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-P01-1008, CR004213 **Title of Study:** Pivotal bioequivalence study with 15 mg ER OROS paliperidone comparing the Phase 3 formulation with the to-be-marketed formulation and evaluation of food effect on the to-be-marketed formulation in healthy male subjects		
Principal Investigator: Darren Wilbraham, M.D. - Guy's Drug Research Unit, London, U.K.		
Publication (Reference): None		
Studied Period (years): Clinical Conduct: 29 July 2004 - 18 December 2004 Sample Analysis: 4 November 2004 - 24 January 2005		**Phase of development:** 1
Objectives: The primary objectives of this study were to evaluate the bioequivalence between the Phase 3 and the to-be-marketed formulations of extended release (ER) OROS paliperidone, and to evaluate the effect of food on the highest to-be-marketed tablet strength. Additionally, the safety and tolerability of the treatments in healthy subjects were assessed.		
Methodology: This was a single-center, open-label, randomized, 3 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 3 treatments of study drug in a random order and separated by a washout period of 10 to 14 days. Treatment A consisted of a single oral dose of 15 mg ER OROS paliperidone Phase 3 formulation in the fasted state; Treatment B consisted of a single oral dose of 15 mg ER OROS paliperidone to-be-marketed formulation in fasted state; and Treatment C consisted of a single oral dose of 15 mg ER OROS paliperidone to-be-marketed formulation after consumption of a high-fat breakfast.		
Number of Subjects (planned and analyzed): Sixty-six subjects were planned to be enrolled to ensure that at least 54 subjects completed all assigned treatments. Eighty subjects were randomly assigned to treatment and 58 subjects completed the study.		
Diagnosis and Main Criteria for Inclusion: Healthy male subjects aged 18 to 55 years, inclusive; acceptable weight; normotensive; healthy on the basis of a prestudy physical examination, medical history, electrocardiogram (ECG), and the laboratory results of serum chemistry, 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.		
Test Product, Dose and Mode of Administration, Batch No.: ER OROS paliperidone tablets for oral use. The following tablet strengths were used: 3 mg Phase 3 formulation (MV0301019/F016); 9 mg Phase 3 formulation (MV0301025/F017); and 15 mg to-be-marketed formulation (0406659/F050)		
Duration of Treatment: Three 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 liquid chromatography coupled to mass spectrometry/mass spectrometry (LC-MS/MS method). The lower limit of quantification was 0.100 ng/mL.		

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Pharmacogenomics: A single blood sample was collected at any time on Day 1 in Period 1 from subjects who gave informed consent to participate in this part of the study. 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 (AEs): 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 urine 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, Day 4, and Day 5; end of study. ECG: screening, before drug administration in Period 1, end of study.

Statistical Methods:

Pharmacokinetics: For each treatment, descriptive statistics were calculated for plasma concentrations at each time point, and for all pharmacokinetic parameters of paliperidone. Individual plasma concentration versus time profiles, and mean profiles per treatment were plotted.

To evaluate the bioequivalence between the Phase 3 and the to-be-marketed formulations of ER OROS paliperidone, and to evaluate the effect of food on the pharmacokinetics of the highest to-be-marketed tablet strength, the treatment ratios B/A and C/B for the area under the curve (AUC) and the maximum plasma concentration (C_{max}) and their 90% confidence intervals (CIs) were calculated. Calculations were based on the estimates of least square means and intrasubject variability obtained from fitting a mixed model on the log-transformed pharmacokinetics parameter estimates. After back-transformation to the original scale the limits of these intervals were compared with the classical 80-125% bioequivalence limits. Of primary interest was the pairwise comparison of both fasted treatments. If the 90% CI of the ratio B/A fell within these limits, both formulations were considered bioequivalent. In addition, if the 90% CI for the fed/fasted-ratio C/B fell within these limits, absence of food-effect was concluded. If the fed/fasted-ratio C/B fell within the 80-125% limits, and the 90% CIs fell outside these limits, specific recommendations on the clinical significance of the food-effect were to be provided. If both the fed/fasted-ratio C/B and the 90% CIs fell outside the 80-125% bioequivalence limits, it was concluded that a food-effect was present and recommendations regarding intake with or without food were to be made.

Safety: AEs 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:

Plasma paliperidone pharmacokinetic parameters are provided in Table A.

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Table A: Pharmacokinetic Parameters of Plasma Paliperidone (Study R076477-P01-1008)

Parameter (Units) [a]	Paliperidone ER OROS 15 mg		
	Phase 3, fasted (N=66)	To-be-marketed, fasted (N=63)	To-be-marketed, fed (N=72) [b]
C_{max} (ng/mL)	22.1 (8.16)	22.8 (9.84)	32.1 (15.6)
t_{max} (h)	22.07 (16.00-28.05)	24.00 (12.00-28.00)	22.00 (12.00-33.52)
t_{lag} (h)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-2.00)
AUC_{last} (ng.h/mL)	815 (294)	799 (320)	1162 (533)
AUC_{∞} (ng.h/mL)	886 (329)	867 (349)	1262 (598)
$t_{1/2term}$ (h)	22.9 (3.55)	22.7 (3.82)	23.0 (3.40)

[a] Values are mean (SD), except for t_{lag} and t_{max}: median (minimum-maximum)

[b] N=72 subjects administered but N=71 for C_{max} and t_{max}, N=70 for AUC_{last}, and N=69 for AUC_{∞} and $t_{1/2term}$

Paliperidone bioavailability pharmacokinetic parameters were similar between the Phase 3 and the to-be-marketed formulation administered in the fasted state: average C_{max} was 22.1 and 22.8 ng/mL, AUC_{last} was 815 and 799 ng.h/mL, and AUC_{∞} was 886 and 867 ng.h/mL, respectively.

Paliperidone bioavailability pharmacokinetic parameters were increased after the to-be-marketed formulation administered with a high-fat breakfast: C_{max}, AUC_{last} and AUC_{∞} averaged respectively 32.1 ng/mL, 1162 ng.h/mL and 1262 ng.h/mL.

T_{max} and $t_{1/2term}$ were similar for the 3 treatments. No lag time was observed after administration of the treatments in the fasted state, while an apparent lag time was observed in a number of subjects (n=13) when the to-be-marketed formulation was administered after a high-fat breakfast.

The statistical analysis (mixed-effect analysis of variance [ANOVA]) of bioavailability parameters was performed on 58 subjects (57 for AUC_{∞}) who received all 3 treatments. The statistical analysis did not reveal any significant difference between the Phase 3 and the to-be-marketed formulation administered in the fasted state, with all 90% confidence intervals for the least-square geometric mean ratios within the 80.00% to 125.00% bioequivalence limits. The bioavailability parameters of the to-be-marketed formulation increased by 42-46% after a high-fast breakfast, with the 90% confidence intervals for the least-square geometric mean ratio above 125.00%. Results of the statistical analysis are provided in Table B.

Table B: Pairwise Comparisons of Paliperidone Plasma Pharmacokinetic Parameters (R076477-P01-1008: Statistical Dataset)

Test	Reference	Test/Reference ratio (90% confidence interval)		
		C_{max} (N=58)	AUC_{last} (N=58)	AUC_{∞} (N=57)
To-be-marketed, fasted	Phase 3, fasted	100.68 (91.62-110.63)	96.10 (88.42-104.46)	96.00 (88.21-104.48)
To-be-marketed, fed	To-be-marketed, fasted	142.26 (129.41-156.39)	145.62 (133.92-158.33)	145.78 (133.91-158.68)

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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: Seventy-three (91%) of 80 subjects reported at least 1 AE during the study. The highest incidence of AEs was observed following treatment with 15 mg ER OROS paliperidone to-be-marketed formulation in fed state: 56 (78%) of 72 subjects, compared with 43 (65%) of 66 subjects following treatment with paliperidone Phase 3 formulation in fasted state, and 42 (67%) of 63 subjects following treatment with the paliperidone to-be-marketed formulation in the fasted state.

The most common AEs were rhinitis, somnolence, headache, back pain, epistaxis, pharyngitis, agitation, anxiety, and dystonia. All AEs were of mild or moderate intensity. Dystonia, headache, epistaxis, agitation, and anxiety were always considered study treatment-related. Rhinitis, somnolence, and back pain were mostly considered study treatment-related, and pharyngitis was considered study treatment-related occasionally by the investigator. There were no serious AEs in this study.

Sixteen subjects discontinued due to the occurrence of an AE. Five subjects discontinued during treatment with paliperidone Phase 3 formulation in fasted state; 3 subjects during treatment with paliperidone to-be-marketed formulation in the fasted state; and 8 subjects during treatment with paliperidone to-be-marketed formulation in fed state. The most common AEs that led to subject discontinuation from the study were dystonia (n=6), and anxiety, depression, and hyperkinesia (n=2 each).

Elevated mean serum prolactin levels were observed at the end of the study. These were not considered clinically relevant. All other laboratory values outside the laboratory reference range were isolated cases and not considered clinically relevant.

An increase in mean supine pulse and in mean supine systolic and diastolic blood pressure (SBP, DBP) was observed during the study, starting on Day 2, and lasting until 96 hours after study drug administration in each treatment period. The largest mean increases from baseline were observed 36 hours after the treatment in fed state. The mean increase in pulse at that time point was 22.3 bpm, and the mean increases in SBP and DBP were 13.5 mmHg and 6.8 mmHg, respectively.

Nine subjects experienced AEs related to postural hypotension. These events were mild or moderate in intensity, and were considered possibly related to the study drug by the investigator. No cases of orthostatic hypotension were confirmed by measurement of vital signs in supine and standing positions.

Different QT correction methods (Bazett, Fridericia, and linear regression) were used to evaluate the effects of ER OROS paliperidone. The most appropriate correction factors in the presence of a drug effect on heart rate are the method according to Fridericia and a linear regression correction method. None of the subjects had a QTc value above 500 milliseconds or a QTc increase from baseline above 60 milliseconds. None of the subjects had a prolonged QTcF or QTlc interval during the study. No clinically noteworthy changes in mean ECG parameters were noted during this study.

CONCLUSION:

When administered in the fasted state, the 15 mg to-be-marketed formulation and 15 mg of the Phase 3 ER OROS paliperidone formulation were bioequivalent with respect to rate and extent of absorption. After intake of a standard high-fat breakfast, the bioavailability of the to-be-marketed formulation was increased by 42% (C_{max}) to 46% (AUC).

The highest incidence of adverse events was observed following treatment with 15 mg ER OROS

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paliperidone to-be-marketed formulation in fed state, compared with the 2 paliperidone treatments in fasted state. There were no unexpected or unusual clinically relevant findings with respect to laboratory test results, vital signs and ECG parameters or physical examination findings. Date of the report: 27 October 2005		

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