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	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: R076477-REI-1001 CR004207		
Title of Study: The Pharmacokinetics of ER OROS Paliperidone in Subjects with Varying Degrees of Impaired Renal Function (Mild, Moderate, and Severe) as Compared to Subjects with Normal Renal Function		
Principal Investigator: K-H Molz, M.D., APEX GmbH, D-81241 München, Germany. **Second Investigator:** J. Arvid, M.D., PHAROS GmbH, D-89081 Ulm, Germany.		
Publication (Reference): None		
Studied Period (years): Clinical Conduct: 19 April 2004 – 1 February 2005		**Phase of development:** 1
Objectives: The primary objective of the study was to evaluate the pharmacokinetics (PK) of a single oral dose of 3 mg Extended-release paliperidone (ER OROS® paliperidone) in subjects with varying degrees of renal impairment (mild, moderate, and severe), compared to subjects with normal renal function. Data from 12 subjects per renal function group were considered sufficient for explorative purposes. Secondary objectives were: to assess the disposition of the (+) and (–) enantiomers by means of an enantioselective liquid chromatography-mass spectrometry (LC MS/MS) assay and to determine plasma protein binding (PPB) of the enantiomers in subjects with impaired renal function, compared with subjects with normal renal function. The tolerability and safety profile of ER OROS paliperidone was also assessed in subjects with varying degrees of renal impairment (mild, moderate, and severe) compared with subjects with normal renal function.		
Methodology: This was a single-dose, parallel-group, open-label, 2-center PK study, consisting of a pretreatment (screening) period of between 1 and 3 weeks, an open-label treatment period (single dose of ER OROS paliperidone on Day 1 only, and with end-of-study procedures and discharge ending on Day 6). All subjects came to the study site between Day -21 and Day -1 for screening procedures, including collection of plasma samples for the prediction of creatinine clearance (CL_{CR}) according to the Cockcroft-Gault formula on 2 occasions at least 1 week apart. The mean of the 2 values was used in assigning subjects to 1 of 4 renal function groups. On Day 1, all subjects received a single oral dose of 3 mg ER OROS paliperidone and underwent a 120-hour follow-up with serial blood collections for PK, safety and tolerability assessments. Subjects were discharged after giving a PK blood sample and completing end-of-study assessments in the morning of Day 6. Group matching was applied to the renal function groups to reduce bias and increase comparability of age, weight, gender, and ethnicity		
Number of Subjects (planned and analyzed): Planned: 48 subjects (12 subjects in normal subjects, mild renal impairment-, moderate renal impairment-, and severe renal impairment groups). Analyzed: normal, 12; mild renal impairment, 11; moderate renal impairment, 12; severe renal impairment, 10.		
Diagnosis and Main Criteria for Inclusion: Men and women aged 18 to 75 years, inclusive, and who met the inclusion and exclusion criteria for this study, were enrolled with the intent that at least 48 subjects would complete the treatment. Group matching was applied to make the renal function groups demographically balanced in age (±10 years), weight (±20%), gender, and ethnicity. Subjects were classified at screening into renal function groups based on the means of their 2 predicted CL_{CR} values determined using the Cockcroft-Gault formula.		
Criteria for Evaluation: Pharmacokinetics: Venous blood samples were collected at specified time points from predose through 12 hours postdose. A complete urinary output for CL_{CR} was collected at specified intervals from dosing on Day 1 through 120 hours on Day 6. Safety: Evaluated by examining the incidence, severity and type of adverse events, changes in clinical laboratory results, physical examination results, vital sign measurements, 12-lead electrocardiograms, and concomitant medications. Urine pregnancy test, urine drug screening and alcohol breath test results were assessed. 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.		
Duration of Treatment: Treatment on Day 1, followed by 5 days of PK and safety assessments.		

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Test Product, Dose and Mode of Administration, Batch No.: ER OROS paliperidone 3 mg tablets; oral administration on Day 1, Batch No. MV0307085.

Statistical Methods: Sample size determination: No formal sample size calculation was performed. A sample size of 12 subjects per renal function group was considered sufficient for exploratory purposes.

Plasma and urine concentrations: Individual plasma concentrations-time profiles of paliperidone and its enantiomers were plotted both on a linear and log scale for each renal functional group. Mean and median plasma concentration-time profiles were also graphically presented for each renal function group. Plasma and urine concentration data at each time point were summarized by mean, median, standard deviation (SD), minimum, maximum, and coefficient of variation (CV%) for all renal function groups. The enantiomer disposition between the renal function groups was compared using descriptive statistics.

Pharmacokinetic results: All estimated PK parameters were summarized by renal function group, and expressed as the mean, median, minimum, maximum, SD, and CV. PK parameters were graphically presented for each renal function group, and plotted versus CL_{CR} on a continuous scale. A linear regression model was fitted to evaluate the relationship between the estimated PK parameters and CL_{CR} as a continuous variable. Confidence limits for predicting of PK parameters over a range of CL_{CR} to support dosing recommendations were not produced.

Safety Analyses: Safety data were summarized using descriptive statistics and incidence tables

Demographic data and Baseline Characteristics: Forty-seven subjects completed the study as per the study protocol. The 4 renal functional groups were well balanced with regard to age, weight, BMI, sex, and ethnicity.

Pharmacokinetics Results: Plasma protein binding of paliperidone and its enantiomers was comparable between the four different renal function groups. Overall, mean plasma protein binding values were about 80% for R078543 (+) and about 60% for R078544 (-). Plasma concentrations of total and unbound paliperidone were the highest in subjects with moderate and severe renal impairment, followed by subjects with mild renal impairment and those with normal renal function. The median time to reach the maximum plasma concentration was 20.5 hours for healthy subjects and 24 hours for each renal impairment group. Intersubject variability was high but similar between the different renal function groups. The mean terminal half-life of paliperidone increased from 23.2 hours in healthy subjects to 51.0 hours in subjects with severe renal impairment. The mean terminal half-lives of the enantiomers were very similar to those of paliperidone.

Pharmacokinetic Parameters of Paliperidone and its Enantiomers

	Paliperidone							
	Healthy Subjects		Mild Renal Impairment		Moderate Renal Impairment		Severe Renal Impairment	
	n	Total	n	Total	n	Total		Total
C_{max}, ng/mL	12	2.63 ± 1.61	11	4.29 ± 2.39	12	6.65 ± 5.46	10	5.55 ± 2.81
AUC_{∞}, ng.h/mL	12	114 ± 74.0	11	169 ± 83.1	12	416 ± 444	10	429 ± 247
t_{max}, h	12	20.5 (12.0 – 26.0)	11	24.0 (12.0 – 26.0)	12	24.0 (12.0 – 28.0)	10	24.0 (16.0 – 26.0)
$t_{1/2}$, h	12	23.2 ± 7.8	11	23.6 ± 4.9	12	40.2 ± 18.3	10	51.0 ± 15.4
CL/F, mL/min	12	561 ± 225	11	433 ± 400	12	271 ± 253	10	217 ± 261
V_{dz}, L	12	1045 ± 374	11	751 ± 349	12	770 ± 653	10	779 ± 653
CL_R, mL/min	12	70.5 ± 26.8	11	49.2 ± 16.8	11	21.9 ± 11.9	10	12.9 ± 9.64
CL_{NR}, mL/min	12	491 ± 204	11	384 ± 386	11	268 ± 250	10	204 ± 253
Ae, %dose	12	13.2 ± 3.74	11	15.2 ± 6.81	11	9.80 ± 5.40	10	7.47 ± 2.40

Mean ± SD; for t_{max}: median (range)

Apparent total clearance (CL/F) of both total and unbound paliperidone declined with increasing degree of renal impairment and was about 60% lower in subjects with severe renal impairment compared to healthy subjects. Regardless of the degree of impairment, renally-impaired subjects had about 25-30% lower volumes of distribution for total paliperidone.

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Pharmacokinetics Results (continued):

In all renal function groups the exposure to total R078543 (+) was higher than the exposure to total R078544 (-). However, for unbound plasma concentrations, the exposure to R078543 (+) was lower than the exposure to R078544 (-). The enantiomer disposition ratio based on the (+)/(-) AUC ratio for the total plasma concentrations increased with increasing degree of renal impairment (i.e., from 1.50 to 1.73). Based on unbound concentrations only a higher (+)/(-) AUC ratio was observed for subjects with severe renal insufficiency. Mean renal function, as determined by the measured creatinine clearance (CL_{CR}) was 107, 79.9, 40.4 and 20.4 mL/min, for the subjects with no, mild, moderate and severe renal impairment, respectively.

Mean renal clearance (CL_R) of paliperidone decreased from 70.5 mL/min in healthy volunteers to 12.9 mL/min in subjects with severe renal impairment. Mean non-renal clearance (CL_{NR}) of paliperidone also decreased with increasing degree of renal impairment, from 491 mL/min to 204 mL/min. The % of the dose excreted in the urine as unchanged paliperidone only decreased about 1.8-fold (from 13.2% to 7.5%, respectively). Unchanged R078544 (-) accounted for about 60% of the excretion of paliperidone into urine. Active renal clearance accounted on average for approximately 50% of the renal clearance of paliperidone, regardless of the renal function group. This indicates that the active renal elimination process is not saturable in the studied plasma concentration range.

Safety Results: After a single dose of 3 mg paliperidone, the most common adverse event across all renal function groups was hyperprolactinaemia (normal renal function group: 83%; mild impairment group: 75%; moderate impairment group: 92%; severe impairment group; 100%). Dizziness, postural hypotension, and headache occurred in 6% of all subjects.

Treatment emergent markedly low RBC (<3tera/L) was observed in 1 subject with moderate renal impairment and 1 subject with severe renal impairment. Other treatment emergent marked abnormalities (1 per subject) were reported for 4 subjects at the end of the study: hematocrit decrease, alkaline phosphatase increase, chloride increase and chloride decrease.

Five subjects experienced orthostatic hypotension as determined by vital sign measurements. One subject with borderline QTcF, QTlc, and prolonged QTcB at baseline had a borderline QTcF, QTlc and QTcB on Day 2 and prolonged QTcF, QTlc, and QTcB on Day 6. The subject's plasma paliperidone levels on Day 2 and Day 6 suggest that there was probably no relation between the increased QTc values and plasma paliperidone levels. No subject had a greater than 60 ms increase in QTc during the study.

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 PK approach using data across multiple clinical trials.

Conclusion: After administration of a single dose of 3 mg ER OROS paliperidone, subjects with mild, moderate and severe renal impairment, had mean C_{max} and AUC_{∞} values of paliperidone that were respectively, about 1.6, 2.5 and 2.1 times, and about 1.5, 2.8 and 3.4 times higher compared to healthy volunteers. The mean terminal half-life of paliperidone increased from 23.2 hours in healthy volunteers to 51.0 hours in subjects with severe renal impairment. The increase in exposure to paliperidone in subjects with renal impairment was related to a decrease in both renal and non-renal clearance in combination with a lower apparent volume of distribution. Protein binding did not differ between the different renal function groups. Overall, mean plasma protein binding was about 80% for R078543 (+) and about 60% for R078544 (-).

A single 3 mg dose of paliperidone was well tolerated by subjects with varying degrees of renal impairment (mild, moderate, or severe), compared to subjects with normal renal function.

Based on the PK data, a reduction in dose of paliperidone should be considered for subjects with moderate and severe renal impairment.

Date of the report: 27 October 2005

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