SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: NAME OF ACTIVE INGREDIENT: Paliperidone	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: R076477-P01-1006, CR004936

Title of Study: A Randomized, Open-Label, Crossover Study to Evaluate the Effect of Food on the Pharmacokinetics of ER OROS® Paliperidone in Healthy Japanese Subjects

Principal Investigator: M. Leibowitz, M.D. – California Clinical Trials, Glendale, CA; USA

Publication (Reference): None

Studied Period (years): Clinical Conduct: 15 March 2004 – 18 May 2004 Sample Analysis: 07 June 2004 - 11 June 2004	**Phase of development:** 1

Objectives: To evaluate the effect of food on the pharmacokinetics of extended-release (ER) OROS paliperidone in healthy Japanese adults and to assess the safety and tolerability.

Methodology: This was a randomized, open-label, single-center, crossover study to evaluate the effect of food on the pharmacokinetics of extended-release (ER) OROS paliperidone in healthy Japanese adults. Of the 20 Japanese subjects who were enrolled, at least 6 were to be men and 6 were to be women. All subjects received single doses of 3 mg ER OROS paliperidone with and without a standard Japanese breakfast. There was a 1-week washout between treatments, for total treatment duration of approximately 2 weeks. Subjects were randomly assigned to 1 of 2 treatment sequence groups. The pharmacokinetics of paliperidone were assessed for 96 hours after each dosing. Safety and tolerability were monitored throughout the study.

Number of Subjects (planned and analyzed):

	Pharmacokinetics (male:female)	Statistical Analysis of Food Effect (male:female)	Safety (male:female)
Planned	20 (at least 6 of each sex)		20 (at least 6 of each sex)
Enrolled	20 (12:8)		20 (12:8)
Analyzed	20 (12:8)	18 (10:8)	20 (12:8)

Diagnosis and Main Criteria for Inclusion: Healthy Japanese subjects who were born in Japan of Japanese parents, and have not lived outside of Japan for more than 5 years, between the ages of 20 and 45 years (inclusive); Body Mass Index (BMI) 18 to 25 kg/m^2 (inclusive); normotensive with systolic blood pressure (SBP) between 100-139 mmHg and diastolic blood pressure (DBP) between 60-89 mmHg; considered healthy based on physical examination, medical history, electrocardiogram (ECG) and the results of blood chemistry, hematology tests and urinalysis.

Test Product, Dose and Mode of Administration, Batch No.: ER OROS paliperidone (formulation number: F016; batch number: MV0307085), 3 mg tablets, single oral dose, once under fasting and once under fed conditions.

Reference Therapy, Dose and Mode of Administration, Batch No.: None

Duration of Treatment: Two single-dose periods with 1-week washout in between. The duration of the open-label treatment period was approximately 2 weeks.

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: NAME OF ACTIVE INGREDIENT: Paliperidone	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Criteria for Evaluation:

Pharmacokinetics: Based on the actual pharmacokinetic blood sampling times, the following pharmacokinetic parameters were determined for paliperidone: C_{max}, t_{max}, $t_{1/2}$, λ_z, AUC_{last} and AUC_∞.

The lower limit of quantification of the LC-MS/MS method was 0.100 ng/mL (all samples).

Safety: Safety evaluation was based on reports of adverse events, change from baseline in clinical laboratory analyte values, vital sign measurements, postural changes in blood pressure and heart rate and orthostatic hypotension (based on the Orthostatic Hypotension Questionnaire), sedation (based on the Sedation Visual Analog Scale [VAS] and Sedation Questionnaire), electrocardiograms, and physical examination findings.

Statistical Methods:

Pharmacokinetics: Descriptive statistics and graphical presentation of the paliperidone plasma concentrations and derived pharmacokinetic parameters. Statistical analysis of log-transformed AUCs and C_{max} (only data of subjects who completed both treatments were included). Calculation of the classical 90% confidence intervals for ratio of mean AUCs and C_{max} obtained when administered in fed state to those obtained in fasted state. Absence of food effect would be concluded if the 90% confidence interval fell within 70 to 143% range.

Safety: Safety data were summarized by descriptive statistics and frequency counts.

SUMMARY – CONCLUSIONS

BASELINE CHARACTERISTIC–SUBJECT DISPOSITION:

A total of 20 healthy male (12) and female (8) Japanese subjects, between ages 20 and 41 years, with a BMI ranging from 18.7 to 24.8 kg/m^2 were enrolled in the study. One subject was withdrawn from the study by the sponsor after Period 1 because of a positive drug screen, and 1 subject withdrew his consent after Period 1.

PHARMACOKINETIC RESULTS:

The following table shows the pharmacokinetic parameters of paliperidone (mean ± SD) in Japanese subjects after single-dose administration of 3 mg ER OROS paliperidone under fed and fasted conditions. The treatment ratios and associated 90% confidence intervals are presented for C_{max}, AUC_{last} and AUC_∞.

Summary of pharmacokinetic parameters for paliperidone (mean ± SD)

	FED (n=20)	FASTED (n=18)	FED/FASTED ratio (%) (n=18)	90% CI (n=18)
C_{max} (ng/mL)	5.49 ± 4.59	3.81 ± 2.24	135.58	100.06-183.70
t_{max} (h)	21.06 ± 4.08	22.46 ± 3.32	-	-
$t_{1/2}$ (h)	19.2 ± 3.42	20.1 ± 4.03	-	-
AUC_{last} (ng.h/mL)	167 ±135	117 ± 70.8	137.11	104.05-180.68
AUC_∞ (ng.h/mL)	178 ±148	124 ± 74.5	136.52	103.50-180.08

Note: Two subjects completed only 1 of the 2 periods; these subjects were excluded from the statistical analysis.

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: NAME OF ACTIVE INGREDIENT: Paliperidone	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Peak plasma concentrations occurred after approximately 22 hours, both in fed and fasted conditions. Peak plasma concentrations under fed conditions were higher compared with fasting conditions. The half-life was similar for both treatments, at about 19 hours. Exposure to paliperidone was higher under fed conditions (mean AUC_{∞} = 178 ng.h/mL) compared with fasting conditions (mean AUC_{∞} = 124 ng.h/mL). AUC values showed large intersubject variability, indicated by the high %CV (about 80% in the fed condition and 60% in the fasted condition).

The treatment ratios for C_{max}, AUC_{last} and AUC_{∞} were 135.58%, 137.11% and 136.52%, respectively. The associated 90% confidence intervals for the pharmacokinetic parameters fell outside the 70 to 143% range, with respect to the upper end of the confidence interval.

SAFETY RESULTS:

Fifty percent of subjects reported 1 or more adverse events (a total of 23 treatment-emergent adverse events). The most frequently reported events were diarrhea, abdominal pain, dizziness and orthostatic hypotension. Twenty-five percent of subjects reported 1 or more adverse events that were considered to be possibly related to the treatment (12 adverse events). Of the adverse events possibly related to treatment, orthostatic hypotension and dizziness were most frequently reported. Most events were mild. There were no adverse events of severe intensity. Three adverse events of moderate intensity were reported: abdominal pain and back pain (considered not related) and orthostatic hypotension (possibly related). There were no deaths, other serious events or events leading to discontinuation of treatment.

There were no clinically relevant changes in laboratory parameters and ECG findings. Mean values for vital signs did not change over the study period. A low incidence of orthostatic hypotension was observed. In the majority of subjects, no significant sedation was observed following both treatments, as assessed by sedation VAS and questionnaire.

The safety observations were in line with those made earlier in healthy volunteer studies in non-Japanese subjects.

CONCLUSION:

There was an increased exposure to paliperidone in the fed condition compared with the fasted condition (about 40%). The associated 90% confidence intervals of the treatment ratios of C_{max} and AUCs fell outside the 70 to 143% range, with respect to the upper end of the confidence interval. Therefore, the absence of food effect cannot be concluded.

Single oral doses of 3 mg ER OROS paliperidone were safe and generally well tolerated in Japanese males and females, in fed and fasted conditions.

Date of the report: 13 January 2005

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.