SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: Paliperidone ER NAME OF ACTIVE INGREDIENT(S): (+)-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	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: R076477-SCH-1016 CR007561 **Title of Study:** A Randomized, Open-Label, Single-Center, Crossover Study of the Potential Effects of Paroxetine on the Pharmacokinetics of a Single Dose of Paliperidone Extended-Release in Healthy Men		
Principal Investigator: Paul van Hoek, M.D. - Farma Research B.V., Nijmegen; Netherlands		
Publication (Reference): None.		
Studied Period (years): Clinical Conduct: 5 April 2006 – 25 July 2006 Sample Analysis: 3 July 2006 - 4 August 2006		**Phase of development:** 1
Objectives: The objective of this study was to evaluate the effects of a CYP2D6 inhibitor, paroxetine, on the pharmacokinetics of a single dose of orally administered paliperidone ER. The safety and tolerability of the 3-mg tablet of paliperidone ER administered with and without paroxetine to healthy men were also assessed.		
Methodology: This was a randomized, open-label, single-center, single-dose, 2-treatment, 2-way crossover study. It consisted of 3 phases: a screening phase beginning within 21 days before the first study drug administration; an open-label treatment phase consisting of 2 treatment periods (Period 1 and Period 2), during which subjects received 2 single doses of 3 mg paliperidone ER; and end-of-study evaluations upon completion of all the study procedures in Period 2 or at early withdrawal. All subjects received each of the following 2 treatments in random order: Treatment A: 1 tablet of 3-mg paliperidone ER in the fasted state; Treatment B: one 20-mg paroxetine tablet once a day from Day 1 to Day 13 and 1 tablet of 3-mg paliperidone ER on Day 10 in the fasted state.		
Number of Subjects (planned and analyzed): Sixty subjects were planned with the intention that at least 50 complete the study. Sixty subjects were enrolled and 50 completed the study. Pharmacokinetic data were analyzed from 57 subjects and safety data were analyzed from 60 subjects..		
Diagnosis and Main Criteria for Inclusion: Subjects were healthy males between the ages of 18 and 55, inclusive, and were extensive metabolizers of CYP2D6. They were healthy on the basis of physical examination, medical history, 12-lead ECG, and laboratory results of serum chemistry, hematology, and urinalysis performed within 21 days before the first dose.		
Test Product, Dose and Mode of Administration, Batch No.: Paliperidone ER 3-mg tablets for oral use, batch no. 0500130, formulation F016.		
Reference Therapy, Dose and Mode of Administration, Batch No.: None		
Duration of Treatment: Two separate doses of paliperidone ER, separated by a washout period of 14-28 days. One 20-mg paroxetine tablet once a day for 13 days.		
Criteria for Evaluation: Pharmacokinetics: In each treatment period, for the determination of the plasma concentration of paliperidone, venous blood samples of 4 mL were taken from an antecubital vein within 2 hours before dosing, and during the 96 hours following dosing with paliperidone ER. Venous blood samples of 4 mL for determination of paroxetine plasma concentrations were collected predose in the morning of Day 1 in Treatment A and predose in the morning of Days 10, 11, and 12 in Treatment B. Prior to dosing on Day 1 of Period 1, a 15-mL venous blood sample was taken for the determination of plasma-protein binding of paliperidone and paroxetine (alone and in combination).		

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Criteria for Evaluation (continued):

Based on the individual plasma concentration-time data, using the actual sampling times, the following pharmacokinetic parameters of paliperidone were estimated for each of the treatments: C_{max}, t_{max}, t_{last}, AUC_{last}, AUC_{∞}, $\%AUC_{\infty,ex}$, CL/F, CL_u/F, λ_z, $t_{1/2term}$.

Safety: Adverse events: The occurrence of all adverse events was documented in the CRF. Laboratory tests: hematology, serum chemistry, and urine were analyzed at screening and at end-of-study or at early withdrawal. Twelve-lead ECGs and physical examination were performed at screening and at end-of-study or at early withdrawal. Vital signs were measured at various time points throughout the study.

Statistical Methods:

Pharmacokinetics: Descriptive statistics were calculated for the plasma paliperidone and paroxetine concentrations at each sampling time and for all derived plasma pharmacokinetic parameters of paliperidone for both treatments. The treatment ratios (with vs. without coadministration of paroxetine) of AUCs and C_{max} of paliperidone were listed for all individuals and were summarized similarly. For statistical analysis, the pharmacokinetic parameters C_{max}, AUC_{∞}, and AUC_{last} of paliperidone were compared between both study treatments. The natural logarithm-transformed estimated primary pharmacokinetic parameters were fitted in a mixed-effect model that included sequence, period, and treatment as fixed effects, and subject as random effect. The least-square means and intrasubject variability estimated from the mixed-effect model were used to construct 90% confidence intervals (CIs) for the difference in means on the natural logarithm scale between the 2 treatments.

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

SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS: Pharmacokinetic parameters were available from 57 subjects after administration of paroxetine plus paliperidone ER and from 50 subjects after administration of paliperidone ER alone. Overall, paliperidone plasma concentrations were higher after administration of paliperidone ER and paroxetine than after administration of paliperidone ER alone. The terminal elimination half-life was similar for both treatments. The fraction of unbound paliperidone was 23% when measured both alone and in the presence of paroxetine.

Summary of Pharmacokinetic Parameters (Mean ± SD) of Paliperidone

Treatment	C_{max} (ng/mL)	AUC_{last} (ng.h/mL)	AUC_{∞} (ng.h/mL)	CL/F (L/min)	$t_{½term}$ (h)
Paliperidone ER alone (N=50)	5.10 ± 1.92	185 ± 73.4	200 ± 82.3	0.301 ± 0.148	22.4 ± 3.80
Paliperidone ER + paroxetine (N=57)	5.72 ± 2.21	214 ± 77.4[a]	236 ± 86.6	0.249 ± 0.114	23.5 ± 3.85

[a] N=56

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PHARMACOKINETIC RESULTS: (continued)

Median time to peak paliperidone plasma concentration was 24 hours for both treatments.

Difference in exposure to paliperidone between the treatments was evaluated using a mixed-effect model. The 90% confidence interval of the treatment ratio of peak concentration (98.03-121.69%) fell within the acceptable range of 80-125% for bioequivalence. AUCs were increased by an estimated 16% after administration of paroxetine (90% confidence interval for the treatment ratio: 102.79-127.91% for AUC_{last} and 104.49-129.84% for AUC_{∞}).

SAFETY RESULTS: The most common adverse events reported by subjects who received only paliperidone ER were somnolence and headache (20% and 22%, respectively). There was no clinically relevant increase in the incidence of adverse events in subjects who received both paliperidone ER and paroxetine compared to those who received paliperidone ER alone. The overall incidence of adverse events was lower in subjects who received both paliperidone ER and paroxetine compared to subjects who received paroxetine alone (68% versus 77%). Events that occurred with a higher frequency in subjects who received the combination were headache (17.5% vs. 11.7%) and fatigue (8.8% vs. 6.7%). There were no deaths or other serious adverse events during the study. There were no clinically relevant changes in vital signs, laboratory values, or ECGs.

CONCLUSION: Paliperidone ER was well tolerated in this study, and there were no unexpected safety findings. Slight increases in the C_{max}, AUC_{last} and AUC_{∞} of paliperidone resulting from the coadministration of paliperidone ER and paroxetine are not clinically relevant. Initiation or discontinuation of treatment with a CYP2D6 inhibitor does not warrant an adjustment in the dosage of paliperidone ER.

Date of the report: 03 NOVEMBER 2006

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