# CLINICAL STUDY REPORT SYNOPSIS

**Document No.:** EDMS-PSDB-6051628:2.0

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| Name of Sponsor/Company | Johnson & Johnson Pharmaceutical Research & Development | |
| Name of Finished Product | Paliperidone ER | |
| Name of Active Ingredient(s) | -[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 | |

**Protocol No.:** R076477-SCH-1015 CR011437

**Title of Study:** Evaluation of the Dose Proportionality of Two Dose Strengths (1.5 and 3 mg) of Extended-Release Paliperidone After a Single Administration to Healthy Men

**Principal Investigator:** Annemieke Mertens, M.D. - Clinical Pharmacology Unit, Johnson & Johnson Pharmaceutical Research and Development, Antwerp; Belgium

**Publication (Reference):** None

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| **Study Period:** Clinical Conduct: 26 June 2006 – 6 September 2006<br>Sample Analysis: 31 August 2006 - 14 September 2006 | **Phase of Development:** 1 |

**Objectives:** The objective of this study was to evaluate the dose proportionality of 1.5- and 3-mg tablets of paliperidone ER. Secondary objectives of this study were to document the pharmacokinetics of a 1.5 mg dose of paliperidone ER in healthy men, and to assess the safety and tolerability of the 1.5- and 3-mg tablets of paliperidone ER in healthy men.

**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 a single oral 1.5 or 3 mg dose of study drug; and end-of-study evaluations upon completion of all the study procedures in Period 2. All subjects received each of the following 2 treatments in random order: Treatment A: One tablet of 1.5 mg paliperidone ER to-be-marketed formulation in the fasted state; Treatment B: One tablet of 3 mg paliperidone ER Phase 3 formulation in the fasted state.

**Number of Subjects (planned and analyzed):** Sixty subjects were planned with the intention that at least 54 complete the study. Fifty-eight subjects were enrolled and all completed the study. PK and safety data were analyzed from all 58 subjects.

**Diagnosis and Main Criteria for Inclusion:** Subjects were healthy males between the ages of 18 and 55, inclusive. 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 1.5-mg tablets for oral use, batch no. 517753, formulation F071. Paliperidone ER 3-mg tablets for oral use, batch no. 426911, formulation F016.

**Reference Therapy, Dose and Mode of Administration, Batch No.:** None.

**Duration of Treatment:** A single dose of 1.5 mg and 3 mg paliperidone ER, separated by a washout period of 9 to 21 days.

**Criteria for Evaluation:**

Pharmacokinetics: In each treatment period, venous blood samples of 3 mL were taken from an antecubital vein within 2 hours before dosing and during the 96 hours following dosing. Based on the individual plasma concentration-time data, using the actual sampling times, the following PK parameters of paliperidone were estimated for each of the treatments: $C_{max}$, $t_{max}$, $AUC_{last}$, $AUC_{\infty}$, $\%AUC_{\infty ex}$, CL/F, $\lambda_z$, and $t_{1/2}$.

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, before study drug administration in each treatment period, and at the end of the study. Twelve-lead ECGs and physical examination were performed at screening, before study drug administration in each treatment period, and at the end of the study. Vital signs were measured throughout the study.

**Statistical Methods:** Statistical analysis was performed on log-transformed PK parameters after dose

# SYNOPSIS (CONTINUED)

normalization. Mixed-effects analysis of variance models were fit to the data with one of the estimated PK parameters of interest as the dependent variable, treatment-sequence group, period, and treatment as fixed effects, and subject as a random effect. Testing for the treatment-sequence group and period effects was carried out at the 10% and 5% levels of significance, respectively, using the appropriate error terms. The estimated least square means and intrasubject variance from the mixed-effects model were used to construct 90% confidence intervals for the difference in means on the log scale between the 2 dose groups. The limits of the confidence intervals were retransformed using antilogarithms to obtain 90% confidence intervals for the ratio of the mean PK parameters of 1.5 mg paliperidone ER relative to 3 mg paliperidone ER.

**SUMMARY - CONCLUSIONS**

PHARMACOKINETICS: The mean actual and dose-normalized PK bioavailability parameters for both treatments are presented in Table A.

Table A: Mean (±SD) Actual and Dose-normalized Pharmacokinetic Parameters of Paliperidone after Single Dose Administration of 1.5 mg or 3 mg Paliperidone ER
(Study R076477-SCH-1015: Pharmacokinetic Analysis Set)

| | | Actual | | Dose-normalized |
|---|---|---|---|---|
| | | 1.5 mg | 3.0 mg | 1.5 mg - DN |
| Parameter | n | Mean ± SD | Mean ± SD | Mean ± SD |
| $t_{max}$, h | 58 | 24.00 (9.00 - 28.00) | 24.00 (9.00 – 28.03) | - |
| $C_{max}$, ng/mL | 58 | 1.92 ± 0.796 | 4.11 ± 1.84 | 3.84 ± 1.59 |
| $AUC_{last}$, ng·h/mL | 58 | 69.6 ± 27.6 | 146 ± 58.8 | 139 ± 55.2 |
| $AUC_{\infty}$, ng·h/mL | 58 | 76.5 ± 30.4 | 158 ± 62.2 | 153 ± 60.9 |
| $t_{½}$, h | 58 | 24.9 ± 6.2 | 23.5 ± 5.3 | - |

DN: dose-normalized (to 3 mg); -: not applicable.
Data presented as arithmetic mean ± SD; $t_{max}$ presented as median (range)

The mean paliperidone bioavailability PK parameters, after dose normalization to 3 mg, were similar for the 1.5 and 3 mg treatments (Table A).

For both dosages, the median time to reach peak paliperidone plasma concentrations was 24 hours and the average apparent terminal half-life was comparable: 24.9 and 23.5 hours for 1.5 and 3 mg, respectively (Table A).

Paliperidone dose proportionality was evaluated by comparing the log-transformed dose-normalized bioavailability PK parameters among treatments using a mixed-effect ANOVA model. All 58 subjects who completed both treatment periods were included in the inferential statistics. The 90% confidence intervals for the least-square geometric means ratios were entirely within the 80.0% to 125.0% bioequivalence criteria for $C_{max}$ (86.42% – 103.94%), $AUC_{last}$ (87.02% – 104.95%), and $AUC_{\infty}$ (88.56% – 106.18%).

SAFETY RESULTS: The incidence of treatment-emergent adverse events was comparable between both treatments: 19 subjects (33%) after 1.5 mg paliperidone ER and 21 subjects (36%) after 3 mg paliperidone ER. The most common adverse events were fatigue (17%), headache (12%), and somnolence (9%). There were no serious adverse events and no subjects discontinued the study due to an adverse event. There were no clinically relevant changes in chemistry, hematology, or urine laboratory values, in vital signs, or in electrocardiograms.

CONCLUSION: Dose proportionality of paliperidone pharmacokinetics was shown from 1.5 to 3 mg paliperidone ER for $C_{max}$, $AUC_{last}$, and $AUC_{\infty}$.

Single doses of 1.5 and 3 mg paliperidone ER were well tolerated by healthy male subjects and there were no unexpected safety findings.

**Issue Date of the Clinical Study Report:** 23 January 2007

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