SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: Paliperidone NAME OF ACTIVE INGREDIENT(S): (+-)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2- a]pyrimidin-4-one	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: R076477-P01-102 CR004279

Title of Study: A comparative evaluation of the pharmacokinetics and pharmacodynamics under fasting and fed conditions of 2 paliperidone extended-release pellet formulations with paliperidone oral solution in healthy adults

Investigator: F. Vanhoutte, M.D. - Clinical Pharmacology Unit, Merksem; Belgium

Publication (Reference): None

Studied Period (years): Clinical Conduct: 09 Sep 2003 – 25 Nov 2003 Sample Analysis: 08 Oct 2003 - 09 Dec 2003	**Phase of development:** 1

Objectives: To compare the bioavailability of 2 extended release (ER) paliperidone pellet formulations under fasting and fed conditions with 2 mg paliperidone oral solution under fasting conditions. Additional objectives were to compare the pharmacodynamic effects (postural changes in blood pressure and heart rate), to evaluate the safety and tolerability, and to explore the relationship between CYP2D6 genotype and paliperidone exposure.

Methodology: Single-center, open-label, randomized, 5-way crossover Phase 1 study in non-smoking healthy men and women, aged between 18 and 55 years. The study consisted of a screening period; a 5-way crossover, open-label treatment phase with 14 days washout between treatments; and end-of-study evaluations upon completion or at early withdrawal. Eligible subjects were randomly assigned to 1 of 5 treatment sequences. Each subject received the following treatments in random order: (A) paliperidone ER pellet formulation-1, as 1 capsule of 2.5 mg, under fasting conditions; (B) paliperidone ER pellet formulation-1, as capsule of 2.5 mg with food (high-fat breakfast); (C) paliperidone ER pellet formulation-2 as 1 capsule of 2.5 mg, under fasting conditions; (D) paliperidone ER pellet formulation-2 as 1 capsule of 2.5 mg with food (high-fat breakfast); (E) immediate release (IR) paliperidone oral solution, 2 mg (2 mL) of a 1-mg/mL solution, under fasting conditions.

Criteria for Evaluation:

Pharmacokinetics: Blood samples for determination of paliperidone plasma concentrations were collected up to 96 hours after each drug administration. Paliperidone plasma concentrations were determined using a validated LC-MS/MS method. The LLOQ was 0.100 ng/mL

Pharmacodynamics: Pharmacodynamic evaluation was based on postural changes in blood pressure and heart rate at scheduled time points until 48 hours after each drug administration, and on reports of dizziness and faintness from a questionnaire.

Safety: Safety assessment was based on reported adverse events, clinical laboratory tests, vital sign measurements, physical examinations, and electrocardiogram (ECG) findings.

Statistical Methods:

Pharmacokinetics: For each treatment, descriptive statistics were calculated for plasma concentrations at each time point, and for all pharmacokinetic (PK) parameters of paliperidone. Individual plasma concentration versus time profiles, and mean profiles per treatment were plotted. Calculation of point estimates and 90% confidence intervals (CIs) for the ratios of AUC_{last}, AUC_{∞}, and C_{max} (log-transformed data) for Treatments A vs. E, C vs. E, B vs. A, D vs. C.

Pharmacodynamics: Pharmacodynamic data were analyzed descriptively (raw data, changes from baseline) and graphically displayed.

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

SYNOPSIS (CONTINUED)

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SUMMARY – CONCLUSIONS

The study population consisted of white (100%) male (19; 54%) and female (16; 46%) subjects, 20 to 55 years old. Most subjects were extensive metabolizer of CYP2D6 (91%) and had low CYP3A5 levels (89%).

Thirty-five subjects were randomized and treated. One subject withdrew consent after completion of Treatment C and D, and prematurely discontinued. Thirty-four subjects completed the study and received all 5 treatments.

PHARMACOKINETIC RESULTS:

Two subjects with missing data were excluded from the statistical analysis of the PK parameters.

Both paliperidone ER pellet formulations had lower mean C_{max} and lower mean AUC_{last} and AUC_{∞} values compared to the IR paliperidone oral solution, all under fasting conditions. The relative bioavailability compared to IR paliperidone oral solution is shown in the table below. The 90% CIs were rather small.

	N	Test Treatment	Reference Treatment	Ratio %[a)]	90% CI[a)]
C_{max}, ng/mL	33	A: 9.15	—E: 16.9	43.41	(40.66; 46.34)
	33	C: 8.04	—E: 16.9	37.80	(35.41; 40.36)
AUC_{last}, ng.h/mL	33	A: 261	—E: 343	60.94	(57.22; 64.91)
	33	C: 246	—E: 343	56.47	(53.02; 60.15)
AUC_{∞}, ng.h/mL	33	A: 281	—E: 367	61.39	(57.57; 65.48)
	33	C: 266	—E: 367	56.98	(53.42; 60.78)

[a)] Ratios and 90% CI corrected to 2-mg dose
Treatment A: 2.5 mg PEL-1/FASTED; Treatment C: 2.5 mg PEL-2/FASTED; Treatment E: 2 mg SOL/FASTED.

The effect of food on the PK parameters of both paliperidone ER pellet formulations is summarized in the table below. There was no consistent effect of food on the primary PK parameters. The 90% CIs for C_{max}, AUC_{last} and AUC_{∞} (fed/fasted) for the ER pellet formulation-2 were contained in the bioequivalence interval of 80-125%. The 90% CIs for AUC_{last} and AUC_{∞} (fed/fasted) for the ER pellet formulation-1 were also contained in the bioequivalence interval of 80-125%, but the 90% CIs of C_{max} were below the 80-125% bioequivalence limits.

	N	Test Treatment	Reference Treatment	Ratio %	90% CI
C_{max}, ng/mL	33	B: 6.76	—A: 9.15	74.08	(69.39; 79.09)
	33	D: 7.48	—C: 8.04	94.14	(88.18;100.51)
AUC_{last}, ng.h/mL	33	B: 243	—A: 261	92.89	(87.20; 98.94)
	33	D: 276	—C: 246	114.43	(107.42;121.88)
AUC_{∞}, ng.h/mL	33	B: 263	—A: 281	93.40	(87.57; 99.61)
	33	D: 304	—C: 266	116.28	(109.03;124.02)

Treatment A: PEL-1/FASTED; Treatment B: PEL-1/FED; Treatment C: PEL-2/FASTED; Treatment D: PEL-2/FED

There was no apparent relationship between genotype and paliperidone exposure (C_{max}, AUC_{∞}).

PHARMACODYNAMIC RESULTS:

Between 83% and 91% of the subjects had orthostatic hypotension. The highest incidence was seen following treatment with the IR paliperidone oral solution formulation. No clinically relevant differences were observed between the 2 paliperidone ER pellet formulations. The incidence of orthostatic hypotension was lower in the presence of food. The incidence of worst case orthostatism within 3 minutes of standing with each treatment is shown in the table on the next page.

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Parameter	PEL-1/FASTED (N=34) n (%)	PEL-1/FED (N=34) n (%)	PEL-2/FASTED (N=35) n (%)	PEL-2/FED (N=35) n (%)	SOL/FASTED (N=34) n (%)	Total (N=35) n (%)
Pulse (bpm)	21 (62)	17 (50)	24 (69)	18 (51)	28 (82)	32 (91)
SBP (mmHg)	17 (50)	12 (35)	17 (49)	9 (26)	25 (74)	29 (83)
DBP (mmHg)	18 (53)	13 (38)	17 (49)	15 (43)	24 (71)	32 (91)

Note: The incidence of worst orthostatism was calculated as the percentage of subjects for whom the maximal decrease in BP or the maximal increase in pulse was above the predefined limits, or who could not stand. Percentages calculated with the no. of subjects in each group as denominator.
Orthostatic Hypotension criteria: Standing-supine Pulse > +50 bpm or unable to remain standing
Standing-supine SBP < -20 mmHg or unable to remain standing
Standing-supine DBP < -10 mmHg or unable to remain standing
Worst within 3 minutes of standing: most extreme orthostatic hypotension change and worst position (supine > sitting > standing)

SAFETY RESULTS:

All subjects reported at least 1 adverse event during the study. Thirty (88%) of 34 subjects had one or more adverse events following treatment with the IR paliperidone oral solution. The incidence of adverse events under fasting conditions and after consumption of a high-fat breakfast was 79% and 85%, respectively, with the ER pellet formulation-1, and 69% and 74%, respectively, with the formulation-2.

Somnolence (91%), headache (34%), and insomnia and nausea (both 31%) were the most commonly reported adverse events. The majority of adverse events were of mild or moderate intensity. Somnolence, insomnia, headache and viral infection were of severe intensity in more than 10% of the subjects overall. There were no deaths or other serious adverse events during this study, and no subjects withdrew due to an adverse event.

There were no consistent or clinically relevant changes in mean laboratory values at endpoint, and none of the subjects had a laboratory abnormality reported as an adverse event.

No clinical relevant changes in mean ECG parameters were noted during this study. There were no QTc values above 500 ms and none of the subjects had a prolonged QTc interval. Two subjects had a borderline QTcB interval at the end of the study; one of these subjects also had a borderline abnormal QTcF and QTlc value. There were no increases from baseline above 60 ms.

CONCLUSION:

A single oral dose of paliperidone given as 2 mg IR oral solution, or as 2 different ER pellet formulations of 2.5 mg paliperidone under fasting conditions and after consumption of a high-fat breakfast was safe and tolerated.

The incidence of orthostatic hypotension following treatment with the 2 paliperidone ER pellet formulations was lower than with the IR paliperidone oral solution formulation, with no clinically relevant differences between the 2 ER pellet formulations. The incidence of orthostatic hypotension was lower in the presence of food.

The relative bioavailability based on AUC was around 61% for the ER pellet formulation-1, and 57% for the ER pellet formulation-2. The 90% CIs were rather small.

There was no food effect for the ER pellet formulation-2, since the 90% CIs for C_{max}, AUC_{last} and AUC_{∞} (fed/fasted treatment) were contained in the bioequivalence interval of 80-125%. The 90% CIs for AUC_{last} and AUC_{∞} (fed/fasted treatment) for the ER pellet formulation-1 were also contained in the bioequivalence interval of 80-125%, but the 90% CI of C_{max} was 69-79%, which is below the 80-125% bioequivalence limits. Based on these results, a food effect can not be excluded for the ER pellet formulation-1.

There was no apparent relationship between CYP2D6 genotype and paliperidone exposure.

Date of the report: 24 January 2005

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