SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: ER OROS paliperidone NAME OF ACTIVE INGREDIENT(S): Paliperidone /R076477	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: R076477-P01-1010, CR004210 **Title of Study:** Dose-Proportionality Study of the Five ER OROS Paliperidone To-Be- Marketed Tablet Strengths (3, 6, 9, 12, and 15 mg) in Healthy Male Subjects		
Principal Investigator: S. Warrington, M.D. - Hammersmith Medicines Research, London, U.K.		
Publication (Reference): None		
Studied Period (years): Clinical Conduct: 19 July 2004 – 01 October 2004 Sample Analysis: 4 October 2004 – 27 October 2004		**Phase of development:** 1
Objectives: The primary objective of this study was to evaluate the dose proportionality of the 3-, 6-, 9-, 12-, and 15-mg tablets of ER OROS paliperidone. Additionally, the safety and tolerability of the treatments in healthy subjects were assessed.		
Methodology: This was a single-center, open-label, randomized, 5 treatment-period, crossover study in healthy male adults. The study consisted of a screening phase and an open-label treatment phase during which each subject received 5 treatments of study drug in a random order and separated by a washout period of 10 to 14 days. Treatments consisted of a single oral dose of: A) 1 tablet containing 3 mg ER OROS paliperidone; B) 1 tablet containing 6 mg ER OROS paliperidone; C) 1 tablet containing 9 mg ER OROS paliperidone; D) 1 tablet containing 12 mg ER OROS paliperidone; E) 1 tablet containing 15 mg ER OROS paliperidone. All treatments were administered after an overnight fast. Subjects were to remain in bed for 4 hours after dosing and were strongly advised to remain in bed for up to 36 hours.		
Number of Subjects (planned and analyzed): Fifty subjects were enrolled and treated to ensure that at least 42 subjects completed all assigned treatments. Forty-five subjects completed the study.		
Diagnosis and Main Criteria for Inclusion: Healthy male subjects aged 18 to 55 years, inclusive; body mass index between 18 to 28 kg/m², inclusive; normotensive; healthy on the basis of a prestudy physical examination, medical history, ECG, and the laboratory results of blood biochemistry, hematology and urinalysis performed within 21 days before the first dose; informed consent documents (also for genetic testing) signed. Subjects were excluded if they had a history of smoking or use of nicotine-containing substances within the last 2 months before the study.		
Test Product, Dose and Mode of Administration, Batch No.: ER OROS paliperidone tablets for oral use. The following batch numbers were used: 3-mg tablet: MV0301019/F016; 6-mg tablet: 0406837/F047; 9-mg tablet: 0406836/F048; 12-mg tablet: 0406838/F049; 15-mg tablet: 0406659/F050		
Duration of Treatment: 5 times 1 day separated by a washout period of 10 to 14 days		
Criteria for Evaluation: Pharmacokinetics: blood samples were collected predose and at predefined time points up to 96 hours after each study drug administration. Paliperidone plasma concentrations were determined using a validated LC-MS/MS method. The lower limit of quantification was 0.100 ng/mL. Pharmacogenomics: A single blood sample was collected at any time on Day 1 in Period 1. The *CYP2D6* gene was retrospectively genotyped as it was hypothesized that polymorphisms in this gene may influence pharmacokinetics of or response to ER OROS paliperidone. Safety: *Adverse events*: reported by the subjects, and elicited by the investigator for the duration of the study. *Laboratory tests*: hematology, serum chemistry, and urinalysis (screening, before each drug administration, end of study), urine drug screen (screening, before each drug administration), alcohol breath test (before each drug administration). *Physical examination*: screening, end of study. *Body temperature*: screening, before each study drug administration. *Vital signs*: screening, before each study drug administration; every hour for the first 36 hours after each drug administration and then in the morning of Day 3 and Day 4; end of study. *ECG*: screening, before drug administration in Period 1, end of study.		

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Statistical Methods:

Pharmacokinetics: For each treatment, descriptive statistics were calculated for plasma concentrations at each time point, and for all pharmacokinetic parameters of paliperidone.

The primary comparisons were based on the estimates of the pharmacokinetic parameters AUC_{last}, AUC_{∞}, and C_{max} for paliperidone. A natural logarithm transformation was applied after dose-normalization to 15 mg. These transformed estimates were fitted in a mixed-effect analysis of variance (ANOVA) model (SAS Proc MIXED) that included treatment, period, and sequence as fixed effects, and a random intercept for subjects (nested under sequence) as a random effect. Least-square means and intra-subject variability obtained from the model were used to calculate the pairwise differences between the five treatments and accompanying 90% confidence intervals. After back-transformation to the original scale the limits of these intervals were compared to one, which corresponds to perfect dose-proportionality.

Additionally, the relationship of the log-transformed dose-normalized estimates was fitted to the log transformed dose using a linear regression model, where a zero-slope corresponds to perfect dose-proportionality. This was achieved using a mixed-effect ANOVA model similar to that described above, but with the log-transformed dose considered as a continuous variable rather than as a classification factor. The hypothesis of dose-proportionality was rejected if the slope was significantly (p-value < 0.05) different from zero.

Safety: Adverse events were summarized. Descriptive statistics were calculated and changes from baseline were summarized for laboratory test results, vital signs, and ECG findings. Physical examination, body temperature, and concomitant therapies were listed.

SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS:

Bioavailability parameters (C_{max} and AUC) increased proportionally with the ER OROS paliperidone dose. After dose-normalization to 15 mg, mean C_{max} changed between 24.3 and 26.6 ng/mL, AUC_{last} between 822 and 938 ng.h/mL, and AUC_{∞} between 945 and 1014 ng.h/mL. T_{max} (median = 24 hours for all dose levels) and $t_{1/2term}$ (on average between 22.0 and 23.5 hours) appeared also to be independent of the dose level. Plasma paliperidone pharmacokinetic parameters were available for 46 subjects after 3-, 6-, and 9-mg ER OROS paliperidone, for 47 subjects after 12-mg ER OROS paliperidone and for 48 subjects after 15-mg ER OROS paliperidone.

Table A: Dose Normalized Pharmacokinetic Parameters of Plasma Paliperidone after administration of ER OROS Paliperidone Tablet (Study R076477-P01-1010)

Parameter(Units) [a]	Treatment 3 mg (N=46)	6 mg (N=46)	9 mg (N=46)	12 mg (N=47)	15 mg (N=48)
C_{max} [b] (ng/mL)	24.3 ± 10.8	25.4 ± 9.74	24.6 ± 11.5	24.5 ± 10.0	26.6 ± 11.8
t_{max} (h)	24 (12 - 29)	24 (12 - 29)	24 (8 - 32)	24 (12 - 29)	24 (12 - 29)
AUC_{last} [b] (ng.h/mL)	882 ± 381	919 ± 366	875 ± 404	901 ± 409	938 ± 410
AUC_{∞} [b] (ng.h/mL)	962 ± 425	1003 ± 418	945 ± 448	973 ± 463	1014 ± 454
$t_{1/2term}$ (h)	23.5 ± 5.2	23.4 ± 4.5	22.0 ± 3.4	22.1 ± 4.5	22.3 ± 4.4

[a] Values are mean ± SD, except for t_{max}: median (min-max)

[b] C_{max} and AUCs are dose-normalized to 15 mg

The statistical analysis (mixed-effect ANOVA performed on the 45 subjects who completed the whole study) of dose-normalized bioavailability parameters did not reveal any significant overall dose effect. For pairwise comparisons (*i.e.* between 15 mg and all other dose levels and between consecutive dose levels), the 90% confidence interval of the least-square geometric mean ratios was always included within the generally accepted 80-125% bioequivalence limit. In addition, when applying a linear regression model (ln-transformed dose-normalized parameters *vs.* ln-transformed dose level), the estimated slope was never significantly different from zero. Results of statistical analysis confirm that ER OROS paliperidone PK parameters were dose proportional.

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PHARMACOGENOMICS RESULTS: A composite genotype and, where possible, a predicted phenotype were derived from the raw genotyping data for *CYP2D6* for each subject. The relationship between exposure and CYP2D6 predicted phenotype will be explored using a population pharmacokinetic approach using data across multiple clinical trials.

SAFETY RESULTS: The highest incidence of adverse events was observed following treatment with the 15-mg dose (57.1% vs 25.5 to 41.3% for the lower doses). The most commonly reported adverse events were headache (38.0%), fatigue (30.0%), dizziness (20.0%), somnolence (20.0%), and rhinitis (18.0%). The majority of adverse events were mild or moderate. Two subjects had a severe adverse event, considered very likely related to treatment (with the 15-mg dose). These adverse events were dystonia leading to permanent treatment discontinuation, and hypotension. Eight subjects had extrapyramidal symptoms (EPS)-related adverse events (i.e., hyperkinesia, dyskinesia, dystonia, hypertonia, speech disorder, and tremor), mostly after the 12-mg and the 15-mg dose.

There were no serious adverse events. Two subjects discontinued the study due to the occurrence of an adverse event after treatment with the 15-mg dose: one because of severe dystonia, and one because of moderate fatigue. The latter subject had increased hepatic function tests at screening due to a previous Epstein-Barr virus infection.

Overall, there were no consistent or clinically relevant changes in mean laboratory values at end point. At the end of the study, 13 subjects had prolactin values above the laboratory reference range, and 4 subjects had AST and/or ALT values above the laboratory reference range. All increases were minor, and were not considered clinically important. Two subjects had abnormal laboratory values reported as mild adverse events during treatment: increase of creatine phosphokinase, LDH, and AST.

An increase in mean heart rate was observed until 72 hours after study drug administration. The maximal mean increase (22.2 bpm) was observed at 36 hours after the 15-mg dose. Subjects were strongly advised to remain in bed until 36 hours after dose, which may have contributed to the increase in heart rate at that time.

The incidence of decrease in supine diastolic blood pressure appears to increase with dose (maximal mean decrease in supine diastolic blood pressure: 8.8 mmHg, at 16 hours, after dosing with 15 mg). Four subjects developed treatment-emergent blood pressure-related adverse events. These adverse events were hypotension (1 subject 4 days after the 3-mg dose and 1 subject 3 days after the 9-mg dose); syncope (1 subject approximately 1 day after the 15-mg dose); and hypotension (1 subject approximately 1 day after the 15-mg dose). The adverse events were moderate or severe, and were considered related to study drug by the investigator.

No clinically noteworthy changes in mean ECG parameters were noted. None of the subjects had a QTc value above 500 milliseconds or a QTc increase above 60 milliseconds from baseline. One subject who had a borderline QTcB prior to dosing in Period 1 had a prolonged QTcB interval (458 milliseconds) at the end of the study. Four other subjects had a borderline QTcB interval but normal QTcF and QTlc intervals at the end of the study.

CONCLUSION:

Paliperidone pharmacokinetics increased dose-proportionally after single oral administration of 3-, 6-, 9-, 12- and 15-mg ER OROS paliperidone tablets, both for C_{max} and AUC. For all dose levels, both t_{max} (~24 hours) and $t_{1/2term}$ (~22-23 hours) were comparable.

Single doses of 3, 6, 9, 12, and 15 mg of ER OROS paliperidone were reasonably well tolerated by young healthy male subjects, with headache (38%), fatigue (30%), dizziness (20%), somnolence (20%), and rhinitis (18%) being the most commonly reported adverse events.

There were no clinically noteworthy changes in clinical laboratory analytes, ECG parameters, or physical examination from baseline to the end of the study. Overall a mean increase in heart rate was observed with paliperidone treatment.

No unexpected or unusual safety issues arose during this study

Date of the report: 27 October 2005

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