CLINICAL STUDY REPORT SYNOPSIS

Document No.: EDMS-PSDB-6598760:2.0

Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development, Division of Janssen Pharmaceutica N.V.	
Name of Finished Product	Paliperidone ER	
Name of Active Ingredient(s)	Paliperidone: (+)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-y1)-1-piperidinyl]-ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyridol[1,2-a]pyrimidin-4-one	

Protocol No.: R076477-SCH-1018 CR013474

Title of Study: Pharmacokinetic Evaluation of The Relative Bioavailability of Three Paliperidone Extended Release (ER) Formulations With Different In Vitro Release Profiles, and Comparison to Paliperidone Immediate Release (IR), in Healthy Male Subjects

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Publication (Reference): None

Study Period: 12 March 2007 to 16 May 2007 | **Phase of Development:** 1

Objectives: The primary objective of this study was to evaluate the pharmacokinetics and relative bioavailability of paliperidone ER formulations with slow, target, and fast in vitro release rates after administration of a single 12 mg dose. The slow and fast releasing ER tablets have in vitro release rates outside the current commercial specifications. Therefore, in order to support widening of the specification limits, this study was performed. The target formulation used is representative of the commercial formulation.

The secondary objectives were 1) to compare the relative bioavailability of paliperidone ER formulations with slow, target, and fast in vitro release rates to the paliperidone IR formulation; and 2) to explore the in vitro in vivo correlation (IVIVC) for the paliperidone ER formulation. The secondary objective of assessing IVIVC will be fully described in a separate report.

In addition, the safety and tolerability of the different paliperidone ER formulations were evaluated.

Methodology: This was a randomized, open-label, 4-way crossover, single dose study in healthy male subjects to evaluate the PK profiles of paliperidone ER tablets with slow, target, and fast in vitro release rates and paliperidone IR. The study consisted of a 21-day-screening phase, an open-label treatment phase consisting of 4 single-dose treatment periods (IR, slow, fast, and target formulations), and an end-of-study or early withdrawal phase. A 10- to 21-day washout period (i.e., >5 times $t_{1/2}$) separated each study drug administration (i.e., each open label treatment period).

Number of Subjects (planned and analyzed): It was planned that approximately 78 male subjects, 18 to 55 years of age, would participate in this study. A total of 80 male subjects enrolled in the study, and 69 subjects completed the study. Pharmacokinetic and safety data were analyzed from 80 subjects.

Diagnosis and Main Criteria for Inclusion: Healthy males 18 to 51 years of age were enrolled in this study. Each subject was expected to be a non-smoker, have a body mass index (BMI) between 18 and 30 kg/m^2 (inclusive), a body weight of not less than 50 kg, blood pressure (after the subject is supine for 5 minutes) between 100 and 140 mmHg systolic (inclusive) and 50 and 90 mmHg diastolic (inclusive), and pulse rate (measured over 60 seconds between 40 and 100 beats per minute (bpm).

Test Product, Dose and Mode of Administration, Batch No.: Paliperidone ER 12 mg tablets with different release rates were used in this study. Single 12-mg oral doses were administered as the following treatments:

Treatment B: target release (i.e., representative of the commercial formulation), batch 0701037

Treatment C: slow release, batch 0701038

Treatment D: fast release, batch 0701036

Reference Therapy, Dose and Mode of Administration, Batch No.: The reference therapy (Treatment A) consisted of a single 1 mg oral dose of paliperidone IR solution (batch 07A29/F074).

Duration of Treatment: In Period 1, all subjects received a 1 mg dose of paliperidone IR solution, administered as a single oral dose under fasted conditions (Treatment A). On Day 1 of Period 2, all subjects were randomized to 1 of 6 possible treatment sequences of the 3 OROS tablet formulations and given 1 of 3 possible 12 mg paliperidone ER formulations: Treatment B, Treatment C, or Treatment D. A 10 to 21 day washout period separated each study drug administration.

SYNOPSIS (CONTINUED)

Criteria for Evaluation:

Pharmacokinetics: For the determination of the plasma concentration of paliperidone, venous blood samples of 3 mL were taken predose, and during the 96 hours following dosing with paliperidone.

Based on the individual plasma concentration-time data, using the actual sampling times, the following pharmacokinetic parameters were estimated for paliperidone for each of the treatments: C_{max}, t_{max}, t_{last}, AUC_{last}, AUC_{∞}, $t_{1/2}$, λ_z, CL/F, and F_{rel} (for C_{max} and AUC_{∞}). The estimated relative bioavailability of the slow (Treatment C) and fast (Treatment D) in vitro release rate formulations of paliperidone ER were compared to the bioavailability of the target formulation (Treatment B). In addition, the relative bioavailability of each formulation of paliperidone ER was estimated with respect to the paliperidone IR solution (Treatment B/Treatment A; Treatment C/Treatment A; Treatment D/Treatment A).

Safety: Safety evaluations included serology at screening, physical examinations at screening and at the end of the study, vital sign measurements, clinical laboratory tests, urine alcohol and drug screening, ECGs, and the recording of adverse events throughout the study.

Statistical Methods:

Pharmacokinetics: Descriptive statistics were calculated for all pharmacokinetic parameter estimates as well as for the plasma concentrations at each sampling time point for all treatments.

The primary PK parameters of interest were the natural log-transformed estimated AUCs (AUC_{∞}, AUC_{last}) and C_{max}. Data from subjects who completed the study (paliperidone ER treatments B, C, and D only) were included in the statistical analysis. If one of the PK parameters of interest was not estimable for a given subject in one or more periods, the subject's data were excluded from statistical analysis for that particular parameter. A mixed-effect analysis of variance (ANOVA) model that included treatment, period and treatment sequence as fixed effects, and subject as a random effect, was used to estimate the least squares means and intrasubject variance.

Using these estimated least squares means and intrasubject variance, the point estimate and 90% CIs for the difference in means on a log scale between Treatment C and Treatment B, and between Treatment D and Treatment B were constructed. The limits of the CIs were retransformed using antilogarithms that obtained 90% CIs for the ratios of the mean AUCs and C_{max} of the test to reference formulation (Treatment C/Treatment B; Treatment D/Treatment B).

The secondary objective of this study was to estimate the relative bioavailability of each formulation of paliperidone ER with respect to the paliperidone IR solution (Treatment B/Treatment A; Treatment C/Treatment A; Treatment D/Treatment A).

Statistical analysis for the second objective will involve the log-transformed estimated AUCs (AUC_{∞}, AUC_{last}) and C_{max}. Data from all treatment periods from subjects who completed the study were included in the statistical analysis. If one of the PK parameters of interest was not estimable for a given subject in one or more periods, the subject's data were excluded from statistical analysis for that particular parameter. A mixed-effect ANOVA model that included treatment and treatment sequence as fixed effects, and subject as a random effect, was used to estimate the least squares means and intrasubject variance.

Using estimated least squares means and intrasubject variance, the point estimate and 90% CIs for the difference in means on a log scale between Treatments B, C, D with respect to Treatment A were constructed. The limits of the CIs were retransformed using antilogarithms to obtain 90% CIs for the ratios of the mean AUCs and C_{max} of the test to reference formulation (Treatment B/Treatment A; Treatment C/Treatment A; Treatment D/Treatment A).

Safety: The percentage of subjects with specific treatment-emergent adverse events was summarized per treatment. Laboratory data were summarized by the type of laboratory test. Pulse rate; systolic and diastolic blood pressure; body weight, height, and temperature; and ECGs were descriptively summarized by parameter and time point. Abnormalities were listed.

SUMMARY - CONCLUSIONS

PHARMACOKINETICS: PK parameters were available from 80 subjects after administration of paliperidone IR tablet, 74 subjects after administration of the target release ER tablet, and 73 subjects after administration of the slow and fast release ER tablet. Maximum plasma concentrations were reached on average at 20 hours, 22 hours, and 25 hours after administration of paliperidone ER tablets with fast, target, and slow in vitro release rates, respectively.

Bioavailability of paliperidone administered as slow or fast releasing ER tablets relative to the target releasing formulation was evaluated using ANOVA. The 90% confidence intervals for the ratio of geometric treatment means of AUCs and C_{max} for the fast and slow releasing tablets compared to the tablet with target in vitro release were within the 80% and 125% bioequivalence limits.

The relative bioavailability of the ER formulation compared to IR formulation was 26% (slow release), 29% (target release), and 32% (fast release) based on dose-normalized AUC_{∞}. The mean apparent elimination half-lives of plaiperidone from the ER formulations were comparable to that observed for the IR formulation (mean values between

SYNOPSIS (CONTINUED)

Summary of Pharmacokinetic Parameters (Mean ± SD) of Paliperidone

Treatment	C_{max} (ng/mL)	AUC_{last} (ng.h/mL)	AUC_{∞} (ng.h/mL)	t_{max} (h)
1 mg IR solution (N=80)	9.73 ± 2.58	188 ± 46.6	196 ± 50.1	1.75 ± 0.69
12 mg target release formulation (N=74)	20.2 ± 7.45	685 ± 250	735 ± 274	21.52 ± 3.68
12 mg slow release formulation (N=73)	18.7 ± 10.0	618 ± 302	668 ± 330	24.50 ± 3.59
12 mg fast release formulation (N=73)	22.4 ± 9.26	751 ± 292	802 ± 315	19.63 ± 3.11

21.9 and 24.1 hours).

SAFETY RESULTS: Eighty subjects were enrolled in the study, and 69 subjects completed the study. Four subjects were withdrawn from study due to an adverse event (e.g., 2 subjects were withdrawn after paliperidone IR administration and 2 subjects after paliperidone ER administration). Three of the 4 adverse events were considered doubtfully related to the study drug. The fourth subject had a serious adverse event of dystonia (oromandibular dystonia) that was assessed by the investigator as probably related to the study drug. The most common adverse events reported by subjects who received paliperidone IR were somnolence (5%) and headache (5%). The most common adverse events reported by subjects in any treatment group were insomnia (16%), headache (15%), somnolence (14%), anxiety (13%), nasal congestion (11%), dyspnoea (9%), and fatigue (9%). Adverse events reported by subjects with an incidence in any treatment group ≤5% but with a total (cumulative) incidence of ≥5% included epistaxis (8%), dystonia (5%), chest discomfort (5%), and nausea (5%). The incidences of anxiety, nasal congestion, dyspnoea, fatigue, dystonia, and chest discomfort were slightly higher in subjects who received paliperidone ER (12 mg) as compared to paliperidone IR (1 mg) and may be due to the change in dosage and multiple treatments. There were no clinically relevant differences in the incidences of adverse events in subjects who received paliperidone ER when comparing the slow, target, and fast release rate formulations. Most of the adverse events were described by the investigator as possibly or probably related to the study medication. The majority of the events were classified as mild, and none were classified as severe. There were no clinically relevant changes in chemistry, hematology, or urine laboratory values in any subject during the course of the study. The increases in mean change from baseline in supine pulse rate observed after administration of paliperidone ER are in line with observations from previous clinical studies. It is due to the α1-blocking effect of paliperidone.

CONCLUSION: After administration of a single dose of 12 mg under fasted conditions, paliperidone ER formulations with slow and fast in vitro release rates are bioequivalent to the target (commercial) formulation with respect to maximum plasma concentration (C_{max}) and total exposure (AUC). Paliperidone ER was well tolerated in this study, and there were no unexpected safety findings.

Issue Date of the Clinical Study Report: 21 September 2007

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