SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: 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-SCH-1008 CR004204 **Title of Study:** Pharmacokinetics of Paliperidone in Subjects With Moderate Hepatic Impairment as Compared to Subjects With Normal Hepatic Function		
Principal Investigator: Dr. med. Karl-Heinz Molz – APEX GmbH, München (Munich); Germany		
Publication (Reference): None		
Studied Period (years): Clinical Conduct: 23 Aug 2004 – 03 Dec 2004 Sample Analysis: 21 Jan 2005 – 27 Feb 2005		**Phase of development:** 1
Objectives: The primary objective of this study was to investigate the single-dose pharmacokinetics of immediate-release (IR) paliperidone, after oral administration, in subjects having moderate hepatic impairment ("hepatically-impaired subjects") compared with subjects having normal hepatic function ("healthy subjects"). The secondary objective was to document the plasma protein binding and disposition of the enantiomers of paliperidone. In addition, the tolerability and safety profile of IR paliperidone was compared between hepatically-impaired subjects and healthy subjects.		
Methodology: This was a single-dose, parallel-group, open-label, single-center, Phase 1 study of IR paliperidone in subjects having either normal or moderately-impaired hepatic function. The groups, consisting of 10 subjects each, were demographically matched with respect to age, weight, sex, and ethnicity. The study consisted of a screening period of up to 3 weeks and an open-label, single-dose treatment period (Days 1 through 5). On Day 1, a single dose of 1 mg IR paliperidone oral solution was administered after a fast of at least 10 hours; subjects continued to fast for 4 hours following study drug administration. The 96-hour follow-up consisted of serial sample collections of blood and urine for pharmacokinetic analysis and safety and tolerability assessments. Subjects remained confined to the study site through the 72-hour pharmacokinetics sampling, and consumed standard institutional meals while in the study site. Subjects were released after the 72-hour sampling, then returned to the study site on Day 5 before the 96-hour pharmacokinetics sampling; end-of-study procedures were performed immediately thereafter. A blood sample for DNA isolation was collected to allow for genetic analysis as necessary.		
Number of Subjects (planned and analyzed): Ten subjects were planned for each hepatic function group; 10 subjects in each group completed the study and were analyzed for pharmacokinetics and safety.		
Diagnosis and Main Criteria for Inclusion: The study was conducted in men and women, aged 18 through 75 years, inclusive. One group of subjects had moderate hepatic impairment, with stable hepatic disease, a total Child-Pugh score of between 7 and 9, inclusive, and blood pressure that was controlled and stable on antihypertensive agents; the other group had normal hepatic function.		
Test Product, Dose and Mode of Administration, Batch No.: 1 mg IR paliperidone (R076477) oral solution; batch 04C29/F044.		
Reference Therapy, Dose and Mode of Administration, Batch No.: None		
Duration of Treatment: This was a single-dose study.		

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Criteria for Evaluation:

Pharmacokinetics: Plasma and urine concentrations of the paliperidone enantiomers (+) R078543 and (–) R078544 were determined using an LC-MS/MS method. Concentrations of paliperidone were calculated as the sum of the enantiomer concentrations. In addition, serum and urine concentrations of creatinine were determined for the calculation of CL_{CR}. The protein binding and unbound fraction was determined for the 2 paliperidone enantiomers. The unbound fraction for paliperidone was calculated.

Based on the actual pharmacokinetic blood sampling times and actual urine collection periods, the following plasma and urine pharmacokinetic parameters were determined for paliperidone and its enantiomers: C_{max}, t_{max}, t_{last}, AUC_{last}, λ_z, $t_{1/2}$, AUC_∞, $\%AUC_{\infty,ex}$, CL/F, AUC_∞ +/- ratio, C_t +/- ratio per time point, unbound AUC_∞, unbound CL/F or unbound CL (if relevant), Ae (per collection interval and overall), Ae,%dose, Excr. Rate, Vd_z, CL_R, CL_{GFR}, CL_{act}, CL_{act}/CL_R, $CL_{act}/(CL/F)$, CL_{CR}, and CL_{NR}.

Safety: Adverse events, clinical laboratory tests, including prolactin, vital sign measurements, physical examinations, and 12-lead electrocardiograms (ECGs) were analyzed to assess safety.

Statistical Methods:

Pharmacokinetics: Descriptive statistics were calculated for the plasma concentrations at each sampling time, and for all pharmacokinetic parameters of paliperidone and its enantiomers for each hepatic function group. Graphical exploration of the paliperidone and enantiomer plasma concentrations and urine data, and the derived pharmacokinetic parameters, was performed. In addition, the enantiomer disposition was compared between the groups.

Log-transformed PK parameters were fit to a general linear model with hepatic function group as fixed effect.

Safety: All subjects were analyzed; statistical analyses were descriptive.

SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS:

The fraction of unbound paliperidone in plasma was higher in hepatically-impaired subjects compared with healthy subjects and averaged 0.353 and 0.279, respectively. The difference in plasma protein binding between the groups most likely results from the reduced α_1-acid glycoprotein (α_1-AGP) plasma concentration in hepatically-impaired subjects, since the fraction of unbound drug appears to be inversely related to the α_1-AGP plasma concentration.

Predose Plasma Concentrations of Albumin, α_1-AGP, and Total Protein and Unbound Fraction for Paliperidone, (+) R078543, and (−) R078544
(Study R076477-SCH-1008: Pharmacokinetic Analysis Set)

	Healthy Subjects (n=10)	Hepatically-Impaired Subjects (n=10)
Albumin (g/dL)	4.3 ± 0.2	3.3 ± 0.6
α_1-AGP (mg/dL)	77.0 ± 18.8	46.6 ± 17.1
Total Protein (g/dL)	7.2 ± 0.2	6.9 ± 0.7
Unbound Fraction (+) R078543	0.215 ± 0.0469	0.306 ± 0.0687
Unbound Fraction (–) R078544	0.385 ± 0.0416	0.457 ± 0.0504
Unbound Fraction Paliperidone	0.279 ± 0.0492	0.353 ± 0.0564 [a]

All values are mean (±SD).
[a] Descriptive statistics based on n=8, excluding Subjects 0005 and 0006.

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Overall, hepatically-impaired subjects achieved lower total plasma concentrations than healthy subjects. AUC and C_{max} values of paliperidone and each of its enantiomers were lower for hepatically-impaired subjects than for healthy subjects: in each case, C_{max} was approximately 35% lower and AUC_{∞} approximately 27% lower. After correction for unbound fraction, the exposure was comparable between the groups. The median time to reach maximum plasma concentration was around 1 hour for both groups, although somewhat more variable among the hepatically-impaired subjects.

Paliperidone plasma concentrations declined with a mean terminal half-life of 23.6 hours for healthy subjects and 26.5 hours for hepatically-impaired subjects.

The CL/F for paliperidone was about 35% higher in hepatically-impaired subjects compared with healthy subjects, which is consistent with the lower AUC_{∞}. Moreover, hepatically-impaired subjects had 47% higher volumes of distribution for total paliperidone compared with healthy subjects. Based on unbound concentrations, however, the clearance and volume of distribution were comparable between the groups.

Hepatically-impaired subjects showed more variable renal excretion profiles (i.e., larger %CV) than healthy subjects. There were no other apparent differences in urinary excretion parameters between the hepatic function groups. Approximately 50% of the dose was excreted unchanged into urine and did not differ between the groups. Renal clearance was not much different between the groups (67.4 vs. 51.2 ng/mL), which can be expected because the unbound plasma concentrations between the groups are comparable. Renal function, as determined by the creatinine clearance, was almost identical between the groups. Active renal clearance accounted on average for approximately 35% of the renal clearance in both groups.

Pharmacokinetic Parameters of Paliperidone and its Enantiomers

	Paliperidone							
	Healthy Subjects				Hepatically-Impaired Subjects			
	n	Total	n	Unbound	n	Total	n	Unbound
C_{max}, ng/mL	10	7.14 ± 2.28	10	1.81 ± 0.292	10	4.57 ± 1.05	10	1.59 ± 0.318
AUC_{∞}, ng.h/mL	10	176 ± 64.4	10	45.8 ± 8.72	9	128 ± 42.5	8	45.7 ± 12.6
t_{max}, h	10	1.00 (1.00 – 2.00)	10	1.25 (1.00 – 2.00)	10	1.25 (0.25 – 4.00)	10	1.25 (0.25 – 4.00)
$t_{1/2}$, h	10	23.6 ± 3.6		ND	10	26.5 ± 6.4		ND
CL/F, mL/min	10	106 ± 34.9	10	370 ± 67.1	9	143 ± 43.4	8	386 ± 99.3
V_{dz}, L	10	211 ± 59.6	10	748 ± 144	9	311 ± 65.2	8	857 ± 146
CL_R, mL/min	10	51.2 ± 13.4		ND	9	67.4 ± 34.0		ND
CL_{NR}, mL/min	10	54.4 ± 23.7	10	188 ± 56.8	9	75.1 ± 16.2	8	205 ± 30.7
Ae, %dose	10	50.1 ± 7.94		ND	10	44.7 ± 10.62		ND

Mean ± SD; for t_{max}: median (range); ND: Not determined.

When the data from the two hepatic function groups were pooled, there was no apparent relationship between clearance of paliperidone or its enantiomers and most measures of hepatic function (i.e., albumin and bilirubin concentrations, prothrombin time, and Child-Pugh score); there was an inverse relationship between clearance of paliperidone or its separate enantiomers and α_1-AGP concentration.

Exposure to both enantiomers was higher in healthy subjects compared with hepatically-impaired subjects; furthermore, in both groups, exposure to (+) R078543 was higher than exposure to (–) R078544. The (+)/(–)ratio based on the AUC for the total plasma concentrations was somewhat larger in healthy subjects compared with hepatically-impaired subjects (i.e., 1.67 and 1.38, respectively). Based on unbound concentrations, however, the exposure to both enantiomers was within the same range, and the (+)/(–)AUC ratio was comparable between healthy and hepatically-impaired subjects (i.e., 0.914 and 0.886, respectively).

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SAFETY RESULTS:

The only adverse events that were reported in more than 1 subject in either group were hyperprolactinemia (see below) and dizziness (in 2 hepatically-impaired subjects only). Treatment-emergent increases in hepatic enzymes were noted in 1 hepatically-impaired and 1 healthy subject. These elevations were only slightly above the baseline value in the hepatically-impaired subject and less than twice the upper limit of normal in the healthy subject, and thus were not considered clinically important.

An increase in prolactin from the mean predose levels was seen in both hepatically-impaired and healthy subjects at 36 hours; thereafter mean levels decreased. Because the investigator was unblinded to the laboratory results, increases in prolactin levels were reported as adverse events in 8 hepatically-impaired and 6 healthy subjects; these adverse events were considered mild and very likely related to study drug by the investigator.

There were no unexpected findings in vital signs; no subject in either group met the criteria for orthostatic hypotension. Furthermore, no subjects had clinically important abnormal ECG values (including QT values).

CONCLUSION:

After oral administration of 1 mg paliperidone IR, hepatically-impaired subjects had a lower mean C_{max} (≈35%) and AUC_{∞} (≈27%) for total paliperidone and its enantiomers than did healthy subjects.

The protein binding differed between the hepatic function groups. The unbound fraction of paliperidone was approximately 27% higher in hepatically-impaired subjects. Taking this difference in protein binding into account, C_{max} and AUC_{∞} for the unbound fraction of paliperidone were comparable across the hepatic function groups. C_{max} was approximately 12% lower, and AUC_{∞} approximately 5% lower, in hepatically-impaired subjects compared with healthy subjects.

The mean terminal half-life for IR paliperidone and its enantiomers was between 23.6 and 25.0 hours for healthy subjects, and between 26.5 and 27.5 hours for hepatically-impaired subjects.

Paliperidone IR, 1 mg, was tolerated equally well by healthy and hepatically-impaired subjects.

Date of the report: 27 OCTOBER 2005

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