results: Psychiatric evaluations were conducted to monitor the psychiatric symptoms in the subject population and to adjust concomitant psychiatric medications accordingly. Overall, psychiatric symptoms either improved or remained stable during the open-label phase of the study. Subjects showed slight improvement in psychotic features as assessed by mean changes from baseline in PANSS total scores with approximately 30% of all subjects experiencing a 30% or greater improvement in PANSS total scores from baseline to end point. Subjects also experienced improvement in both the quality of sleep and daytime drowsiness, and there were no clinically meaningful changes in either PSP or CGI-S scores during the study.

Long-term use of paliperidone palmitate 150 mg eq. was generally safe and well tolerated, and there were no deaths reported during the study. Eighty-seven percent (87%) of all subjects in the safety analysis set experienced at least 1 treatment-emergent adverse event during the open-label period. The majority of these adverse events were considered by the investigators to be mild or moderate in severity. Most were considered at least possibly related to the study drug. Overall, the most frequently reported (incidence of 10% or greater) treatment-emergent adverse events by preferred term were nasopharyngitis, insomnia, injection site pain, headache, and tachycardia. Comparable findings were reported for subjects who received paliperidone palmitate 150 mg eq. for at least 1 year.

Schizophrenia and psychotic disorder were the treatment-emergent adverse events most commonly reported as serious. Subjects who received the study drug by deltoid injection only were more likely to discontinue from the study due to an adverse event (20.7%) as compared to all subjects in the safety analysis set (12.7%). Almost twice as many subjects receiving only deltoid injections experienced adverse events leading to discontinuation in the Psychiatric disorder system organ class (13.8%) as compared to all subjects in the safety analysis set (7.5%).

Approximately one-fourth of all subjects experienced at least 1 EPS-related adverse event. The rates of akathisia (1%, as defined on the basis of the BARS global clinical rating at end point) and dyskinesia (2%, as defined on the basis of the AIMS score at end point) were low, but the rates of parkinsonism (16%, as defined on the basis of the SAS global score at end point) and use of anticholinergic medications (22%) were higher. Approximately one-fifth of all subjects experienced at least 1 potentially prolactin-related adverse event, with female subjects reporting at least twice as many potentially prolactin-related adverse events as male subjects. Increases in prolactin levels were

observed in male and female subjects regardless of treatment (Treatment A or Treatment B), with 82% of females and 81% of males experiencing treatment-emergent abnormally high prolactin levels.

Other than the changes in prolactin levels, there were no clinically meaningful changes in clinical chemistry, hematology, or urinalysis parameters. Changes in vital sign parameters were observed with 61% and 32% of subjects, respectively, experiencing increases in standing and supine pulse rates above clinically important limits. In addition, treatment-emergent orthostatic hypotension, as assessed by orthostatic changes in blood pressure and pulse rate, occurred in 22% of subjects. All parameters related to weight gain (body weight, BMI, and waist measurements) increased during the open-label phase of the study. The mean percent change in body weight from baseline to end point was 3.9%, and 31% of subjects had an increase in body weight of 7% or more during the open-label phase.

Assessment of ECG data did not demonstrate evidence of clinically significant QTc prolongation with long-term use of paliperidone palmitate. No subject had a maximum QTcLD value >480 ms during the open-label phase, and no subject experienced an increase of >60 ms from average predose QTcLD interval.

Overall, injection site tolerability was good. Injection site pain was generally classified as mild, and the average intensity of pain generally decreased over time.

Pharmacokinetic Results: The median average plasma concentration (C_{avg}) of paliperidone increased from 34.7 ng/mL after the 2nd injection to 40.0 ng/mL and 47.8 ng/mL after the 8th and 14th injection, respectively.

The median C_{max} of paliperidone was comparable after the 2nd (50.5 ng/mL) and 8th (50.5 ng/mL) injections and slightly higher after the 14th (56.5 ng/mL) injection of paliperidone palmitate. The AUC_{τ} was slightly increased after the 8th injection compared to the 2nd injection. The median fluctuation index gradually decreased from 92.7% (2nd injection) to 55.0% (8th injection) to 41.2% (14th injection).

The median concentrations of paliperidone on Day 36, Day 64 and Day 92 were in line with those obtained from a previous Phase 3 study (R092670-PSY-3007) using multiple doses of paliperidone palmitate 150 mg eq. for up to 3 months.

After the 14th injection (steady state), no difference was seen in AUC_{τ} or C_{max} between the normal BMI and overweight group and only a minor difference was seen in these parameters for the group of obese subjects. During initiation of treatment, the difference in median paliperidone plasma concentrations between the normal BMI and overweight and obese groups was limited, with a 21% to 32% lower exposure on Days 8 and 15 in the overweight and obese groups as compared to the normal BMI group.

The AUC_{τ} increased by 21.5% and 43.8% after the 8th and 14th injections, respectively, compared to the 2nd injection of paliperidone palmitate, and maximum plasma concentrations (C_{max}) increased by 5.8% and 23.6% after the 8th and 14th injections, respectively, compared to the 2nd injection of paliperidone palmitate.

Study Limitations: No notable study limitations were identified by the Sponsor.

Conclusion: Steady-state plasma levels of paliperidone were reached after about 8 to 9 months of multiple, monthly injections of paliperidone palmitate 150 mg eq. and an initiation dosing regimen of 150 mg eq. on Day 1 and Day 8. As of the 2nd injection onwards, the total exposure over the monthly dosing interval approached the exposure at steady state; after the 8th and 14th injections, the exposure was 21.5% and 43.8% higher as compared to the 2nd injection of paliperidone palmitate. During the initiation of treatment, the difference in median paliperidone plasma concentrations between the normal BMI and the overweight and obese groups was limited, with a 21% to 32% lower exposure on Days 8 and 15 in the overweight and obese groups as compared to the normal BMI group.

Long-term use of paliperidone palmitate (administered either at a fixed 150 mg eq. dose or in the flexible dose range of 50 to 150 mg eq.) was generally safe, and the multiple i.m. injections were well tolerated. The overall safety findings in this study were similar to those observed in previous studies with paliperidone palmitate in schizophrenia, and no new safety signal was detected. While efficacy was not evaluated in this Phase 1 study, psychiatric symptoms either improved or remained stable during the open-label phase.

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