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 / R076477	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: R076477-SCH-102 CR004270 **Title of Study:** Comparison of Steady–State Pharmacokinetics of Paliperidone after Extended-Release OROS® Paliperidone 15 mg and Immediate-Release Oral Risperidone 8 mg b.i.d. in Subjects with Schizophrenia or Schizoaffective Disorder		
Coordinating Investigator: M. Bari, M.D. - Synergy Clinical Research Center, San Diego, CA 92105; U.S.A		
Publication (Reference): None		
Studied Period (years): Clinical Conduct: 8 Sep 2003-17 Jan 2004 Sample Analysis: 18 Dec 2003 – 16 Feb 2004		**Phase of development:** 1
Objectives: The primary objectives of the study were to compare the steady-state pharmacokinetics of paliperidone after oral administration of 15 mg extended-release (ER) OROS paliperidone once daily with the steady-state pharmacokinetics of paliperidone after oral administration of 8 mg immediate-release (IR) risperidone twice daily; and to explore the dose-proportionality of 9 mg and 15 mg ER OROS paliperidone. Secondary objectives were (1) to document the disposition of the enantiomers of paliperidone; (2) to explore the relationship between genotype (*CYP2D6*, *CYP3A4*, *CYP3A5*, *UGT1A1*, and *UGT1A6*) and pharmacokinetic parameters; (3) to assess safety and tolerability.		
Methodology: This was an open-label, multiple-dose, parallel-group study in subjects with schizophrenia or schizoaffective disorder. The study consisted of a screening period (2 weeks maximum); a 1-week run-in or washout (Days 1 to 7) during which subjects taking risperidone prestudy and randomly assigned to paliperidone treatment received replacement antipsychotic therapy, and other subjects continued to take their prestudy antipsychotic medication; a 14-day open-label treatment period (Days 8 to 21); and a 5-day follow-up period. On Day 1 of the washout period, eligible subjects were randomized to receive ER OROS paliperidone (PAL) or risperidone (RIS). All subjects received their first dose of study medication on Day 8 after randomization as follows: Subjects randomized to PAL received 9 mg of ER OROS paliperidone q.d. from Day 8 to Day 14, followed by 15 mg of ER OROS paliperidone q.d. from Day 15 to Day 21. Subjects randomized to RIS received dose-escalation up to 7 mg risperidone b.i.d. from Day 8 to Day 14, followed by 8 mg risperidone b.i.d. from Day 15 to Day 21. The study medication on Days 14 and 21 in the PAL group and on Day 21 in the RIS group was administered after completion of a standardized high fat, high caloric breakfast. Subjects were confined to the testing facility from the morning of Day 8 (or earlier at the discretion of the investigator) until completion of the study procedures on Day 23. On all other assessment days, subjects returned to the testing facility and remained there for the duration of the assessments.		
Number of Subjects (planned and analyzed): Subjects were enrolled to ensure that at least 45 subjects (30 in the PAL group and 15 in the RIS group) completed the study. Analyzed: 53 subjects (36 on PAL treatment and 17 on RIS treatment) for safety and pharmacokinetics.		
Diagnosis and Main Criteria for Inclusion: This study was conducted in male and female subjects, aged 18 to 50 years, inclusive, with a diagnosis of schizophrenia or schizoaffective disorder, who were treated with a daily dose of at least 6 mg of risperidone or an equivalent dose of any other antipsychotic medication or a combination thereof.		
Test Product, Dose and Mode of Administration, Batch No.: 3 mg and 9 mg ER OROS paliperidone (R076477) tablets; oral administration of 9 mg q.d. on Day 8 to 14, and 15 mg q.d. on Day 15 to 21; MV0301019 and MV0301025.		
Reference Therapy, Dose and Mode of Administration, Batch No.: 1 mg and 4 mg risperidone (R064766) tablets; oral administration of escalating doses up to 7 mg risperidone b.i.d. between Days 8 and 14, inclusive, and 8 mg risperidone b.i.d. on Day 15 to 21; 3GG086, 3HG128, 3GG079, and 3GG110.		
Duration of Treatment: 2 weeks		

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Criteria for Evaluation:

Pharmacokinetics Based on the actual sampling times, the following pharmacokinetic parameters were determined for paliperidone and its 2 enantiomers on Day 14 and Day 21 (PAL treatment), and for paliperidone, its enantiomers, risperidone and the active moiety (= sum of paliperidone and risperidone) on Day 21 (RIS treatment): $C_{trough,Dx}$, $C_{min,ss}$, $C_{max,ss}$, t_{max}, $AUC_{0\text{-}24h,ss}$, $C_{avg,ss}$, FI, CL/F, λ_z, and $t_{1/2,\lambda}$. For the enantiomer analysis the following additional pharmacokinetic parameters were estimated: C_{max} and AUC ratio of (+)/(-) paliperidone, calculated as $C_{max,R078543}/C_{max,R078544}$ and $AUC_{R078543}/AUC_{R078544.}$ Serum creatinine values, determined on Day 14 (PAL treatment) and Day 21 (PAL and RIS treatment), predose, were used for determination of the creatinine clearance.

The lower limits of quantification for the enantiomers and risperidone were 0.200 ng/mL (most samples), and 0.400 ng/mL (4 samples for risperidone) and 0.800 ng/mL (2 samples for risperidone).

Safety: (Serious) adverse events (AEs), clinical laboratory tests, prolactin levels, vital signs measurements, physical examination, and ECG.

Statistical Methods:

Pharmacokinetics: Descriptive statistics were calculated for the plasma concentrations of paliperidone and its enantiomers (PAL and RIS treatment), the active moiety and risperidone (RIS treatment), at each sampling time and for the derived pharmacokinetic parameters. The enantiomer disposition between the paliperidone and risperidone groups were compared using descriptive statistics.

The primary comparison of PAL 15-mg q.d. and RIS 8-mg b.i.d. were performed by constructing, per treatment, 95% confidence intervals (CIs) on the log-transformed primary pharmacokinetic parameters ($C_{min,ss}$, $C_{max,ss}$, and $AUC_{0\text{-}24h,ss}$). The analysis was performed on log-transformed pharmacokinetic parameters of paliperidone (primary substance) and its enantiomers. These CIs were compared and evaluated for overlap. Secondary, analysis of variance models were fitted to log-transformed data from PAL 15-mg q.d. and RIS 8-mg b.i.d. with treatment as a fixed factor to estimate the least square means and inter-subject variance. Using these estimates, 90% CIs were constructed for the ratio of the mean pharmacokinetic parameters from PAL 15-mg q.d. to RIS 8 mg b.i.d.

For exploration of dose-proportionality, the primary pharmacokinetic parameters $C_{max,ss,}$ and $AUC_{0\text{-}24h,ss}$ of paliperidone and its enantiomers (PAL 9-mg q.d. and PAL 15-mg q.d.) were dose-normalized to a dose of 15 mg q.d. Analysis of variance models were fit to the log-transformed, dose-normalized data from PAL 9-mg q.d. and PAL 15-mg q.d. with treatment as a factor to estimate the least square means and intra-subject variance. Using these estimates, 90% CIs for the ratio of mean pharmacokinetic parameters from PAL 15-mg q.d. to PAL 9-mg q.d. were constructed.

Safety: Safety parameters were summarized with descriptive statistics and incidence tables by randomization group and time point. These summaries were performed in the intent-to-treat population, unless specified otherwise. To support the key numerical summaries, graphical representations were produced.

SUMMARY – CONCLUSIONS

Sixty-two subjects were randomly assigned to treatment: 42 subjects to the PAL group and 20 subjects to the RIS group. Six subjects randomly assigned to PAL and 3 subjects randomly assigned to RIS discontinued during the washout period, so that 53 subjects started treatment on Day 8 (36 subjects with 9 mg PAL q.d. and 17 subjects with an initial dose of 1 mg or 3 mg RIS b.i.d.). Seven subjects discontinued during treatment: 3 subjects during the first week of treatment with 9 mg PAL q.d.; 1 subject during the second week of treatment with 15 mg PAL q.d.; 1 subject during the first week of treatment with 5 mg RIS b.i.d.; and 2 subjects during the second week of treatment with 8 mg RIS b.i.d. Forty-six subjects completed the study. Three subjects discontinued due to adverse events, and 4 subjects discontinued due to withdrawal of consent.

Most subjects were male (81%), 25 to 50 years old, with schizophrenia, mostly of the paranoid type (70%).

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PHARMACOKINETIC RESULTS:

Steady state was reached after approximately 4 to 5 days on the same dose.

The steady-state exposure based upon $AUC_{0\text{-}24h,ss}$, $C_{max,ss}$ and $C_{min,ss}$ of paliperidone and both its enantiomers was lower for the PAL 15-mg q.d. treatment group compared to the RIS 8-mg b.i.d. treatment group for both the means and observed maximums. The primary analysis showed that the associated 95% confidence intervals (CIs) did not overlap.

At steady state, the $AUC_{0\text{-}24h,ss}$ for paliperidone in the PAL 15-mg q.d. group was about 36% of that for active moiety in the RIS 8-mg b.i.d. treatment group (based upon mean $AUC0\text{-}24_{h,ss}$ values). Therefore, 15 mg/day ER OROS paliperidone corresponds to approximately 5.4 mg/daily IR risperidone when comparing paliperidone and active moiety exposures.

The paliperidone $AUC_{0\text{-}24h,ss}$ and $C_{max,ss}$ treatment ratios for PAL 9-mg q.d. and PAL 15-mg q.d. (in reference to PAL 9-mg q.d.) were 87.25% and 83.46%, respectively. The 90% CIs for both parameters fell outside the bioequivalence range of 80-125%, with respect to the lower CI (70.50-107.98 and 66.79-104.28 for $C_{max,ss}$ and $AUC_{0\text{-}24h,ss}$, respectively). When excluding Subject 100106, who was suspected of being non-compliant with study medication intake, the treatment ratios for $C_{max,ss}$ and $AUC_{0\text{-}24h,ss}$ (92.99% and 96.41%, respectively) and associated 90% CIs (81.59-105.98 and 84.34-110.22, respectively) fell inside the bioequivalence range of 80-125%.

The mean $C_{max,ss}$ and mean $AUC_{0\text{-}24h,ss}$ values were higher for R078543 (+) compared to R078544 (-), in both PAL and RIS treatment groups. The ratios $C_{max(R078543/R078544)}$ and $AUC_{(R078543/R078544)}$ ranged from 1.23-2.18 and 1.21-2.02 for the PAL 9-mg q.d. treatment group and 1.22-1.97 and 1.26-1.97 for the PAL 15-mg q.d. treatment group versus 2.33-3.78 and 1.77-3.19 for the RIS treatment group, respectively (all subjects).

There was no difference in (+)/(-) enantiomer ratio in function of the paliperidone dose given. The mean enantiomer ratio at the end of the PAL 9-mg q.d. dosing period (Day 14, 24-hour sample) was 1.57±0.235 and 1.59±0.224 at the end of the PAL 15-mg q.d. dosing period (Day 21, 24-hour sample).

There was no clear relationship between total clearance of paliperidone, its enantiomers (in both PAL and RIS treatments) and active moiety (RIS treatment) and creatinine clearance for both treatments.

Following PAL treatment, no relevant differences were observed in the paliperidone pharmacokinetic parameters for different *CYP2D6* genotypes. Also for other genes determined (*CYP3A4/5* and *UGT1A1/6*), no clear relationship was observed. However, no definitive conclusion can be drawn due to the limited number of CYP2D6 poor metabolizers (n=1) as compared to the number of CYP2D6 extensive metabolizers (n=25), and due to the limited number of subjects with certain allele combinations.

SAFETY RESULTS:

The most commonly reported adverse events (i.e., reported by more than 15% of the subjects) in the ER OROS paliperidone treatment groups were headache (31%), insomnia (25%), anxiety (22%), postural hypotension (19%), and dyspepsia and vomiting (both 17%). The most commonly reported adverse events in the risperidone group were extrapyramidal disorder (41%), postural hypotension (35%), somnolence (29%), headache and dry mouth (both 24%), and anxiety (18%). Overall, ER OROS paliperidone seemed to cause less extrapyramidal disorder (14 versus 41%, respectively) and less postural hypotension (19 versus 35%, respectively) compared to risperidone.

Three subjects discontinued from the open-label treatment phase due to the occurrence of adverse events. The events were: postural hypotension with risperidone treatment (very likely related); peripheral edema, abnormal hepatic function, heart murmur, weight increase, and pulmonary edema with risperidone treatment (possibly or probably related); and agitation with ER OROS paliperidone treatment (not related).

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SAFETY RESULTS: (continued)

Overall, there were no consistent or clinically relevant changes in mean laboratory values at endpoint. Two subjects in each treatment group had abnormal laboratory values reported as an adverse event during open-label treatment. The adverse events preferred terms were: 'hepatic function abnormal' and 'SGPT increased' with risperidone treatment, and 'SGOT increased' and 'hyperkalemia' and 'hypernatremia' with 9 mg ER OROS paliperidone.

There was an increase in mean prolactin concentrations from Day 8 to Day 14, however no further increase was observed on Day 21 and baseline levels were achieved 120 hours after discontinuation of trial medication. Mean prolactin concentrations were slightly higher in the ER OROS paliperidone treatment group. As this increase was low, this was not considered clinically relevant. Three subjects had hyperprolactinemia reported as an adverse event during open-label treatment with ER OROS paliperidone. No subjects had hyperprolactinemia during treatment with risperidone.

Overall, there were no clinically meaningful differences between treatment groups with respect to mean vital signs values, although the increase in pulse rate and the decrease in blood pressure upon standing were somewhat more pronounced in the risperidone treatment group. Changes from a normal standing pulse rate at baseline to an abnormally high standing pulse rate under treatment were also more commonly observed in the risperidone treatment group, especially during the first week of treatment. There were no clinically relevant differences between treatment groups with respect to orthostatic blood pressure decreases.

A variety of methods have been developed to calculate a rate-corrected QT value thus allowing for comparison of QT values obtained at different heart rates. While the Bazett (QTcB) correction method is used almost exclusively in clinical practice, it overcorrects for increases in heart rate. The Fridericia correction method is more accurate in subjects with altered heart rates. Linear regression techniques have also been used to calculate a rate-corrected QT value.

No subjects had prolonged QTcF, QTlc, or QTcLD values in the study. One subject in each treatment group had a prolonged QTcB interval at endpoint (Day 22, the last day of the treatment period). No prolongation of the QTcB, QTcF, QTlc, or QTcLD interval beyond 60 milliseconds was observed in either treatment group when baseline values were compared with endpoint values. There were no subjects with QTc intervals above 500 milliseconds using any correction method.

CONCLUSION:

The steady-state concentrations of paliperidone and both its enantiomers after administration of 15 mg ER OROS paliperidone once daily (i.e., the highest proposed Phase 3 ER OROS paliperidone dose) does not exceed the paliperidone concentrations or that of its enantiomers after administration of 8 mg risperidone twice daily (i.e., the highest approved dose of RISPERDAL).

ER OROS paliperidone 9 mg and 15 mg treatments were dose-proportional (when excluding one subject who was suspected to be non-compliant).

The enantiomeric ratios of (+)/(-) paliperidone for C_{max} and AUC were higher for the risperidone treatment compared with the ER OROS paliperidone treatments.

Following ER OROS paliperidone treatment, there was no apparent relationship between the *CYP2D6* genotype and the paliperidone pharmacokinetic parameters.

The safety profile of ER OROS paliperidone doses of 9 mg administered once daily for 7 days followed by 15 mg once daily for 7 days was similar to that of IR risperidone titrated to 7 mg twice daily over a period of 7 days followed by 8 mg twice daily for 7 days. There were no unexpected or unusual safety issues.

There was no evidence of clinically significant differences between treatments with respect to laboratory test results, mean prolactin concentrations, vital signs and ECG parameters.

Date of the report: 15 November 2004

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