CLINICAL STUDY REPORT SYNOPSIS

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SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: Paliperidone ER NAME OF ACTIVE INGREDIENT(S): [2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyridol[1,2-a]pyrimidin-4-one	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: PALIOROS-PSZ-1001

Title of Study: Open-Label Study to Evaluate the Safety and Pharmacokinetics of Single- and Multiple-Dose Extended-Release OROS Paliperidone in Pediatric Subjects (≥10 to ≤17 Years of Age) With Schizophrenia, Schizoaffective Disorder, or Schizophreniform Disorder

Principal Investigator: V. Chirita, M.D.

Publication (Reference): None

Studied Period (years): Clinical Conduct: 17 March 2006 to 25 August 2006 Plasma Sample Analysis: 02 May 2006 to 27 September 2006. Urine Sample Analysis: 22 September 2006 to 05 October 2006.	**Phase of development:** 1

Objectives: The objectives of this study were to 1) to characterize the pharmacokinetics of paliperidone after single-dose administration and at steady state following multiple oral administrations of extended-release (ER) paliperidone, in children and adolescent subjects (≥10 to ≤17 years of age) with schizophrenia, schizoaffective disorder, or schizophreniform disorder; and 2) to evaluate the safety and tolerability of paliperidone ER in this subject population.

Methodology: This was a multicenter, open-label, multiple-dose study in children and adolescent subjects ≥10 to ≤17 years of age with schizophrenia, schizoaffective disorder, or schizophreniform disorder. The study included 3 dosage groups (0.086, 0.129, and 0.171 mg/kg/day paliperidone ER), which were studied in a sequential ascending design, so that the safety of the drug could be properly evaluated with a lower dosage before proceeding to the next higher dosage. The 3 dosages used approximated 6, 9, and 12 mg/day in adults. Within each dosage group, subjects were randomly assigned to 1 of 2 PK sampling schedules (Schedule A or B) in a 1:1 ratio. For each dosage group, the study consisted of a screening phase (for a maximum of 21 days); a 2-day, single-dose PK and tolerability evaluation phase; a 7-day multiple-dose phase, with evaluation of pharmacokinetics and tolerability; and an end-of-study visit. Following the completion of all subjects in a given dosage group, the sponsor evaluated the safety and tolerability of the treatment, in order to determine whether to proceed to the next higher or lower dosage level. The first group started at 0.086 mg/kg/day.

Number of Subjects (planned and analyzed): Twenty-four subjects (8 subjects in each of the 3 dosage groups) were planned. Every attempt was made to include the lower age groups (10 to 12 years of age and 13 to 15 year of age) in each dosage group. A total of 25 subjects (8, 9, and 8 in the respective dosage groups) were enrolled, and 24 subjects (8, 9, and 7 subjects in the respective dosage groups) completed the study. Pharmacokinetic data were analyzed from 24 subjects (for the single-dose treatment phase) or 23 subjects (for the multiple-dose treatment phase), and safety data were analyzed from all subjects.

Diagnosis and Main Criteria for Inclusion: To be enrolled in the study, subjects had to be male or female and between the ages of 10 and 17 years of age, inclusive, with a height and weight within the 5th to 95th percentile for age and sex. Subjects were required to have a diagnosis of schizophrenia of any subtype, schizoaffective disorder, or schizophreniform disorder, according to the DSM-IV-TR. Subjects had to be otherwise healthy on the basis of screening medical history, physical examination, 12-lead ECG, and clinical laboratory tests (hematology, serum chemistry, and urinalysis). Subjects were required to have a CGI-S score of ≤3, be able to provide informed consent, be accompanied by a parent or legal guardian who also gave written informed consent; and be willing to adhere to the prohibitions and restrictions. All female subjects had to be premenarchal, surgically sterile, abstinent, or, if sexually active, be practicing an effective method of birth control.

Test Product, Dose and Mode of Administration, Batch No.: Paliperidone ER 1-mg oral tablets – F053, batch no. 0500252, expiration date 04-2007. Paliperidone ER 3 mg oral tablets – F016, batch no. 0500130, expiration date: 03-2007. Paliperidone ER 6 mg oral tablets – F055, batch no. 0500129, expiration date: 03-2007.

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

Duration of Treatment: The study consisted of a screening period of approximately 3 weeks (maximum of 21 days), a 2-day single-dose PK and tolerability evaluation phase, a 7-day multiple-dose phase with evaluation of pharmacokinetics and tolerability, and an end-of-study visit.

Criteria for Evaluation:

Pharmacokinetics: Within each dosage group, subjects were randomly assigned to 1 of 2 PK sampling schemes. Plasma (Days 1−10) and urine (Days 9−10) concentrations of the paliperidone (+) and (-) enantiomers 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 were determined for the 2 paliperidone enantiomers; samples were collected at Day −1. The unbound fraction for paliperidone was calculated.

Based on the actual PK blood sampling times and actual urine collection periods, the following plasma and urinary PK parameters at steady state (Day 9) were estimated for paliperidone and its enantiomers, using noncompartmental analysis: total and unbound C_{max}, AUC_t, $AUC_{t,}$ratio of (+)/(-) paliperidone enantiomer and CL/F; Ae (per collection interval and overall), Ae%dose, CL_R, CL_{GFR}, CL_{act}, CL_{CR} (based on urine data and based on Schwartz formula), and CL_{NR}. The plasma concentration time ratio of the (+)/(-) enantiomer was also calculated per time point. Actual and dose-normalized (to 6 mg/day and 0.086 mg/kg/day) plasma concentrations and derived PK parameters were presented.

Safety: Safety and tolerability were assessed at several points during the study. This assessment included review of individual results for physical examinations, clinical laboratory tests, EPS scales, ECG, adverse events, and vital signs. Subject safety was considered adequate only if there were no clinically important deviations in these safety assessments in the opinion of the sponsor in consultation with the investigator. For each subject, safety and tolerability was evaluated after single-dose treatment before continuing with multiple-dose treatment beginning on Day 3. An interim safety evaluation was conducted after completion of the first 4 subjects in the 0.086 mg/kg/day dosage group. Following the completion of all subjects in each dosage group, the sponsor evaluated the safety and tolerability, in order to determine whether to proceed to the next higher dosage level. After completion of the first 2 dosage groups (0.086 mg/kg/day and 0.129 mg/kg/day), a decision was made to go to the 0.171 mg/kg/day as the third dosage, given that the first 2 dosage groups were well tolerated.

Statistical Methods:

Pharmacokinetics: Descriptive statistics were calculated for the plasma concentrations of paliperidone and its enantiomers at each sampling time and for the derived estimated plasma dose-normalized and urine steady-state PK parameters. Graphical exploration of the paliperidone and enantiomer plasma concentrations and urine data, and the derived estimated PK parameters was performed.

Safety: All subjects who received at least 1 dose of study drug were included in the safety analyses. Safety and tolerability data were tabulated and evaluated at the completion of the study using descriptive statistics. Safety data (including adverse events, clinical laboratory tests, QTc intervals, CGI-S, and EPS scales) were analyzed for each dosage group. Descriptive statistics were provided for vital signs, Tanner staging was summarized, and abnormal findings for physical examination were listed.

SUMMARY – CONCLUSIONS

DEMOGRAPHIC RESULTS:

Twenty-five pediatric subjects (18 males, 7 females) diagnosed with schizophrenia, schizoaffective disorder, or schizophreniform disorder were enrolled in this study. Mean (SD) age was 14.6 (2.18) years (range: 10–17 years). One, 7, 6, and 10 subjects in the 10–11, 12–13, 14–15, and 16–17 age strata, respectively, completed the study. Body weight ranged between 31 kg and 89 kg. Overall, 56% of subjects were white, 24% were black, and 20% were Asian. Eight subjects (32%) had schizophreniform disorder, 7 (28%) had schizoaffective disorder, 6 (24%) had paranoid schizophrenia, 3 (12%) had undifferentiated schizophrenia, and 1 (4%) had disorganized schizophrenia. Mean (SD) age at first diagnosis was 13.6 (2.18) years. Total daily dose ranged from 4 to 12 mg/day.

PHARMACOKINETIC RESULTS:

Following single-dose administration, the plasma concentrations of paliperidone rise steadily to reach peak plasma concentration approximately 24 hours after dosing, which is consistent with the release characteristics of paliperidone ER. Steady-state drug concentrations were attained within 4–5 days of the start of multiple-dose administration.

The plasma and urine PK parameters at steady state of paliperidone are presented in the Table below.

Descriptive Statistics of the Plasma Dose-Normalized (to 6 mg/day) and Urine PK Parameters of Paliperidone at Steady State After Repeated Dosing at Day 9
(Study PALIOROS-PSZ-1001: Pharmacokinetic Analysis Set; n=23)

	Mean ± SD	%CV	Median	Min-Max
f_u,%	25.6 ± 5.15	20.1	26.4	14.6–33.6
$C_{max0\text{-}24ss}$, ng/mL	34.2 ± 22.3	65.3	23.2	9.62–89.3
$AUC_{0\text{-}24,ss,}$ ng·h/mL	686 ± 448	65.4	486	215–1750
CL/F, mL/min	209 ± 117	56.3	206	57.1–465
% of the dose renally excreted	24.4 ± 12.7	51.8	23.1	7.88–60.8
CL_R, mL/min	42.4 + 17.4	41.0	37.8	8.01–68.5
CL_{CR}, mL/min	131 ± 50.3	38.4	134	63.3–276
CL_{GFR}, mL/min	33.7 ± 15.7	46.6	29.6	9.81–81.7
CL_{act}, mL/min	8.35 ± 13.3	159.2	8.86	-15.1–41.6

f_u: n=25; CL_{act}: n=22

Within the investigated age range (10–17 years), there was no apparent relationship between dose-normalized plasma exposure and age.

SAFETY RESULTS: Paliperidone ER was generally well tolerated. The most commonly reported treatment-emergent adverse events (>10%) were sedation (n=4) and epistaxis (n=3). Five subjects (20%) reported EPS-related adverse events, which included extrapyramidal disorder (2 subjects), akathisia (1 subject), dystonia (1 subject), and tremor (1 subject). The overall incidence of treatment-emergent adverse events increased with dose: 38%, 67%, and 75%, in the 0.086 mg/kg/day, 0.129 mg/kg/day, and 0.171 mg/kg/day dosage groups, respectively. Most adverse events were considered mild or moderate in intensity across the dosage groups, were of short duration, and resolved spontaneously. Most adverse events were considered by the investigator to have a possible or doubtful relationship to paliperidone ER treatment. There were no deaths or serious treatment-emergent adverse events, and no subjects were discontinued from the study due to an adverse event.

One treatment-emergent, persistent adverse event was observed. This subject experienced nausea of mild intensity beginning the evening of the first administration with 0.171 mg/kg/day.

Mean increases for prolactin from screening to end-of-study approximated 44 ng/mL, 31 ng/mL, and 52 ng/mL in the 0.086 mg/kg/day, 0.129 mg/kg/day, and 0.171 mg/kg/day dosage groups, respectively. Overall, 4, 6, and 3 subjects in Groups A, B, and C, respectively, experienced baseline to postbaseline shifts in prolactin values from the normal to high range. No adverse events that are possibly associated with an increase in prolactin were reported. However, the study duration may not have been long enough to assess the occurrence of adverse events frequently associated with high prolactin.

Treatment-emergent orthostatic hypotension was experienced by 1 subject in Group A, 2 subjects in Group B, and 0 subjects in Group C.

One subject in Group A, 3 subjects in Group B, and 3 subjects in Group C experienced a prolonged value for QTcB, defined as ≥450 ms at some time point during the study. One subject in Group B experienced mild QTc interval prolongation that was classified as an adverse event. The event resolved without intervention and was rated by the investigator as being unrelated to study medication.

CONCLUSION:

Following single-dose administration in pediatric subjects, the plasma concentrations of paliperidone rise steadily to reach peak plasma concentration approximately 24 hours after dosing.

Steady-state drug concentrations are attained within 4–5 days of dosing. PK observations in pediatric subjects are consistent with those observed in adults following single- and multiple-dose administration of paliperidone ER.

Pediatric subjects (≥10 and ≤17 years of age) tolerated doses from 4 to 12 mg paliperidone ER (corresponding to weight-adjusted doses ranging between 0.086 and 0.171 mg/kg) well with no serious treatment-emergent adverse events. The safety profile was similar to that seen in adults.

Date of the report: 29 January 2007

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