SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: Paliperidone NAME OF ACTIVE INGREDIENT: (+-)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2- *a*]pyrimidin-4-one	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: PAL-SCH-101 CR004273 R076477-SCH-101 **Title of Study:** A Randomized, Double-Blind, Placebo- and Active-Controlled, Parallel-Group, Phase 1 Study to Compare the Tolerability of OROS® Paliperidone (Extended-Release) With Immediate-Release (IR) Risperidone in Subjects With Schizophrenia		
Coordinating Investigator: I. Francetic, M.D. – Institute of Clinical Pharmacology, Clinical Hospital Centre, Zagreb; Croatia		
Publication (Reference): None		
Studied Period (years): Clinical Conduct: 13 March 2003 – 18 June 2003 Sample Analysis: 09 May 2003 – 11 July 2003 (R076477, R064766); 22 September 2003 – 20 October 2003 (R078543, R078544).		**Phase of development:** 1
Objectives: The primary objective of the study was a noninferiority comparison of the orthostatic tolerability of a dose of 12 mg ER OROS paliperidone with the current recommended initial titration dose (2 mg) of risperidone in patients with schizophrenia. Secondary objectives were: (1) to compare the tolerability and safety of a clinically equivalent fixed dose of ER OROS paliperidone with the currently recommended dose of risperidone; (2) to compare the early tolerability of the 2 treatments with placebo; (3) to compare tolerability of the 2 treatments, using a population PK/PD model. In addition, an exploratory pharmacogenomic assessment evaluated the relationship between genetic variability in drug metabolizing enzymes and interindividual variability in plasma exposure to paliperidone or risperidone within each treatment group.		
Methodology: This was a randomized, double-blind, placebo- and active-controlled, parallel-group, Phase 1, study conducted at 9 study centers in Europe. The study consisted of a 1-week, open-label, placebo washout period (Days –7 to –1) and a 6-day double-blind treatment period during which subjects received 1 of 3 treatments: placebo on Day 1 and ER OROS paliperidone (12 mg) on Days 2 to 6 (PLAC/PAL OROS group); ER OROS paliperidone (12 mg) on Days 1 to 6 (PAL OROS group); or IR risperidone 2 mg on Day 1 and 4 mg on Days 2 to 6 (RIS IR group).		
Number of Subjects (planned and analyzed): Planned: 120 subjects were planned to be enrolled in the study. Analyzed: 113 subjects for safety; 113 subjects for pharmacokinetics; 101 subjects for pharmacodynamics.		
Diagnosis and Main Criteria for Inclusion: Men and women, 18 to 65 years-of age, with a diagnosis of schizophrenia based on DSM-IV criteria including paranoid type (295.30), disorganized type (295.10), catatonic type (295.20), undifferentiated type (295.90), or residual type (295.60), were eligible for enrollment. Subjects were to have stable schizophrenia defined as absence of acute exacerbation for at least 6 months before screening and to be treated with oral IR risperidone for at least 1 month at study entry.		
Test Product, Dose and Mode of Administration, Batch No.: Encapsulated 2-mg ER OROS paliperidone (R076477) system, 12 mg, oral administration, MV0222552.		
Reference Therapy, Dose and Mode of Administration, Batch No.: Encapsulated 2-mg IR risperidone (R64766) tablet, 2 mg, oral administration on Day 1 and 4 mg from Day 2 to Day 6, 08205.03. Matching encapsulated placebo tablets for oral administration, MV0222551.		
Duration of Treatment: 1-week open-label placebo treatment (washout), followed by 6-days treatment with double-blind study medication.		
Criteria for Evaluation: Pharmacokinetics: Plasma concentrations of risperidone, paliperidone, and active moiety (i.e., the sum of paliperidone and risperidone plasma concentrations) were measured for pharmacokinetic and pharmacokinetic/pharmacodynamic evaluations. The plasma concentrations of both paliperidone enantiomers were measured in a subset of subjects to document the enantiomer disposition after paliperidone and risperidone treatment. The pharmacokinetic parameters of risperidone, paliperidone, and active moiety estimated were: $C_{predose}$, C_{max} , t_{max}, AUC_{24h} on Days 1 and 6, and C_{min}, AUC_{τ}, $V_{d,ss}$,$C_{avg,ss}$, FI, accumulation ratio, MRT and CL/F on Day 6. Enantiomer analyses included: AUC_{22h} on Day 1, C_{max} and AUC ratio of (+)/(-) paliperidone, calculated as $C_{max,R078543}/C_{max,R078544}$ and $AUC_{R078543}/AUC_{R078544}$ on Days 1 and 6. The lower limit of quantification (LLOQ) for paliperidone and risperidone was 0.100 ng/mL and for the enantiomers R078543 and R078544, 0.200 ng/mL.		

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Criteria for Evaluation: (continued)

Pharmacogenomics: Potential relationships between genetic variability in drug metabolizing enzymes (e.g., *CYP2D6, CYP3A4/5, UGT1A1*) and plasma concentrations of paliperidone or risperidone were evaluated.

Pharmacodynamics: Systolic (SBP) and diastolic (DBP) blood pressure and heart rate (HR) measurements were performed after 10 minutes in the supine position and 1, 3, and 5 minutes after standing during the Standing Monitored Test (SMT). Orthostatic intolerance was also assessed on the basis of symptoms (e.g., feeling dizzy or faint) and the results recorded on an Orthostatic Intolerance Visual Analog Scale (VAS).

Serum concentrations of prolactin were determined.

Psychiatric Evaluations: Two psychiatric rating scales, the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression (CGI) Scale, were administered to monitor for any possible deterioration in the subject's condition. Efficacy was not an objective of the study.

Safety: Safety assessments included reports of adverse events, the Extrapyramidal Symptom Rating Scale (ESRS), Sedation Visual Analog Scale (VAS), Leeds Sleep Evaluation Questionnaire (LSEQ), clinical laboratory tests, vital sign measurements, physical examinations, and electrocardiogram (ECG) findings.

Statistical Methods:

Pharmacokinetics: Descriptive statistics for the plasma concentrations and PK parameters of paliperidone for both ER OROS paliperidone treatments and of risperidone, paliperidone and active moiety for the RIS IR treatment; descriptive statistics for the plasma concentrations and PK parameters of the enantiomers in selected subjects.

Pharmacodynamics: The primary variable i.e., the mean of 2 hour and 22 hour orthostatic SBP changes from baseline on Day 1, was analyzed using a linear regression model with treatment as a fixed factor and age as a continuous, linear covariate. A 95% CI for the difference in means between 12 mg ER OROS paliperidone and 2 mg IR risperidone was constructed using the estimates of LS means and intersubject variance from the regression model. The primary analysis was performed in the per-protocol population and repeated in the intent-to-treat population.

Descriptive statistics were calculated for prolactin levels.

Pharmacokinetics/Pharmacodynamics: The relationship between plasma concentrations of paliperidone (for PAL OROS-treated subjects) or plasma active moiety concentration (for the RIS IR-treated subjects) and pharmacodynamic (orthostatic systolic blood pressure) and safety (total ESRS score, change in QTcLD) parameters were examined graphically.

Pharmacogenomics: The possible influence of genotype on the paliperidone pharmacokinetic parameters was examined by graphical analysis.

Psychiatric Evaluations: PANSS and CGI-change results were summarized descriptively.

Safety: The incidence of treatment-emergent adverse events was summarized. Descriptive statistics were provided for the other safety parameters. These summaries were performed in the intent-to-treat population, unless specified otherwise.

SUMMARY – CONCLUSIONS

The study population comprised of 83 men and 30 women (113 subjects in total), who were randomly assigned to receive either PLAC/PAL OROS (n=37), PAL OROS (n=38), or RIS IR (n=38). Subjects had a mean age of 37 years (range: 20 to 63 years). Most subjects (98%) were white. Paranoid schizophrenia (73%) was the most common diagnosis, followed by residual schizophrenia (15%), undifferentiated schizophrenia (10%), disorganized schizophrenia (1%), and other schizophrenias (1%). The combined ER OROS paliperidone group included 2 intermediate and 1 poor metabolizer; the IR RIS group 3 intermediate and 2 poor metabolizers.

PHARMACOKINETIC RESULTS: On Day 1, the mean peak plasma concentration for the active moiety (RIS IR treatment) was reached at 2.7 hours and for paliperidone in the ER OROS paliperidone treatment at 21.8 hours, which is close to the predicted values of 2 and 22 hours, respectively. The obtained mean C_{max} in both treatments was 19.4 and 23.1 ng/mL respectively. On Day 6, the t_{max} in both ER OROS paliperidone treatments was between 20 and 26 hours and steady state was reached after 4 to 5 days. At steady state, the AUC was 14% higher for paliperidone in the ER OROS paliperidone group compared with active moiety in the RIS IR group.

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SUMMARY – CONCLUSIONS (CONTINUED)

PHARMACOKINETIC RESULTS: (continued) The peak/trough variation of ER OROS paliperidone was much lower compared to risperidone IR reflected in a lower fluctuation index for the ER OROS paliperidone treatment versus the RIS IR treatment, 38% and 125% respectively. The intersubject variability for all pharmacokinetic parameters in both ER OROS paliperidone treatments was higher compared with the RIS IR treatment.

No clear relationship between PK parameters and *CYP2D6* genotype was observed for the paliperidone treated subjects. The enantiomeric ratio of (+) versus (-) paliperidone for C_{max} and AUC were higher for the RIS IR treatment compared with the ER OROS paliperidone treatment. No clear relationship with paliperidone pharmacokinetics was observed for other genes determined (*CYP3A4/5* and *UGT1A1*).

PHARMACODYNAMIC RESULTS: On Day 1, mean orthostatic systolic blood pressure changes were -1.16 mmHg in PAL OROS-treated subjects, -0.16 mmHg in RIS-IR-treated subjects, and -0.15 mmHg in placebo-treated subjects. The upper and lower limits of the 95% confidence interval for the difference in means between 12 mg ER OROS paliperidone and 2 mg IR risperidone were –4.07 and 2.02 mmHg indicating that 12 mg ER OROS paliperidone was noninferior to 2 mg IR risperidone with respect to initial orthostatic tolerability (i.e., the lower limit of -4.07 was greater than the predefined limit of -10 mmHg). The number of subjects with orthostatic hypotension or reflex tachycardia within 3 minutes after standing was lower in ER OROS paliperidone-treated subjects (55%) than in IR risperidone-treated subjects (79%). There was no apparent relationship between plasma concentration of paliperidone for the paliperidone-treated subjects or of active moiety for the risperidone-treated subjects and mean change in orthostatic systolic blood pressure on Days 1 or 6. The peak/trough variation of prolactin in the ER OROS paliperidone treatment groups was much lower than the peak/trough variation of prolactin in the IR risperidone treatment group. For subjects in the PAL OROS group, the mean t_{max} of prolactin was 6.5 hours while the mean t_{max} of paliperidone was 21.8 hours.

SAFETY RESULTS: The most commonly reported adverse events in the ER OROS paliperidone groups were extrapyramidal disorder (12%), insomnia (8%), hyperkinesia and headache (both 5%). The most commonly reported adverse events in the IR risperidone group were insomnia (18%), anxiety (11%), extrapyramidal disorder and tachycardia (both 8%), and hyperkinesia (5%) (Table A). In the PLAC/PAL OROS group, all 4 reports of extrapyramidal disorder and 1 report of hyperkinesia had their initial onset on Day 1 during placebo treatment. The majority of adverse events were of mild intensity and resolved spontaneously.

Table A: Common[a] Treatment-Emergent Adverse Events
(Study PAL-SCH-101: Intent-to-Treat Analysis Set)

Body System Preferred Term	PLAC/PAL OROS (N=37) n (%)	PAL OROS (N=38) n (%)	RIS IR (N=38) n (%)	ALL PAL (N=75) n (%)
Total no. subjects with AEs	14 (37.8)	15 (39.5)	19 (50.0)	29 (38.7)
Centr & periph nervous system	9 (24.3)	10 (26.3)	7 (18.4)	19 (25.3)
Extrapyramidal disorder	4 (10.8)	5 (13.2)	3 (7.9)	9 (12.0)
Headache	2 (5.4)	2 (5.3)	0	4 (5.3)
Hyperkinesia	2 (5.4)	2 (5.3)	2 (5.3)	4 (5.3)
Dizziness	1 (2.7)	1 (2.6)	0	2 (2.7)
Psychiatric	8 (21.6)	5 (13.2)	11 (28.9)	13 (17.3)
Insomnia	4 (10.8)	2 (5.3)	7 (18.4)	6 (8.0)
Somnolence	2 (5.4)	1 (2.6)	0	3 (4.0)
Anxiety	1 (2.7)	1 (2.6)	4 (10.5)	2 (2.7)
Psychosis	1 (2.7)	1 (2.6)	1 (2.6)	2 (2.7)
Gastrointestinal system	1 (2.7)	2 (5.3)	2 (5.3)	3 (4.0)
Nausea	1 (2.7)	2 (5.3)	0	3 (4.0)
Heart rate and rhythm	0	3 (7.9)	3 (7.9)	3 (4.0)
Palpitation	0	2 (5.3)	0	2 (2.7)

[a] Includes adverse events reported in 2 or more paliperidone-treated subjects during the double-blind period.
Note: Incidence is based on the number of subjects, not the number of events

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SAFETY RESULTS: (continued)

Eleven (16%) of 69 subjects treated with ER OROS paliperidone and 6 (16%) of 38 subjects in the RIS IR treatment group experienced EPS-related adverse events (extrapyramidal disorder, hyperkinesia, ataxia, dystonia) after receiving at least 1 dose of ER OROS paliperidone or IR risperidone. Consistent with the reports of EPS-related adverse events, ER OROS paliperidone-treated subjects had a mean decrease (improvement) in total ESRS of 0.19 while IR risperidone-treated subjects had a mean increase (worsening) in total ESRS of 0.31.

No serious adverse events occurred in either paliperidone treatment group. Five subjects discontinued double-blind treatment due to adverse events including 2 subjects in the PAL OROS group (psychosis, hypertension), 1 subject in the PLAC/PAL OROS group (hyperkinesia), and 2 subjects in the RIS IR group (psychosis, rhinitis).

There were no clinically noteworthy changes from baseline in sleep quality parameters (LSEQ), level of alertness (sedation VAS and Questionnaire), clinical laboratory analytes, ECG, or body weight measurements.

CONCLUSION:

The results of this study indicate that 12 mg ER OROS paliperidone is noninferior to 2 mg IR risperidone with respect to initial orthostatic tolerability in subjects with schizophrenia.

The safety profile of 12 mg ER OROS paliperidone once daily for 5 to 6 days was similar to that of 2 mg IR risperidone on Day 1 followed by 4 mg IR risperidone on Days 2 to 6, and was consistent with its expected safety profile based on its pharmacologic activity as a serotonin - dopamine antagonist, with no unexpected or unusual safety issues. The early tolerability as observed on Day 1 was comparable between the 3 treatment groups (12 mg ER OROS paliperidone, 2 mg IR risperidone, and placebo).

During administration of 12 mg ER OROS paliperidone for 5 or 6 days in subjects with schizophrenia, t_{max} of paliperidone was between 20 and 26 hours after dosing on Day 6 and steady state was reached within 4 to 5 days. The fluctuation index of ER OROS paliperidone was 69% lower than that of IR risperidone. A comparison of the steady-state pharmacokinetics of 12 mg ER OROS paliperidone in this study with the simulated steady-state profiles after a single 4 mg dose of ER OROS paliperidone in Study C-2002-034 indicate that the pharmacokinetics of the ER OROS paliperidone system are linear. There was no apparent relationship between *CYP2D6*, *CYP3A4/5* or *UGT1A1* genotype and paliperidone plasma concentrations.

Date of the report: 27 October 2005

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